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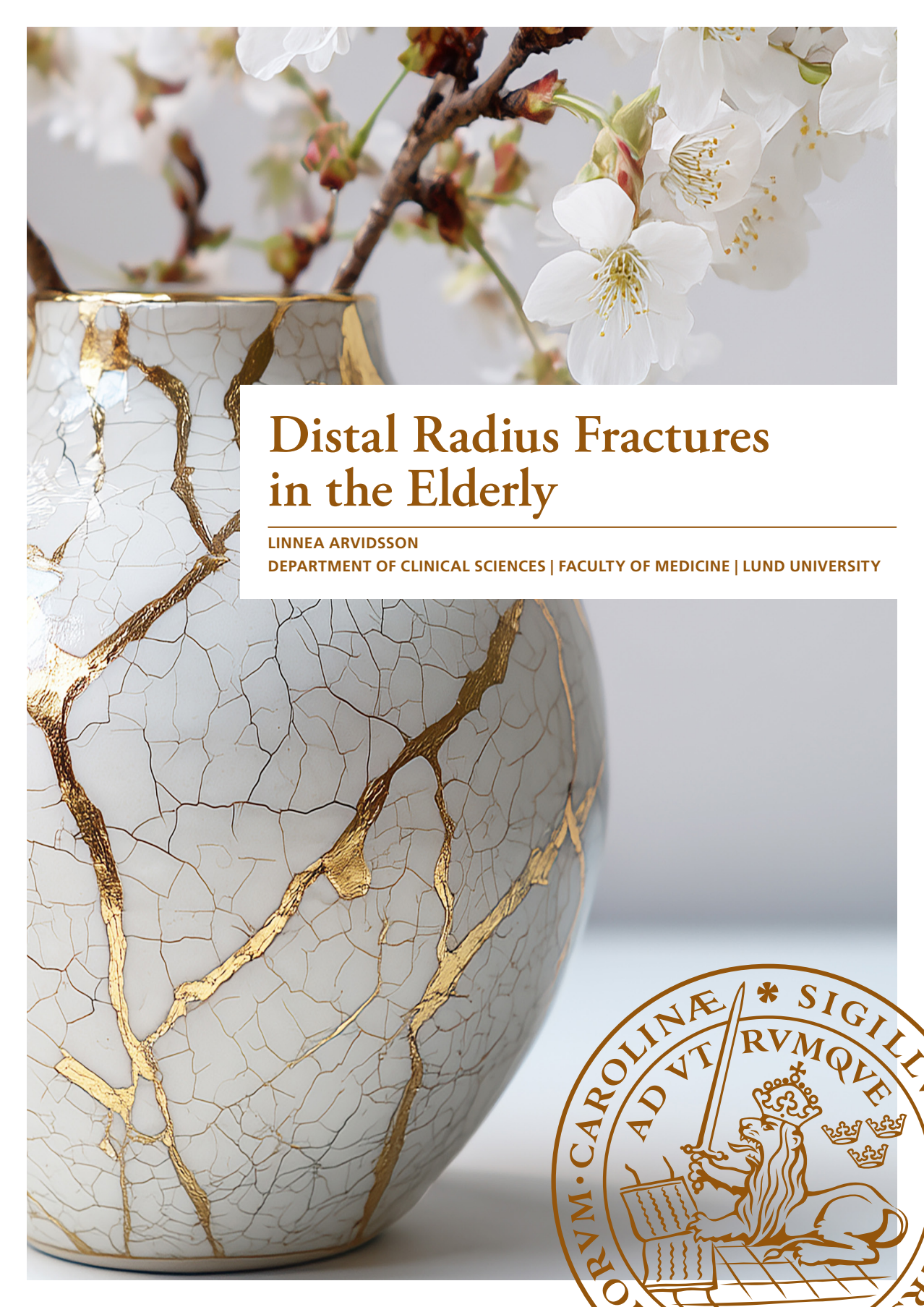
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# Distal Radius Fractures in the Elderly

LINNEA ARVIDSSON

DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY





**LINNEA ARVIDSSON** is a specialist in orthopaedic surgery at Skåne University Hospital, Malmö, Sweden. She currently resides in Lund with her family.

*Distal Radius Fractures in the Elderly* is a comprehensive thesis exploring various aspects of distal radius fractures in older adults through qualitative, quantitative, and experimental research. With the guiding principle that *good care has no age limit*, this work aims to improve the management and outcomes of distal radius fractures in the elderly.

The thesis provides new insights into combined distal radius and ulna fractures, mortality among the oldest patients with distal radius fractures, and the potential of digital postoperative follow-up. Furthermore, it highlights novel opportunities to enhance fracture surgery in osteoporotic bone.

## Distal Radius Fractures in the Elderly



# Distal Radius Fractures in the Elderly

Linnea Arvidsson



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## DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at  
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**Title and subtitle:** Distal Radius Fractures in the Elderly

**Abstract:**

This thesis combines quantitative, qualitative, and experimental approaches to address different aspects of distal radius fractures (DRFs) in the elderly.

Study I was a registry-based cohort study of 5,536 DRF patients, of whom 259 (5%) sustained a concomitant distal metaphyseal ulna fracture. These patients, with a mean age of 73 years (SD 15), had nearly twice the odds of reporting severe symptoms (DASH > 35) 1 year after injury compared with those with isolated DRFs (OR 1.97, 95% CI 1.40–2.75,  $P < 0.001$ ).

Study II evaluated the mortality among 240 DRF patients aged 80 years or older. 1-year mortality was markedly lower than expected (SMR 0.44, 95% CI 0.18–0.69,  $P < 0.01$ ), while at 5 years mortality approximated that of the general population (SMR 0.96, 95% CI 0.78–1.14). Living situation was the strongest predictor of survival, with residents of nursing homes having the worst prognosis.

Study III employed mixed methods, including qualitative interviews with 10 surgically treated patients during the COVID-19 pandemic, to explore experiences of video-based follow-up. Despite the inclusion of both elderly patients and patients with low levels of digital literacy, video consultations were described as simple and accessible. Many expressed a preference for digital follow-up after surgery.

Study IV used an osteoporotic rat model to evaluate the combination of locally applied calcium sulphate/hydroxyapatite (CaS/HA) biomaterial around a metallic screw followed by systemically administered zoledronic acid. The treatment significantly enhanced peri-implant bone formation compared with animals not receiving the CaS/HA material. The method was translated to a small cohort of hip fracture patients, suggesting potential to improve screw fixation in osteoporotic bone and in future wrist fracture surgery.

Taken together, these studies support tailoring DRF treatment to functional status rather than chronological age. They further emphasise the importance of prognostic awareness, the potential of digital follow-up, and opportunities to enhance surgical fixation in osteoporotic bone.

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**MADE IN SWEDEN** 



*To everyone who had a broken wrist,  
fixed a broken wrist,  
or know someone who did*

***Kintsugi*** – the Japanese art of mending broken pottery with gold, honouring wear and the beauty of imperfection, where the old becomes even more precious for having been broken and made whole again.

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## List of Papers

- I. **Arvidsson L**, Landgren M, Harding AK, Abramo A, Tägil M. Double trouble! Concomitant distal ulna fractures predict worse 1-year outcome in distal radius fractures: a registry-based cohort study of 5,536 patients. *Acta Orthop*. 2025;96:606-611. Published 2025 Aug 15.
- II. **Arvidsson L**, Landgren M, Harding AK, Abramo A, Tägil M. Patients Aged 80 or More With Distal Radius Fractures Have a Lower One-Year Mortality Rate Than Age- and Gender-Matched Controls: A Register-Based Study. *Geriatr Orthop Surg Rehabil*. 2024;15:21514593241252583. Published 2024 May 5.
- III. **Arvidsson L**, Hägglund B, Petersson L, Arvidsson E, Tägil M. Virtual Follow up After Distal Radius Fracture Surgery-Patient Experiences During the COVID-19 Pandemic. *J Patient Exp*. 2023;10:23743735231188819. Published 2023 Jul 24.
- IV. Markeviciute V, Puthia M, **Arvidsson L**, et al. Systemically administered zoledronic acid activates locally implanted synthetic hydroxyapatite particles enhancing peri-implant bone formation: A regenerative medicine approach to improve fracture fixation. *Acta Biomater*. 2024;179:354-370.

## Abbreviations

|           |                                                             |
|-----------|-------------------------------------------------------------|
| AO        | Arbeitsgemeinschaft für Osteosynthesefragen                 |
| BV        | Bone volume                                                 |
| CCI       | Charlson comorbidity index                                  |
| COVID-19  | Coronavirus disease 2019                                    |
| CRC       | Closed reduction and casting                                |
| DASH      | Disability of the Arm, Shoulder and Hand                    |
| DRF       | Distal radius fracture                                      |
| DRUF      | Distal radius fracture and distal metaphyseal ulna fracture |
| DRUJ      | Distal radioulnar joint                                     |
| DUF       | Distal ulna fracture                                        |
| FDL       | Functional digital literacy                                 |
| FHL       | Functional health literacy                                  |
| CaS/HA    | Calcium sulphate / Hydroxyapatite                           |
| CT        | Computer tomography                                         |
| ICD       | International Classification of Diseases                    |
| IQR       | Interquartile range                                         |
| OR        | Odds ratio                                                  |
| ORIF      | Open reduction and internal fixation                        |
| PROM      | Patient-reported outcome measure                            |
| QuickDASH | Quick Disability of the Arm, Shoulder and Hand              |
| RCT       | Randomised controlled trial                                 |
| ROI       | Region of interest                                          |
| ROM       | Range of motion                                             |
| SD        | Standard deviation                                          |
| SFR       | Swedish fracture register                                   |
| SMR       | Standardised mortality rate                                 |
| VLP       | Volar locking plate                                         |
| ZA        | Zoledronic acid                                             |

# The Thesis at a Glance

Paper I





## **Double Trouble! Concomitant Distal Ulna Fractures Predict Worse 1-Year Outcome in Distal Radius Fractures: A Registry-Based Cohort Study of 4,936 Patients**

**Research question:** Do distal radius fractures (DRFs) with concomitant distal metaphyseal ulna fractures (DRUFs) predict worse patient-reported outcome, measured by DASH, 1 year after injury?

**Primary outcome:** The 1-year DASH score, dichotomised at  $> 35$  vs  $\leq 35$ .

**Data from years:** 2003-2018

**Study population:** 5,536 patients with DRF of whom 259 had a concomitant distal ulna fracture.

**Main result:** A DRUF increased the odds of a 1-year DASH  $>35$  by 97% (OR 1.97, 95% CI 1.40-2.75,  $P < 0.001$ ).

**Clinical perspective:** Patients with DRUFs tend to have poorer outcomes compared to those with isolated DRFs.

**Year of publication:** 2025

Paper II



## **Patients Aged 80 or More With Distal Radius Fractures Have a Lower 1-Year Mortality Rate Than Age- and Gender-Matched Controls: A Register-Based Study**

**Research question:** What is the 1- and 5-year survival after a DRF in patients aged 80 years or more and which factors affect survival?

**Primary outcome:** The 1- and 5-year standardised mortality rates (SMRs)

**Data from years:** 2010-2012

**Study population:** 240 DRF-patients aged 80 years or more.

**Main result:** Elderly DRF-patients had a lower 1-year SMR compared to the age- and sex-matched standard population. The SMR was 0.44 (95% CI, 0.18–0.69;  $P < 0.01$ ), indicating that mortality was 44% of the expected rate. At 5 years, the SMR was 0.96 (95% CI, 0.78–1.14). The strongest predictor of mortality was the patient's living arrangement, residence in a nursing home was associated with the worst prognosis

**Clinical perspective:** Many older patients with DRFs have long life expectancies, meaning they will live with their fracture outcomes for several years. This underscores the need to base treatment on functional status rather than age and to optimise management for long-term function.

**Year of publication:** 2024

Paper III



## **Virtual Follow up After Distal Radius Fracture Surgery — Patient Experiences During the COVID-19 Pandemic**

**Research question:** How do surgically treated DRF-patients experience video-based follow up?

**Primary outcome:** An in-depth understanding of patients' experiences with video-based follow-up after DRF surgery, explored using qualitative methods and presented as categorical themes.

**Data from years:** 2020

**Study population:** 10 patients with surgically treated DRFs.

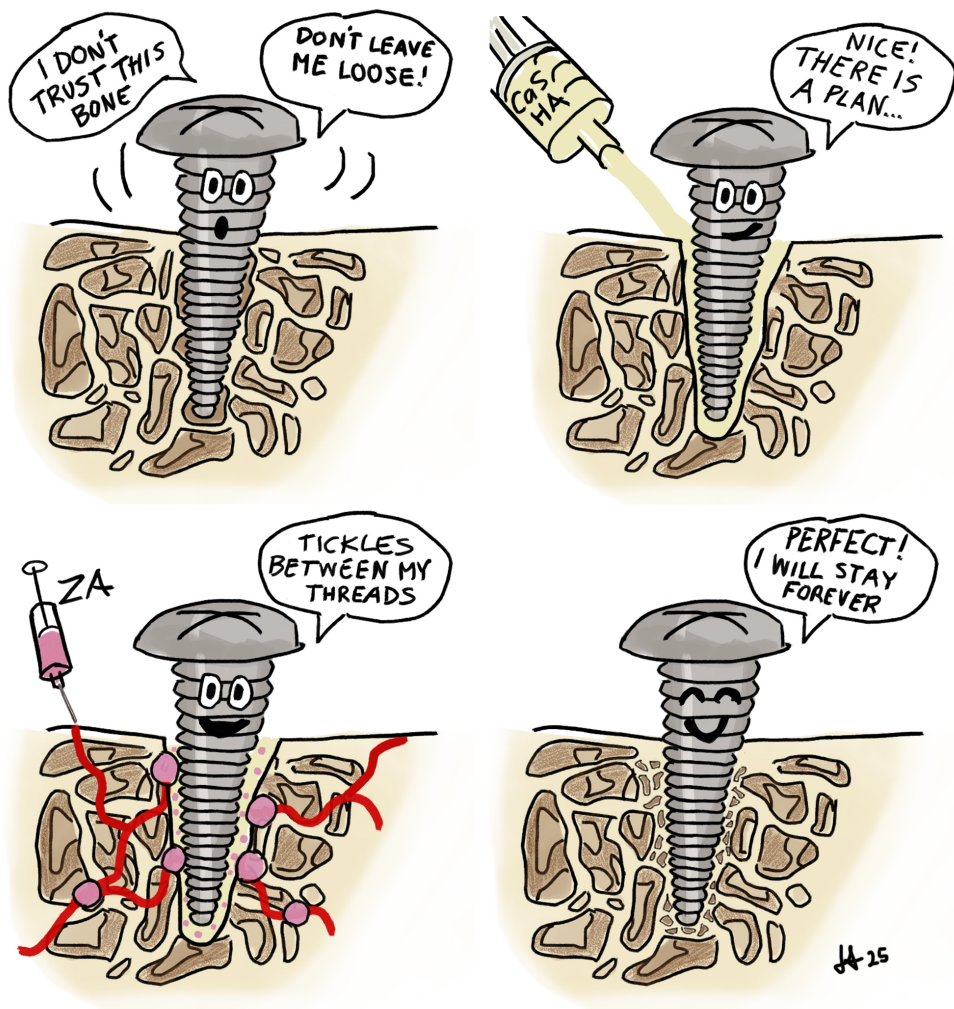
**Main result:** 2 major themes were identified: “The video call—new, but surprisingly simple” and “Video calls—the patient's choice”. Digital follow-up was highly appreciated, even among elderly and patients with low levels of digital literacy.

**Clinical perspective:** Patients, as well as healthcare professionals require digital tools with intuitive design and high usability. When such tools are available, also older patients appear ready to transition to more digitalised follow-ups.

**Year of publication:** 2023

## Paper IV

(Paper IV consists of 5 sub-studies, of which this thesis focuses on sub-study 1)



**Systemically administered zoledronic acid activates locally implanted synthetic hydroxyapatite particles enhancing peri-implant bone formation: A regenerative medicine approach to improve fracture fixation**

**Research question:** Does the local application of a calcium sulphate hydroxyapatite (CaS/HA) biomaterial followed by systemic zoledronic acid (ZA) enhance peri-implant bone formation in an osteoporotic rat model?

**Primary outcome:** CT and histology based periimplant bone formation.

**Data from years:** For substudy 1: 2020-2021

**Study sample:** 38 ovariectomized and four SHAM-operated Sprague-Dawley female rats.

**Main result:** Robust peri-implant bone formation was achieved when local CaS/HA was combined with systemic ZA in an osteoporotic rat model, highlighting the material's role as a recruiting moiety for systemically circulating bisphosphonate.

**Clinical perspective:** This method could potentially be used to improve screw fixation in osteoporotic bone during wrist surgery in older patients. In the continuation of Study IV (Substudy 4), the method is already being tested clinically in a small cohort of patients with hip fractures.

**Year of publication:** 2024

# Abstract

This thesis combines quantitative, qualitative, and experimental approaches to address different aspects of distal radius fractures (DRFs) in the elderly.

Study I was a registry-based cohort study of 5,536 DRF patients, of whom 259 (5%) sustained a concomitant distal metaphyseal ulna fracture. These patients, with a mean age of 73 years (SD 15), had nearly twice the odds of reporting severe symptoms (DASH > 35) 1 year after injury compared with those with isolated DRFs (OR 1.97, 95% CI 1.40–2.75,  $P < 0.001$ ).

Study II evaluated the mortality among 240 DRF patients aged 80 years or older. 1-year mortality was markedly lower than expected (SMR 0.44, 95% CI 0.18–0.69,  $P < 0.01$ ), while at 5 years mortality approximated that of the general population (SMR 0.96, 95% CI 0.78–1.14). Living situation was the strongest predictor of survival, with residents of nursing homes having the worst prognosis.

Study III employed mixed methods, including qualitative interviews with 10 surgically treated patients during the COVID-19 pandemic, to explore experiences of video-based follow-up. Despite the inclusion of both elderly patients and patients with low levels of digital literacy, video consultations were described as simple and accessible. Many expressed a preference for digital follow-up after surgery.

Study IV used an osteoporotic rat model to evaluate the combination of locally applied calcium sulphate/hydroxyapatite (CaS/HA) biomaterial around a metallic screw followed by systemically administered zoledronic acid. The treatment significantly enhanced peri-implant bone formation compared with animals not receiving the CaS/HA material. The method was translated to a small cohort of hip fracture patients, suggesting potential to improve screw fixation in osteoporotic bone and in future wrist fracture surgery.

Taken together, these studies support tailoring DRF treatment to functional status rather than chronological age. They further emphasise the importance of prognostic awareness, the potential of digital follow-up, and opportunities to enhance surgical fixation in osteoporotic bone.



# Populärvetenskaplig sammanfattning

Handledsfrakturen, även benämnd distal radiusfraktur, är den vanligaste frakturtypen och kan drabba människor i alla åldrar. Skadan uppstår oftast vid fall där man tar emot sig med en utsträckt arm. Frakturen är vanligast hos äldre, med stark koppling till benskörhet (osteoporos). Behandlingen kan se olika ut beroende på frakturmönster, patientens egenskaper, läkarens erfarenhet och patientens egna önskemål. Vanligast är gipsbehandling, men drygt var fjärde patient opereras.

Vi lever i en tid med en allt äldre befolkning, vilket innebär att det totala antalet handledsfrakturer också kommer att öka. Idag utgör personer i åldern 80 år eller äldre cirka 7,5 % av Sveriges befolkning. Enligt SCB:s befolkningsprognoser beräknas denna andel öka till ungefär 9 % år 2050, motsvarande cirka 1,1 miljoner personer. Detta leder till stora utmaningar, inte minst för vården. Traditionellt har patienter som behandlas för handledsfrakturer i vårdprogram och i forskningsstudier ofta definierats som "äldre" redan vid 65 års ålder. Men i Sverige är de flesta 65-åringar idag aktiva. Många arbetar ännu och ställer samma krav på sina händer och handleder som de yngre patienterna. Det finns betydligt mindre forskning om våra allra äldsta patienter, en grupp som rymmer både sköra äldre och mycket gamla, men ändå friska och starka, individer.

Frågan om huruvida kirurgisk behandling av handledsfrakturer tillför något värde hos våra allra äldsta patienter är omdiskuterad. För att väga nytta mot risker och för att spara samhällsresurser har man tidigare i Sverige tillämpat åldersgränser för när kirurgi rekommenderas. I flera andra länder gör man fortfarande det. Allt fler moderna studier pekar dock på att även de äldsta patienterna i många fall har nytta av kirurgi. Trots att själva kirurgin kan vara tekniskt svår i ett skört, osteoporotiskt skelett, har man visat att kirurgisk behandling av äldre inte leder till en större andel komplikationer. Utmaningen idag ligger dock i att identifiera vilka patienter som faktiskt gynnas av operation. Ålder är i det sammanhanget sannolikt en dålig metod att kategorisera behov och patientens funktionsnivå mer relevant, men svårare att mäta. I behandlingen av handledsfrakturer hos äldre ingår mycket mer än frågan om operation eller inte. Från det första mötet på akutmottagningen till beslut om reponering, gipsning, uppföljning och träning fattas en rad avgörande beslut. Även dessa delar av vårdkedjan kan behöva anpassas för våra äldsta patienter.

Den här avhandlingen belyser distala radiusfrakturer hos äldre ur olika perspektiv genom två registerstudier, en intervjustudie och en experimentell studie.

De två första studierna har hämtat patientdata från Lunds handledsfrakturregister. I den första studien analyseras över 5 500 patienter. Resultaten visar att de 5% som samtidigt med frakturen i radius också hade en fraktur i ulna (armbågsbenet), rapporterade en betydligt sämre funktion ett år efter skadan jämfört med dem som enbart hade en radiusfraktur. En stor majoritet av dessa patienter var äldre kvinnor.

I nästa studie analyserades dödlighet efter handledsfraktur hos 240 patienter som var 80 år eller äldre då de fick sin fraktur. Vi vet att dödligheten efter höftfraktur är kraftigt ökad, men överraskande nog var dödligheten i gruppen med handledsfraktur lägre än i befolkningen i stort under det första året. Den faktor som bäst förutspådde överlevnad var patientens boendesituation. De som bodde på äldreboende hade sämst prognos.

I den tredje studien intervjuades tio patienter opererade för handledsfraktur under Covid-19-pandemin om sina erfarenheter av digital uppföljning med videomöten efter kirurgi. Även äldre och digitalt ovana patienter upplevde metoden som enkel och till och med att föredra framför fysiska besök. Detta visar att även äldre patienter kan uppskatta moderna uppföljningssätt.

Den sista studien testade i djurmodeller en ny behandling vid kirurgi. En kombination av ett särskilt benmaterial och ett läkemedel mot benskörhet gavs till råttor. Metoden gav en förbättrad benläkning kring skruvar som används vid handledskirurgi. Metoden undersöktes i samma studie vid höftfrakturopoperationer i en pilotserie på människor. I framtiden kan metoden kanske användas för att förbättra resultatet vid handledsoperationer hos äldre med benskörhet.

Sammanfattningsvis stödjer avhandlingen principen att behandlingen av handledsfrakturer hos äldre bör anpassas efter patientens funktionsnivå snarare än enbart kronologisk ålder, eftersom även de allra äldsta tycks ha många aktiva år framför sig. Resultaten visar att digitala lösningar kan fungera väl även i denna åldersgrupp, samt att vissa frakturtyper med sämre prognos är särskilt vanliga hos äldre. Slutligen framträder ett behov för, och nya möjligheter att, utveckla och förbättra kirurgiska metoder för patienter med benskört skelett. Förhoppningen är att resultaten ska bidra till en bättre förståelse för våra äldsta patienter och deras frakturer, och vara en del av det fortsatta arbetet för att kunna ge dem ännu bättre vård.

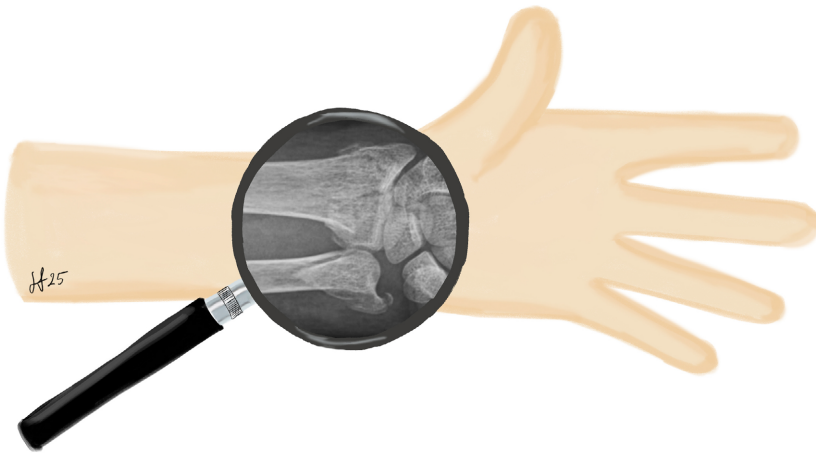
# Introduction

## First Things First: What is a Distal Radius Fracture?

The forearm consists of two bones: the radius and the ulna. The radius runs along the thumb side of the forearm, extending from the elbow to the wrist. For this reason, the thumb side is referred to as the radial side. The part of the radius closest to the wrist is called the distal radius, which includes the distal articular surface of the bone, the radiocarpal and distal radioulnar joints, and the adjacent metaphyseal area.<sup>1</sup>

A bone fracture is defined as a complete or partial break in the continuity of a bone. Distal radius fractures (DRFs) can occur as a result of various types of trauma to the forearm, but most commonly follow a fall onto an outstretched hand.<sup>2,3</sup>

DRFs vary greatly in severity, ranging from small cracks to complex, comminuted fractures. The most severe fractures often involve the joint surface and are frequently accompanied by soft-tissue injury. Several classification systems and specific terms are used to describe different fracture types; however, the term distal radius fracture is frequently used as a general descriptor for any fracture of the radius occurring close to, and just above, the wrist (Figure 1).<sup>2</sup>



**Figure 1.** The forearm is formed by the radius and ulna. The magnifying glass reveals an X-ray view showing fractures of the distal radius and ulna at the wrist region.

# Epidemiology

DRFs represent the most common type of orthopaedic fracture, accounting for approximately 18% of all fractures in adults.<sup>4</sup> Although DRFs occur across all age groups, the incidence peaks among younger men and postmenopausal women.<sup>3,5</sup> In Sweden, the overall incidence among adults has been estimated at 28 per 10,000 person-years. The incidence increases markedly with age to 125 per 10,000 in women, and 30 per 10,000 in men aged 80-89 years and to 161 per 10,000 in women, and 48 per 10,000 in men aged 90 years or older.<sup>5</sup>

Data from 23,394 DRFs in 22,962 adult patients, recorded in the Swedish Fracture Register (SFR), a nationwide database that collects detailed information on orthopaedic fractures, show that 78% of cases occurred in women. The overall mean age at the time of fracture was 63 years (SD 18), (range 18–104), with women averaging 65 years (SD 16) and men 54 years (SD 20).<sup>3</sup> While some epidemiological studies show that there is no seasonal variation in incidence<sup>6</sup>, the incidence in Sweden seem to be higher during the winter months (November to February).<sup>3</sup>

## Global Perspective of Epidemiology

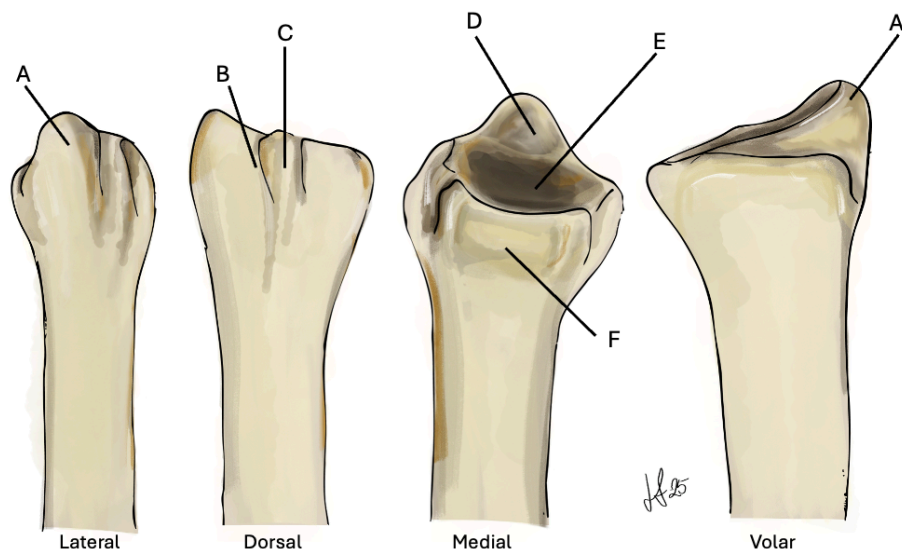
Most studies on DRFs originate from Western countries, and reliable data from low-income or less-developed countries are almost non-existent. This makes it difficult to determine how well the findings can be generalised to other regions of the world. In many studies, DRFs are reported to predominantly affect older women.<sup>3,7,8</sup> However, data from Malawi indicate a different pattern. Malawi is a low-income country in sub-Saharan Africa with a population of approximately 18.6 million, more than half of whom live on less than USD 1 per day. In a study from Malawi including 1,440 adults with DRFs, the mean age was 41 years (SD 15), and most patients were men (62%).<sup>9</sup>

# Anatomy

## Bony Anatomy

The distal radius extends from the level of the metaphysis to the tip of the radial styloid. Key bony landmarks include the radial styloid process, a lateral projection that serves as the attachment site for important stabilising ligaments, and Lister's tubercle on the dorsal surface, which acts as a pulley for the extensor pollicis longus

tendon. The volar surface of the distal radius is concave and provides attachment for the volar radiocarpal ligaments.<sup>1,2</sup>

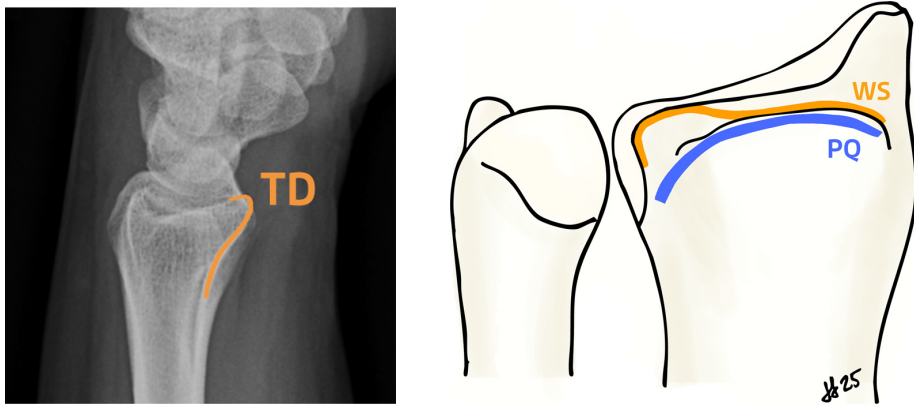


**Figure 2.** Bony anatomy of the distal radius, (A) radial styloid, (B) extensor pollicis longus groove, (C) Lister's tubercle (D) lunate fossa, (E) scaphoid fossa, (F) sigmoid notch.

The radiocarpal articular surface has a triangular shape. The base of the triangle forms the sigmoid notch, and the apex corresponds to the radial styloid. This concave surface articulates with the proximal carpal bones to form the radiocarpal joint. It is subdivided into two fossae: the scaphoid fossa and the lunate fossa (Figure 2).<sup>1</sup>

The volar part of the lunate facet, *the teardrop*, is crucial for wrist stability. On lateral radiographs of the distal radius, the teardrop is seen as a U-shaped contour of the lunate facet<sup>10</sup> (Figure 3). This part acts as a mechanical buttress to prevent lunate subluxation. In fractures involving the volar rim, insufficient fixation of the volar rim fragments can lead to carpal instability with a volar carpal subluxation.<sup>10</sup>

The *watershed line* represents the attachment of the volar capsule at the distal margin of the volar radius, and is considered the limit for safe placement of a volar plate during DRF fixation<sup>10</sup> (Figure 3).



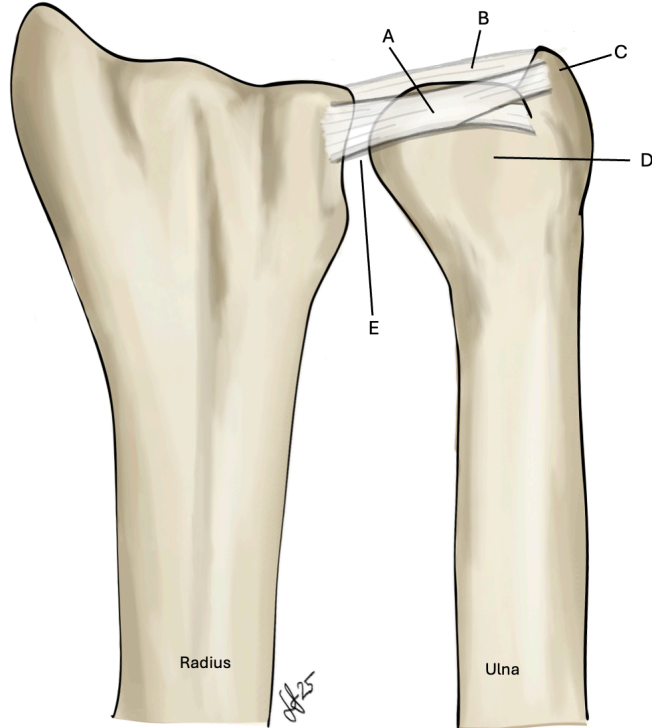
**Figure 3.** Distal radius anatomy illustrating the teardrop region (TD), the watershed line (WS) and the insertion of the pronator quadratus muscle (PQ).

The ulnar head is roughly cylindrical and covered with cartilage over about three-quarters of its surface. It has two main articular areas: the pole and the seat. The ulnar pole connects with the articular disc of the triangular fibrocartilage complex (TFCC), forming the ulnocarpal joint, which contributes to wrist movement and load transfer on the ulnar side. On the medial aspect of the radius articular surface, the sigmoid notch articulates with the seat of the ulnar head to form the distal radioulnar joint (DRUJ),<sup>2</sup> (Figure 4).

The DRUJ is the distal part of the forearm joint complex, which also includes the proximal radioulnar joint and the interosseous membrane.<sup>11</sup> It provides bony stability between the distal radius and ulna and allows the hand and radius to rotate around the relatively fixed ulna.<sup>1,2</sup>

The ulnar pole tapers into the ulnar styloid, an extension of the bone's outer ridge, which typically measures two to six millimetres in length.<sup>11,12</sup>

A depression known as the fovea is located just lateral to the ulnar styloid, within the ulnar pole. It serves as the attachment for the apex of the TFCC and also marks the distal central axis of forearm rotation.<sup>11</sup>

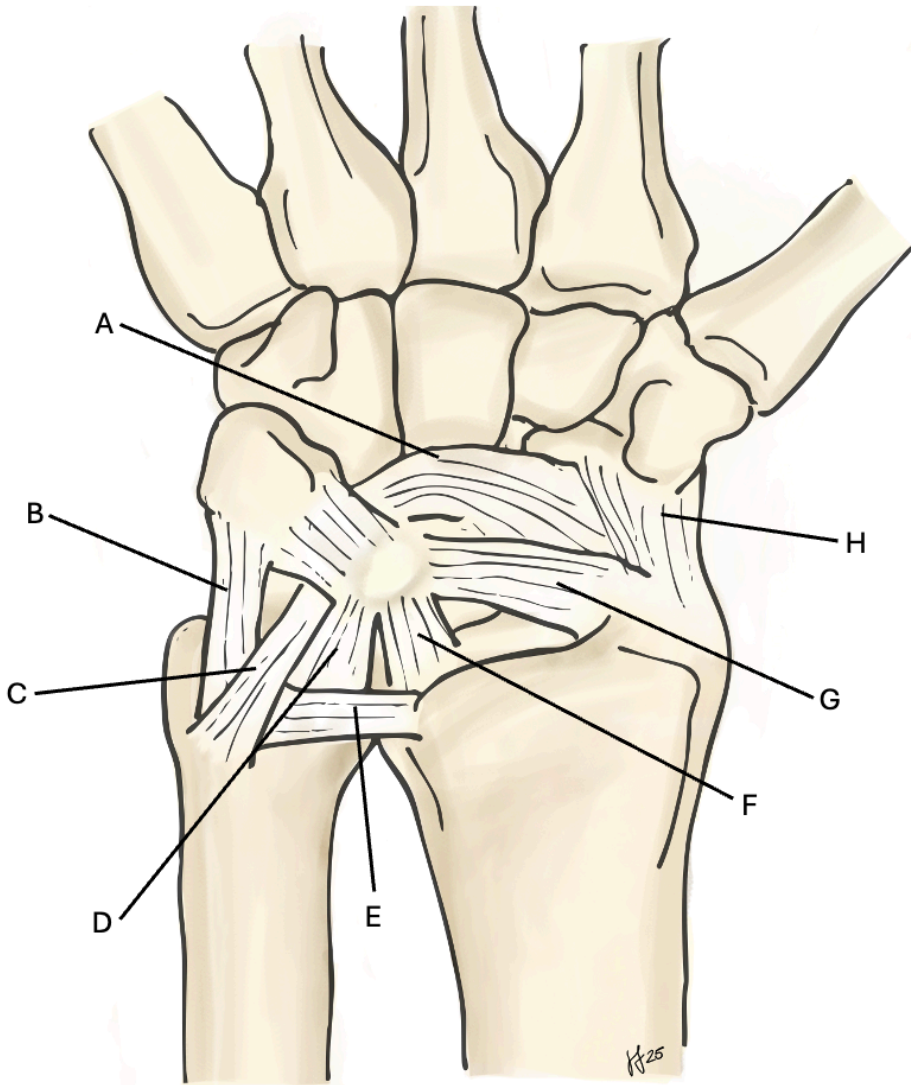


**Figure 4.** Anatomic overview of the distal radius and distal ulna, (A) dorsal radioulnar ligament (DRUL) (B) volar radioulnar ligament (VRUL), (C) ulnar styloid process (D) ulnar head (E) distal radioulnar joint (DRUJ). A and B are components of the TFCC.

## Soft Tissue Anatomy

Originating from the volar rim of the radius, the volar ligaments are thickened bands within the robust volar joint capsule. They consist of the radioscapocapitate ligament (RSC), the long radiolunate ligament (LRL), and the short radiolunate ligament (SRL). The radial collateral ligament (RCL) on the lateral side of the wrist contributes to radial stability by connecting the radial styloid to the scaphoid and trapezium<sup>12</sup> (Figure 5).

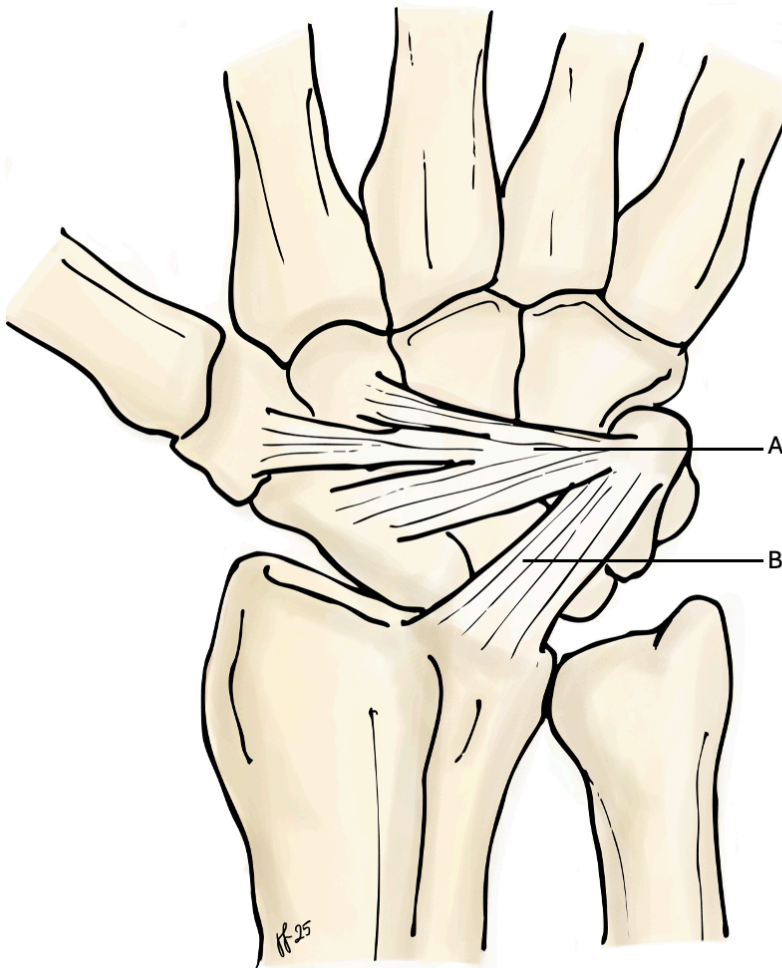
The dorsal part of the capsule contains one thickened portion, the dorsal radiocarpal ligament (DRC). It originates broadly from Lister's tubercle to the sigmoid notch on the dorsal surface of the distal radius, attaching to the dorsal lunate and inserting on the dorsal ridge of the triquetrum.<sup>12</sup>



**Figure 5.** Volar view of the ligaments of the wrist. (A) radioscaphocapitate ligament (RSC), (B) ulnotriquetral ligament, (C) ulnocarpal ligament, (D) ulnolunate ligament, (E) volar radioulnar ligament, (F) short radiolunate ligament (SRL), (G) long radiolunate ligament (LRL), (H) radial collateral ligament.

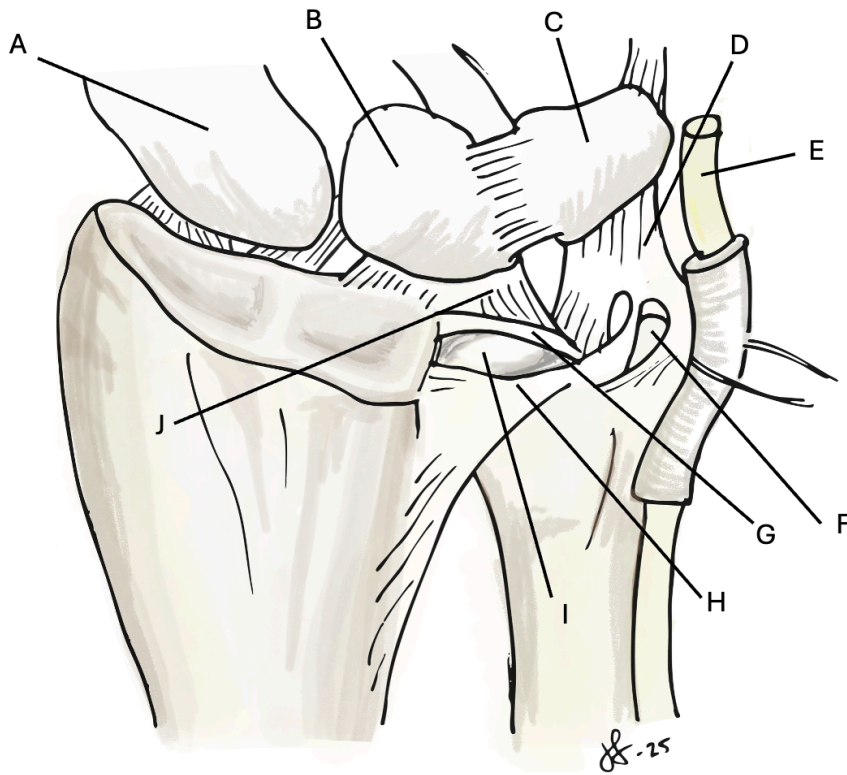
The dorsal intercarpal ligament (DIC) extends from the dorsal tubercle of the triquetrum to the dorsal aspect of the scaphoid, with additional attachments to the lunate and occasionally to the trapezium, trapezoid, and capitate<sup>11,12</sup> (Figure 6).





**Figure 6.** Dorsal view of the ligaments of the wrist. (A) dorsal intercarpal ligament (DIC), (B) dorsal radiocarpal ligament (DRC).

The stability of the DRUJ relies primarily on ligamentous and muscular support, as only about 20% is provided by bony articulation. Most of this stability comes from the complex of soft tissue structures collectively known as TFCC<sup>11,13</sup> (Figure 7). The volar and dorsal radioulnar ligaments of the TFCC arise from the front and back edges of the articular disc, extending from the sigmoid notch of the radius to the ulnar styloid. Each ligament consists of two layers: deep fibres inserting into the fovea, and superficial fibres attaching to the midportion and base of the ulnar styloid.<sup>11</sup>



**Figure 7.** Major stabilising components of TFCC and related anatomy, seen from the dorsal side of the wrist, (A) Scaphoid, (B) Lunate, (C) Triquetrum, (D) Ulnotriquetral ligament (UTL), (E) Extensor carpi ulnaris (ECU) tendon in sheath, (F) Ulnar styloid process, (G) Volar radioulnar ligament (VRUL), (H) Dorsal radioulnar ligament (DRUL), (I) Articular disc, (J) Ulnolunate ligament (ULL).

Originating at the distal margin of the sigmoid notch, the articular disc of the TFCC extends to the ulnar pole, where it merges with the volar and dorsal radioulnar ligaments at the fovea. This biconcave structure, composed of Type II collagen, has a relatively avascular centre, and its thickness varies with ulnar length. It functions as a cushion, absorbing load and providing stability to the ulnar side of the wrist, particularly during pronation.<sup>11</sup>

The ulnocarpal ligaments, included in the TFCC, consist of the ulnotriquetral, ulnolunate, and the more superficial ulnocapitate ligament. In clinical practice, these ligaments are often difficult to distinguish, as they anatomically blend together.<sup>11,12</sup>

The distal radioulnar and ulnocarpal capsules, which are also part of the TFCC, consist of loose, disorganized connective tissue. The extensor carpi ulnaris sheath reinforces the dorsal capsule and also contributes to DRUJ stability.<sup>11</sup>

# An Evolutionary Tale of the Human Wrist

Over some 400 million years, the wrist evolved from the fins of primitive fish into the highly functional joint we rely on today.<sup>14</sup> Standing upright liberated our hands for precision and dexterity, helping us shape human civilization. Yet this progress came with a cost: our wrists, though remarkable, are not always strong enough to absorb the full weight of a falling body. In this sense, wrist fractures may be considered the price we pay of walking tall instead of swimming like fish.

## Fish First

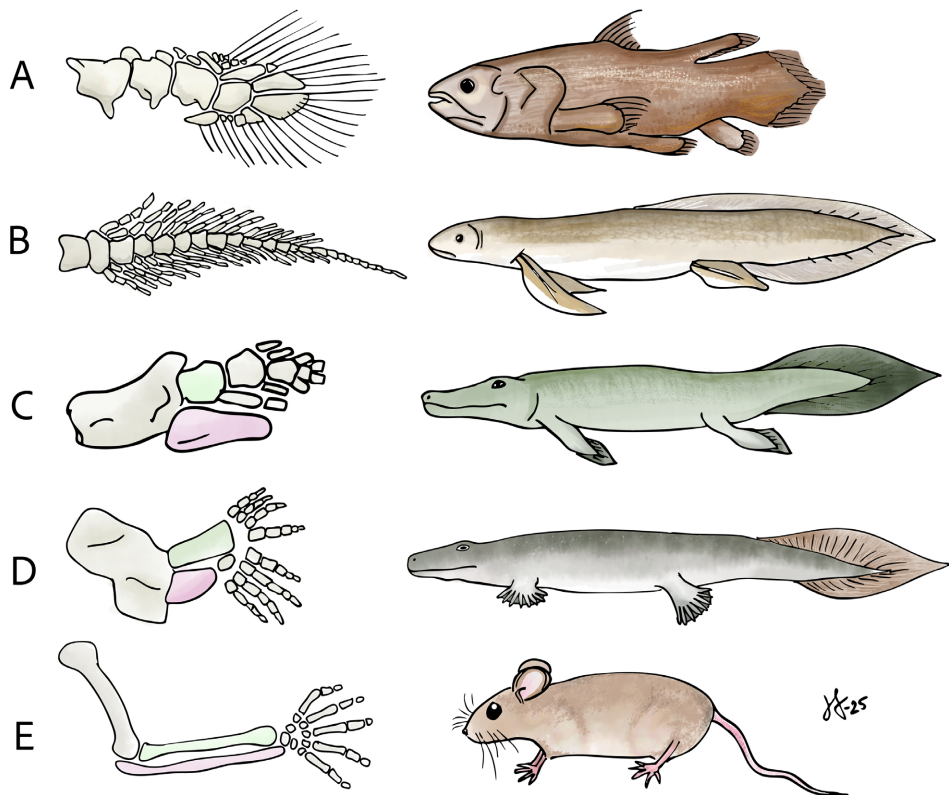
In the Devonian “Age of Fishes”, the story of the wrist began<sup>15</sup>. While today’s fish mostly have ray-supported fins, it was the lobe-finned fishes, *sarcopterygians*, that set the stage for life on land. With muscular, bone-supported fins, they carried the precursors of arms and wrists. Most species vanished 400 million years ago, but the surprising discovery of a living *coelacanth* (a large, lobe-finned fish thought to be long extinct) in 1938 revealed their legacy. Today, coelacanths and lungfish remain as living fossils of our evolutionary past.<sup>14,16</sup>

## Turning into Tetrapods

The transition from sarcopterygians (lobe-finned fishes) to tetrapods (vertebrates with four limbs) was a turning point.<sup>17</sup> Fossils such as Tiktaalik (375 million years ago) illustrate the blend of fish and tetrapod traits: gills and scales, alongside a neck, ribcage, and primitive wrist-like bones. *Acanthostega* (365 million years ago), an early tetrapod, still lived in water but had four limbs with elbows and parallel radius and ulna bones, providing stability and support in shallow habitats.<sup>15</sup>

As tetrapods diversified, forelimbs became increasingly specialised. Early mammals refined the DRUJ enabling limited rotation of the forearm, a crucial adaptation for climbing, digging, and manipulating food.<sup>14,15</sup>

Today, we rely on this mobility for everything from turning over a stone to typing on a keyboard or using a smartphone. The human DRUJ, stabilised by the TFCC, allows both strength and precision.<sup>11,16</sup>



**Figure 8.** Schematic illustration of the evolutionary transition from fins to forelimbs. (A) Coelacanth (*Latimeria*), (B) Lungfish (*Neoceratodus*), (C) *Tiktaalik*, (D) *Acanthostega*, (E) Mouse (*Mus musculus*). Ulna is highlighted in purple and radius in green.

## Our Rise Became our Fall

Yet evolution's gifts come with trade-offs and new vulnerabilities. The shift to bipedalism in early hominins, such as *Australopithecus* (4 million years ago), made falls more likely. Compared with chimpanzees, humans are more prone to wrist fractures. Our proud, upright posture comes at a cost: when we lose balance, we fall from greater heights.<sup>18</sup>

Still, there is a silver lining. Our wrists, combining strength, mobility, and fine motor skills, gave us the ability to treat the very fractures they are predisposed to.

# History of Distal Radius Fracture Treatment

As we leave the Devonian seas behind and step into an era where humans walk upright, rotate their wrists, and occasionally fall, it is safe to assume that our ancestors, like us, sometimes fractured their wrists. Our knowledge of how such injuries were treated in ancient times is limited. Many undoubtedly healed on their own with various degrees of residual symptoms.<sup>19</sup>

## Treatments that have Gone Down in History

The earliest preserved records of fracture management originate from the New Kingdom of ancient Egypt, around 1300 BCE. The Edwin Smith Papyrus describes 48 clinical cases, many orthopaedic in nature. For each, the physician had to decide whether the injury was curable, manageable, or hopeless (and hence best left untreated due to poor prognosis). Open fractures were especially feared: with infection almost inevitable, and often fatal. Although the papyrus does not explicitly mention wrist fractures, it does describe the reduction and stabilisation of humeral and clavicular injuries, suggesting that similar principles may have been applied to the wrist.<sup>19</sup>

Archaeological findings provide further evidence of ancient fracture care. A forearm fracture stabilised with bark splints was discovered in a tomb at Naga-ed-Der, dating to the Fifth Dynasty, around 2400 BCE. It has been suggested that the individual may have died from an infection resulting from an open fracture and was therefore buried with the splint still in place.<sup>20</sup>

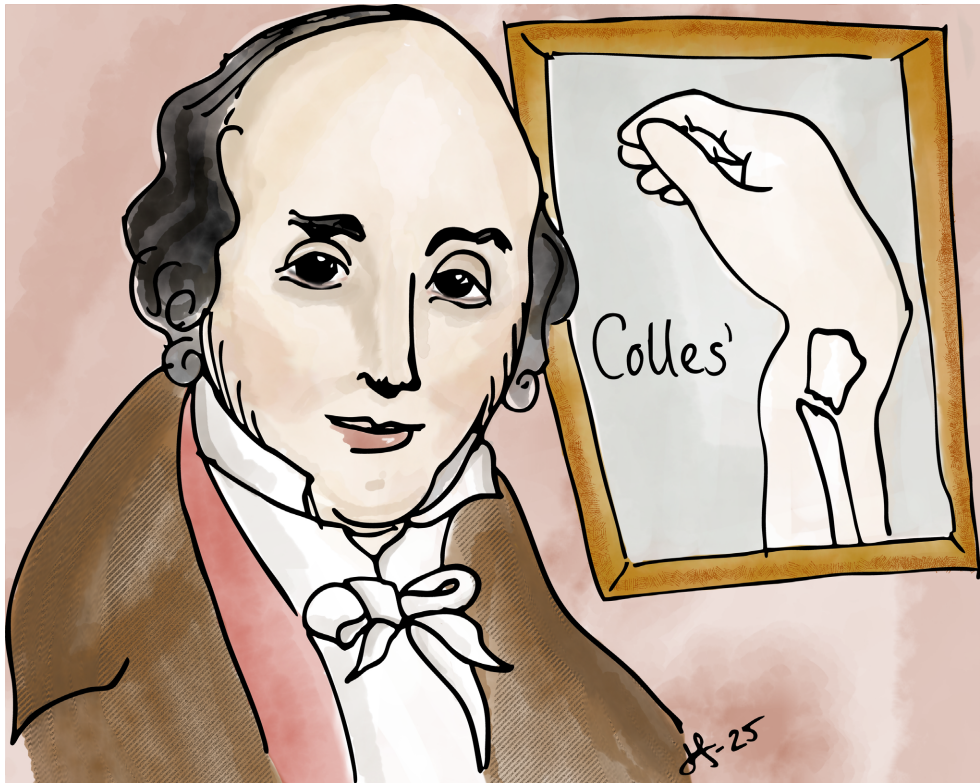
In ancient Greece, around 400 BCE, Hippocrates wrote about treating wrist injuries with reduction and bandaging. However, the Greeks interpreted what we now recognise as DRFs as dislocations of the wrist joint, a misconception that would persist for centuries.<sup>18</sup>

It was not until the 18th century that this idea was seriously challenged. In France, surgeons Jean-Louis Petit (1674–1750) and Claude Pouteau (1725–1775) argued that these common injuries were in fact fractures of the distal radius. Their observations, however, were published in a provincial journal and attracted little notice.<sup>21</sup> It was Guillaume Dupuytren (1774–1835), through his postmortem examinations, who finally established this interpretation and brought it to the wider medical community.<sup>18</sup>

## Abraham Colles and the Colles' Fracture

Abraham Colles (1773–1843) was a pioneering Irish surgeon who played a key role in shaping the foundations of orthopaedic practice. He is best known for his

description of the most common DRF subtype that still bears his name: the Colles' fracture.<sup>22,23</sup>



**Figure 9.** Abraham Colles, the Irish surgeon that named the Colles' fracture.

Before Colles' work, wrist injuries were still misdiagnosed as dislocations, which led to inadequate and ineffective treatment. In 1814, Colles published a landmark paper in which he clearly described the typical features of the DRF, including dorsal displacement and angulation, commonly resulting from a fall on an outstretched hand.<sup>22</sup>

But Colles did not stop at diagnosis. He also proposed a structured method of treatment focused on restoring the limb's natural alignment. This included careful palpation and movement to assess the fracture, followed by reduction using moderate extension and transverse compression. For immobilisation, he recommended a gutter-type splint, initially made from tin and later simplified to wooden versions, applied to the anterior and posterior surfaces of the forearm and hand.<sup>22</sup> His approach to reduction and splinting laid the groundwork for many principles still central to modern fracture treatment.<sup>23</sup>

## More Major Milestones

The next great leap happened in the Netherlands. Dutch military surgeon Antonius Mathijssen (1805–1878) introduced the plaster cast in 1851. Gypsum-soaked cloth replaced wooden splints, offering far better stability and healing outcomes. Within a few years, plaster casts had spread across Europe, revolutionising fracture care.<sup>24</sup> Still, physicians could not see the fracture or its healing, and could only judge results by physical examination.<sup>18</sup>

A true revolution arrived in 1895, when Wilhelm Conrad Röntgen (1845–1923) discovered X-rays. For the first time, doctors could see inside the body without cutting it open.<sup>18,25</sup> By the 1920s, radiography had become a standard diagnostic tool, allowing fractures to be classified and alignment to be assessed during and after treatment. This new window into the skeleton also opened the door for scepticism. Doctors began asking whether conservative treatment really gave patients the outcomes they deserved. The debate over whether, and how, fractures should be operated on had begun.<sup>18</sup>

## The Surgical Era

Surgical treatment of fractures was initially risky due to infection. Joseph Lister's (1827-1912) introduction of antiseptic techniques made it safer. Albin Lambotte (1866-1955) was an influential surgeon who introduced the term “osteosynthesis” and was among the first to advocate immediate mobilisation and muscle activation after surgery.<sup>26</sup> In 1908, he pioneered surgical fixation of DRFs using a wire through the radial styloid. However, it wasn't until over 40 years later, results using Kirschner-wires (K-wires) were published.<sup>18</sup>

Comminuted fractures remained a major challenge, as reduction was difficult to maintain and often led to radial shortening. The concept of ligamentotaxis inspired the development of external traction devices designed to preserve radial length during healing. Early methods, such as Böhler's pins-in-plaster and Murray's adhesive traction, eventually evolved into more modern external fixators<sup>18</sup>. In 1944 Roger Anderson and Gordon O'Neil presented the first external fixator that was used across the wrist joint. Dr. Raoul Hoffmann (1881-1971), a surgeon and carpenter, collaborated with a Swiss instrument-making company in 1934 to develop the Hoffmann External Fixation Set, which went on to become the global standard for external fixation.<sup>27</sup>

Prior to 1960, primary open reduction and internal fixation (ORIF) of DRFs was not documented in the literature. By the mid-1960s, foundational principles for DRF management began to emerge in modern orthopaedics. Operative techniques were introduced to address the frequent malunions associated with conservative treatment. Over the following decades, various surgical approaches gained

popularity, including Kapandji's intrafocal pinning in the 1970s, external fixators in the 1980s, and later significant advances in internal fixation.<sup>18</sup>

In 1996, Rikli and Regazzoni presented the influential "three-column theory," proposing that the distal radius should be regarded as three structural pillars: radial, intermediate, and ulnar, an insight that has since guided both fracture classification and fixation strategies,<sup>13</sup> (Figure 11). Robert Medoff divided the columns further into typical fragments and appropriate plates which together with the theories of Rikli and Regazzoni started fragment-specific fixation.<sup>28,29</sup>

The introduction and widespread adoption of volar locking plates (VLPs) in the 1990s and 2000s marked a major milestone in DRF treatment.<sup>18</sup> The development of the VLP is primarily credited to Dr. Juan Orbay, a Cuban-American orthopaedic surgeon. In the early 2000s, Dr. Orbay introduced the concept of volar fixed-angle plate fixation for unstable DRFs, particularly in elderly patients.<sup>30</sup> The evolution of this implant involved collaboration among several orthopaedic surgeons and surgical instrument manufacturers. This innovation marked a pivotal shift in fracture management and ultimately led to the VLP becoming a standard implant in DRF-surgery.<sup>18,30</sup>

In the late 20th century came the introduction of wrist arthroscopy, which enabled direct visualization of intra-articular fractures and associated ligament injuries, improving diagnostic precision and treatment outcomes.<sup>31</sup>

## Classifications

### **Distal radius fractures**

Several classification systems exist for DRFs. Compared with the historical 'curable, manageable, or hopeless' system<sup>19</sup> described earlier, none of the modern systems provide a definitive algorithm for treatment decision-making.<sup>32</sup> However, systems such as Melone's can help identify fracture fragmentation patterns, which are useful for planning internal fixation. Mechanism-based classifications, such as Fernandez's, provide insight into injury patterns and the energy involved. The Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) classification is a valuable tool for research and for comparing patient groups (Figure 10).<sup>33</sup>



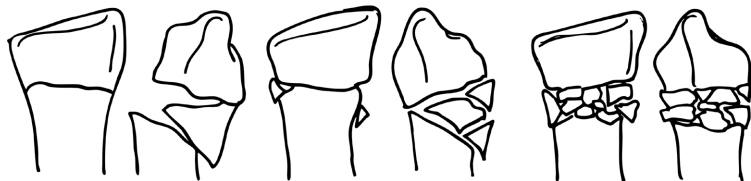
2R3A Radius, distal end segment, extraarticular fracture



2R3A1 Radial styloid avulsion fracture



2R3A2.1 Transverse, no displacement/tilt    2R3A2.2 Dorsal displacement/tilt    2R3A2.3 Volar displacement/tilt



2R3A3.1 Intact wedge fracture    2R3A3.2 Fragmentary wedge fracture    2R3A3.3 Multifragmentary fracture

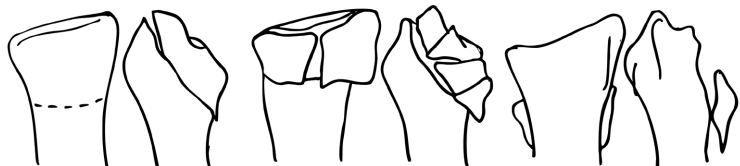
2R3B Radius, distal end segment, partial articular fracture



2R3B1.1 Sagittal, involving scaphoid fossa



2R3B1.3 Sagittal, involving lunate fossa



2R3B2.1 Dorsal rim, simple fracture    2R3B2.2 Dorsal rim, fragmentary fracture    2R3B2.3 Dorsal rim, dorsal dislocation



2R3B3.1 Volar rim, simple fracture



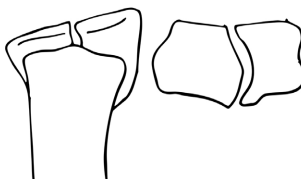
2R3B3.1 Volar rim, fragmentary fracture

## 2R3C Radius, distal end segment, complete articular fracture

### 2R3C1 Simple articular and metaphyseal



2R3C1.1 Dorsomedial articular fracture



2R3C1.2 Sagittal articular fracture



2R3C1.3 Frontal/coronal articular fracture

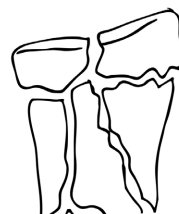
### 2R3C2 Simple articular and metaphyseal multifragmentary



2R3C2.1 Sagittal articular fracture

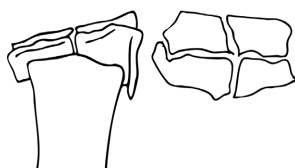


2R3C2.2 Frontal/coronal fracture



2R3C2.3 Extending into the diaphysis

### 2R3C3 Articular multifragmentary, simple or multifragmentary metaphyseal



2R3C3.1 Simple metaphyseal fracture



2R3C3.2 Metaphyseal multifragmentary



2R3C3.3 Extending into the diaphysis

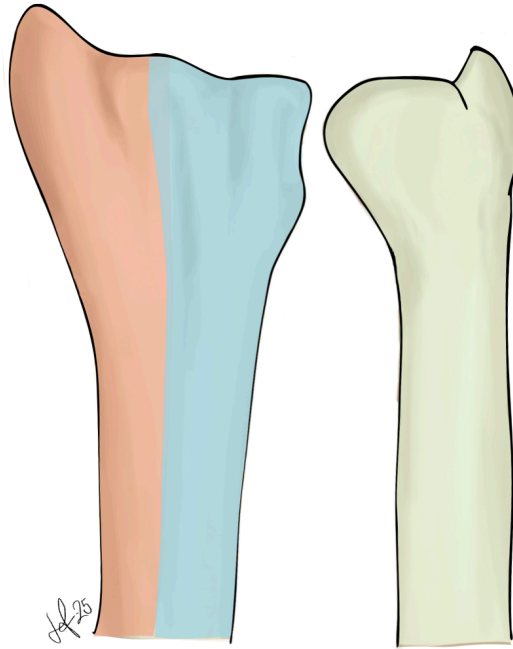
**Figure 10.** AO/OTA Classification system for the distal end segment of distal radius, 2R3. 2R3A: extraarticular DRFs, 2R3B: partial articular DRFs and 2R3C: complete articular DRFs. Additional qualifications: t – DRUJ stable or u – DRUJ unstable can be added to a given fracture classification.

There are several versions of the AO classification system. In the latest version from 2018, fractures are divided into 3 main groups: A) extra-articular, B) partially intra-articular, and C) completely intra-articular. Based on fragments and their displacement each group is further divided into subcategories, resulting in a total of 7 type A fractures, 7 type B fractures and 9 type C fractures. In the studies presented in this thesis, the 3 main AO groups (A-C) were used to classify DRFs.<sup>34</sup>

## The Three Column Theory

Rikli and Regazzoni proposed that the wrist can be conceptualised as a three-column structure<sup>13</sup> (Figure 11) which helps guide both the understanding of fracture patterns and their surgical treatment:

1. Radial column: Comprises the radial styloid and scaphoid fossa. It is important for radial length, inclination, and stability of the scaphoid.
2. Intermediate column: Includes the lunate fossa and the sigmoid notch of the distal radius. This column is considered the key load-bearing axis of the wrist, transmitting force from the hand to the forearm through the lunate.
3. Ulnar column: Formed by the distal ulna and the TFCC. It plays a crucial role in DRUJ stability and load transfer across the ulnar side of the wrist.<sup>13</sup>



**Figure 11.** The three-column theory describes the distal radius as a biomechanical structure divided into 3 columns: the radial, intermediate, and ulnar. This model helps classify DRFs and guides treatment by considering the stability of each column.

## Concomitant Distal Ulna Fractures

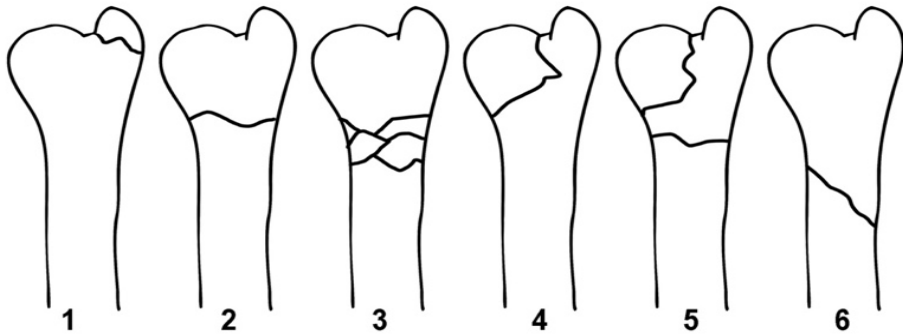
In addition to the classification of DRFs, there are also several classification systems for concomitant distal ulna fractures (DUFs). At the time when most of the studies in this thesis were conducted, the most commonly used classification systems for DUFs were the Biyani classification<sup>35</sup> (Figures 12 and 13) and the AO q-modifier for concomitant DUFs<sup>33</sup> (Figure 12).

The AO Q-modifier classification consists of six groups: Q1 – ulnar styloid base fracture; Q2 – simple neck fracture; Q3 – comminuted neck fracture; Q4 – ulnar

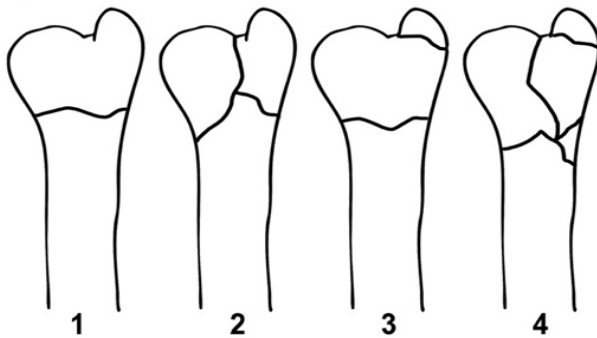
head fracture; Q5 – combined ulnar head and neck fracture; and Q6 – fracture of the ulnar diaphysis.<sup>33</sup>

The Biyani classification system for ulnar metaphyseal fractures associated with DRFs consists of four groups: Type 1 – simple extra-articular fracture with minimal comminution; Type 2 – inverted T- or Y-shaped fracture with an ulnar styloid fragment involving a part of the metaphysis; Type 3 – fracture of the lower end of the ulna with avulsion of the ulnar styloid; and Type 4 – comminuted fracture of the lower ulnar metaphysis, with or without a styloid fracture.<sup>35</sup>

#### AO/OTA Q-modifier



#### Biyani



**Figure 12.** Classification of distal ulna fractures. The AO Q-modifier subclassification, Q1-6 and the Biyani classification system for distal ulnar metaphyseal fracture in the setting of distal radius fractures, 1-4.



Biyani 1



Biyani 2



Biyani 3



Biyani 4

**Figure 13.** Radiographs of distal radius fractures with concomitant distal ulna fractures (DUFs) with DUFs classified according to Biyani's classification system.

## Treatment Today

Sustaining a wrist fracture can be seen as an unplanned journey beginning at the moment of trauma. This journey extends from the acute event through fracture healing and the often lengthy rehabilitation period that follows. Each individual's experience is unique in both duration and nature, but there are several key "stations" along the way where important decisions must be made.

At each of these "stations," recommendations exist that are applicable to most patients. Equally important, however, is knowing when to deviate from evidence-

based principles based on an individualised assessment, taking into account the patient's needs and preferences, as well as the knowledge, experience, and priorities of both patient and clinician.



**Figure 14.** Woman rehabilitating with dumbbells after bilateral distal radius fracture surgery.  
Photo: Ingvar Eliasson.

## Swedish National Guidelines for DRF Treatment

The goal of DRF treatment is to minimise pain and achieve fracture union in a position that maximizes recovery of mobility, strength, and overall function. Current treatments in Sweden are based on the 2021 Swedish National Guidelines for DRFs.<sup>36</sup>

The following is a summary of the current recommendations in Sweden:

- 1. Initial assessment:** Conduct thorough anamnesis and clinical examination. Assess activity level, and the patient's subjective perception of functional impairment. Confirm the diagnosis with conventional radiography.
- 2. Radiological evaluation:** Characterise fracture type, displacement, and associated injuries. Measure dorsal or volar angulation, radial inclination, and ulnar variance. Assess articular step-offs and DRU joint congruency. Use computed tomography (CT) for complex fractures or preoperative planning and MRI if concomitant carpal fractures are suspected.
- 3. Desired fracture alignment:** Depends on the patient's assessed functional demands (Table 1). There are in general 3 paths to acceptable alignment: A) Non-displaced fracture treated in its existing position; B) Achieving acceptable

alignment through closed reduction; C) Improving alignment through surgical intervention.

**4. Reduction:** Correct reduction and immobilisation alone may avoid the need for surgery, saving both patient and healthcare resources, therefore reduction should be applied liberally even if fracture initially meets radiological criteria for non-operative management.

**5. Immobilisation:** Apply a supportive functional splint for 4–5 weeks. Allow free motion of fingers and elbow. Use 3-point support for dorsally displaced fractures.

**6. Early rehabilitation:** Initiate contact with an occupational or physical therapist soon after injury. Provide follow-up contact at splint removal.

**7. Radiographic follow-up:** Is indicated (after approximately 10 days) for patients with high/moderate functional demands, displaced fractures, post-reduction, or dorsal comminution.

## 8. Decision-making based on radiology:

1. Unchanged alignment → continue immobilisation.
2. Changed alignment but within radiological thresholds → consider surgery.
3. Alignment outside thresholds for functional demand → offer operative treatment.

**Table 1.**

Recommendations for when surgery should be considered in patients with DRFs in Sweden.

Immediate Surgical Indications (high/moderate functional demands)

**Comminuted volar cortex**

**Volar angulation >15°**

**Barton fracture**

**Dorsal comminution with osteopenia/osteoporosis and a dorsal angulation >30° or ulnar variance >3 mm**

Post-reduction Surgical Considerations

|                    | High functional demands | Moderate functional demands |
|--------------------|-------------------------|-----------------------------|
| Dorsal angulation  | >10°                    | >20°                        |
| Volar angulation   | >15°                    | >15°                        |
| Radial inclination | <15°                    | <10°                        |
| Ulnar variance     | >2–3 mm                 | >2–3 mm                     |
| Articular step-off | >2 mm                   | >2 mm                       |
| Incongruent DRUJ   | yes                     | yes                         |

**Low demand patients:** fracture alignment should not result in persistent skin, nerve, or vascular compromise

DRF = Distal radius fracture, DRUJ = Distal radioulnar joint

**9. Surgical method:** For simple dorsally angulated fractures, there is according to the guidelines no scientific evidence to recommend a single preferred method among volar angular stable locking plate (VLP) fixation, external fixation, or pin fixation. From an economic perspective, external fixation and pinning may be advantageous; however, the need for rapid rehabilitation and fewer secondary interventions may favour VLP fixation.

For VLP fixation, a modified Henry approach should be used. The volar plate should be positioned immediately proximal to the watershed line and lie flush against the volar cortex of the radius. The distal screws in a volar plate should be placed subchondrally, close to the articular surface. The screw length for the distal screws should be 2 mm shorter than the measured distance to the dorsal cortex. A minimum of 4 distal locking screws should be used.

After surgical fixation of a DRF with a VLP, the recommendation is to apply a plaster cast that is removed 2 weeks postoperatively.

## **International Differences Regarding Treatment of the Elderly**

Several countries have developed national guidelines for the management of DRFs. Since all guidelines are based on the available evidence at the time of their publication, they are largely consistent. However, certain differences exist, particularly regarding whether elderly patients should primarily be treated non-surgically. In the Danish guidelines for DRF management from 2017 and the Swedish and German guidelines from 2021 and 2022, chronological age is not mentioned as a criterion when considering surgical versus non-surgical treatment.<sup>36-38</sup>

The Norwegian guidelines from 2015, recommend surgical treatment for unstable fractures in patients aged over 65 years, although they state that the evidence supporting this recommendation is weak. They also emphasise that surgery should not be performed in low-demand patients.<sup>39</sup>

In contrast, in the American and British guidelines, published in 2020 and 2017 respectively, for patients aged 65 years or older non-surgical management is generally recommended as the first-line treatment.<sup>40,41</sup> The Finnish guidelines from 2016 state that there is strong evidence for non-surgical treatment of unstable DRFs in this group.<sup>42</sup> Similarly, the Dutch guidelines from 2021<sup>43</sup>, note that non-operative treatment is generally preferred in older patients, as they are considered capable of managing daily activities even with reduced wrist function; however, no specific age cut-off is defined.



## Global Perspective on DRF Treatment

Studies addressing the management of DRFs in low-income countries are exceedingly scarce. A publication from Malawi describes the limited access to orthopaedic expertise and the general tendency to avoid surgery in almost all patients, unless the condition is life-threatening rather than limb-threatening. The prevailing principle, “*never close an open fracture, nor open a closed one*”, is widely followed, resulting in very few DRFs being considered for surgical treatment.<sup>44</sup>

## Disabilities of the Arm, Shoulder and Hand

Patient-reported outcome measures (PROMs) are increasingly used in both research and clinical practice to capture the patients’ perspectives on function, symptoms, and quality of life.

Several validated PROMs exist for the upper extremity, with *the Disabilities of the Arm, Shoulder and Hand* (DASH) questionnaire being among the most widely used. The DASH provides a comprehensive assessment of upper-limb function and disability and has demonstrated high reliability, validity, and responsiveness to clinical change<sup>45-49</sup>.

However, its length (30 items) can limit feasibility in some settings, and its broad scope may reduce specificity for distal injuries such as DRFs. The shorter *QuickDASH* (11 items) was developed to improve practicality, although it may be less sensitive to subtle changes in function. The 2 versions are strongly correlated (Spearman’s  $\rho = 0.97$ ,  $P < 0.001$ ).<sup>50</sup> Both versions have been validated in Swedish.<sup>47,48</sup>

It is also well established that DASH scores tend to increase with advancing age, reflecting age-related declines in general upper-limb function rather than injury-specific disability, which can make interpretation more challenging in older populations<sup>46,49</sup>.

## Distal Radius Fractures in the Elderly

### Global Ageing

One of humanity’s most notable achievements is the dramatic increase in life expectancy, which in Sweden has risen from around 47 years for women in 1850<sup>51</sup> to 85 years in 2024.<sup>52</sup> We are now living in a time with an increasingly older

population, a phenomenon seen not only in Sweden but across the globe. Every country is experiencing growth in both the absolute number and the proportion of older persons.<sup>53,54</sup> The number of people aged 80 years or older is expected to triple between 2020 and 2050 to reach 426 million globally. These demographic shifts bring major challenges for the health and social systems, which must adapt to care for an increased number of older adults while also seizing the opportunities that come with an ageing population.<sup>54</sup> In response to this, the scientific interest in ageing has grown markedly in recent decades, aiming to find sustainable ways to support well-being in later life.<sup>53</sup>

The processes of biological ageing unfold in unpredictable ways and do not correspond linearly to chronological age.<sup>54</sup> To make matters even more complex, ageing is not shaped solely by biology. It often coincides with major life transitions such as retirement, moving into more suitable housing, or the loss of close friends and partners. These social aspects interact with biological change to create highly varied experiences of ageing.<sup>53,54</sup>

## Rethinking Age in an Ageing World

Despite an increased attention to ageing, there is no universally accepted definition, of when a person is considered old.<sup>53</sup> In orthopaedic research, individuals are often classified as elderly from age 65, for long the most common retirement age. Yet in many Western societies, 65-year-olds are still employed, active, and anticipate living for decades more.<sup>55</sup> For them, limitations in daily life often originate not from age itself, but from illness or accelerated biological ageing.<sup>53</sup> Many patients in this age group feel uncomfortable being labelled as elderly, and clinicians may be equally uneasy about withholding treatments solely on the basis of age.<sup>55</sup> Some 80-year-olds retain levels of physical and cognitive functioning comparable to people decades younger, while others experience serious decline much earlier.<sup>53,54</sup>

Efforts to better capture the diversity of the ageing person have led to various new classifications, though the definitions remain inconsistent. Terms like “*super elderly*”, “*elderly elderly*” or “*oldest old*” may refer to individuals over 80, 85, or 90, depending on the context.<sup>56-58</sup> More precise terms, such as *octogenarians* (80–89), *nonagenarians* (90–99), and *centenarians* (100+), help specify age ranges, but still rely solely on chronology.

Yet shifting the age threshold does not solve the underlying issue; that even within older groups, individuals vary widely in health, function, and lifestyle.<sup>59</sup> Similarly, some younger people may be biologically aged or chronically ill. Chronological age alone is therefore inadequate for defining subgroups with different needs in orthopaedic practice and research.<sup>60</sup>

To address this, some classifications incorporate health status. For example, “*super-seniors*” refers to individuals aged 85–105 with no history of major age-related

diseases such as cancer, cardiovascular disease, diabetes, or dementia.<sup>61</sup> However, even these definitions face challenges, as diagnostic codes often fail to reflect actual lifestyle, survival prospects, or personal expectations.

## **Functional Levels and Frailty**

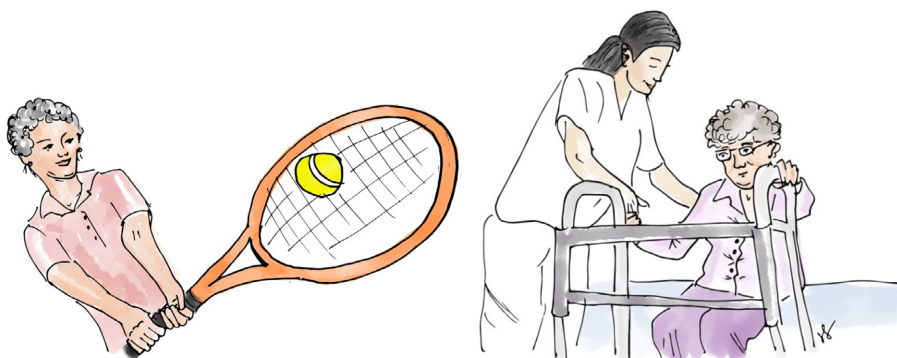
One approach addressing age-related bias in clinical decision-making is to move away from defining age purely by chronological number, or to avoid focusing on age altogether. As an example, the Swedish national guidelines for DRFs from 2021 removed chronological age as a triaging factor for treatment selection. Instead, treatment algorithms are based on functional needs.<sup>36</sup> This marks a clear shift towards a more person-centred model of care.

However, if defining old age is inherently challenging, assessing what constitutes a high level of functional ability may be even more complex. Notably, surgeons' assessments of patients' activity levels often show weak correlations with patients' own perceptions.<sup>62</sup>

Functional capacity is a dynamic, multidimensional construct influenced by physical, cognitive, psychosocial, and environmental factors. The absence of a unified definition and standardised assessment methods makes it difficult to consistently integrate functional status into clinical decision-making, despite its increasing relevance in modern, person-centred care.<sup>63</sup>

In this context, frailty-based risk assessment is gaining traction as a tool to guide preoperative decisions and minimise adverse surgical outcomes. Frailty reflects a multidimensional loss of physiological reserve and incorporates comorbidities, functional deficits, nutritional status, and social vulnerabilities. This reduced reserve heightens susceptibility to complications from illness or surgery and is recognised as an independent risk factor for increased morbidity, mortality, and delayed recovery following orthopaedic procedures.<sup>63</sup>

A recent systematic review underscores the expanding literature on frailty as a predictor in orthopaedic preoperative risk stratification. However, with over 25 distinct frailty metrics currently in use, there remains a clear need to identify and standardise those with the greatest predictive validity.<sup>63</sup>



**Figure 15.** Functional ability can vary widely among individuals of the same age.

The Clinical Frailty Scale (CFS) is a 9-point scale designed to evaluate patient frailty and support prognostic decision-making in healthcare. It is also translated and culturally adapted to Swedish and used in Swedish health care.<sup>64</sup> CFS classifies patients according to their level of frailty, from very fit to terminally ill. Each level reflects a combination of factors such as mobility, independence in daily activities, and overall health status. For example, very fit patients are active and energetic with no evident frailty, while those who are moderately or severely frail require assistance with basic daily activities. The assessment is based on clinical judgement, considering patient history, observation, and functional status prior to any acute illness. The CFS provides a quick, global overview of frailty, helping to guide prognostic decisions, risk assessment, and care planning.<sup>64</sup>

Higher CFS scores in orthopaedic patients are associated with poorer outcomes, including increased mortality, longer hospital stays, and a higher risk of post-procedural complications. However, it does not capture the patient's own perception of their abilities or limitations.<sup>60</sup> Additionally, the CFS is not specific to any particular body region, such as the upper extremities, it instead reflects a broad, global measure of function. As a result, while it is useful for predicting overall outcomes and guiding clinical decision-making, it may not fully reflect the functional demands or recovery potential of specific limbs or activities.<sup>65</sup>

The Adolfsson–Björnsson Activity Scale (ABAS) was developed to provide a self-assessment tool for the entire upper extremity, defining patients' subjective activity levels and functional demands, and serving as a practical aid in clinical decision-making for upper extremity injuries or disorders.<sup>65</sup> It categorises arm use into 8 levels, ranging from no use to high-demand activities such as elite sports or heavy work. The scale was constructed using input from patients and healthy individuals, refined through expert discussion, and adapted separately for the dominant and non-dominant arms. 2 versions exist: one to assess pre-injury activity and another for

follow-up to evaluate current function. The ABAS shows only a weak correlation with sex, age, and hand function, emphasising that functional demand can vary widely within patient groups. It has demonstrated good intra-rater reliability and provides a patient-centred measure of activity that complements traditional functional scores in orthopaedic and wrist surgery research.<sup>65</sup>

## **Osteoporosis**

Osteoporosis is a systemic skeletal disease characterised by reduced bone mass and deterioration of bone microarchitecture, which together compromise bone strength and increase fracture risk.<sup>66,67</sup> It is among the most common metabolic bone disorders worldwide, primarily affecting older adults, with women, particularly postmenopausal women, being at highest risk due to hormonal changes.<sup>68</sup> A large meta-analysis estimated the global prevalence of osteoporosis among individuals aged 15–105 years to be 18% (95% CI 16.2–20.7).<sup>67</sup> Based on the population within this age range (approximately 6.3 billion), this suggests that around 1.15 billion people worldwide are affected, highlighting osteoporosis as a major public health concern.

Fragility fractures are the most serious consequence of osteoporosis. These occur when low-energy trauma, such as a fall from standing height, exceeds the weakened bone's capacity to withstand mechanical stress. The most common sites for osteoporotic fractures are the proximal femur, vertebrae, proximal humerus, and distal radius. Lifetime risk estimates indicate that 1 in 3 women over 50 and 1 in 5 men over 65 will experience a fragility fracture.<sup>66</sup> Such injuries are associated with substantial morbidity, loss of independence, and increased mortality, representing a significant burden to patients and healthcare systems worldwide.<sup>68</sup>

The pathophysiology of osteoporosis is complex, arising from an imbalance between bone formation and resorption mediated by osteoblasts, osteoclasts, and osteocytes, along with structural changes such as trabecular thinning, reduced connectivity, and altered collagen cross-linking.<sup>68</sup> Osteoporosis is classified as primary, related to postmenopausal hormonal changes and ageing (affecting postmenopausal women and adults over 70), or secondary, resulting from systemic disease, endocrine disorders, malignancy, chronic glucocorticoid therapy, or lifestyle factors. Risk factors are either modifiable (e.g., low body weight, smoking, alcohol consumption, physical inactivity, low dietary calcium, long-term glucocorticoid use) or non-modifiable (e.g., age, sex, race, genetics).<sup>67</sup>

Diagnosis is typically established using dual-energy X-ray absorptiometry (DXA), with a T-score  $\leq -2.5$  SD (compared with the mean of a young adult reference population) defining osteoporosis according to WHO criteria. Osteopenia is defined as a T-score between  $-1.0$  and  $-2.5$  SD, while severe or established osteoporosis

refers to low bone mineral density in combination with one or more fragility fractures.<sup>66,67</sup>

## **Treatment of DRFs in the Elderly**

Although DRFs are very common injuries in the elderly, they should not be considered trivial.<sup>69</sup> These fractures impose a substantial burden on both individuals and society, leading to significant healthcare costs<sup>70,71</sup> and considerable functional limitations, even in otherwise healthy and active older adults.<sup>69</sup> In fact, DRFs have been shown to contribute to functional decline in elderly women at a level comparable to chronic conditions such as diabetes and arthritis.<sup>69</sup>

Management of DRFs in elderly patients remains a topic of ongoing debate.<sup>72,73</sup> The patient population ranges from active, independent older adults to frail and dependent individuals. Traditionally, it was assumed that the oldest patients would recover “well enough” regardless of treatment strategy and therefore did not require advanced surgical management. However, as life expectancy increases and older adults remain more functionally independent,<sup>57</sup> this assumption warrants re-evaluation.

With limited healthcare resources and a rapidly ageing population, discussions also focus on how to allocate care effectively and determine which patients are most likely to benefit from surgical intervention.<sup>72-74</sup> Surgical treatment entails substantially higher initial costs than non-surgical management, but how this balances against potential later costs due to productivity loss, increased need for assistance, and reduced activity and independence has not been studied.<sup>70,75</sup>

Conservative treatment remains the standard approach for most DRFs in elderly patients, particularly for non-displaced fractures.<sup>76,77</sup> Treatment typically involves a below-elbow, non-circumferential plaster cast (splint), with an immobilisation period of no longer than 4 weeks, as longer immobilisation has not been shown to improve outcomes.<sup>78</sup> However, predicting fracture instability can be challenging; increasing age and dorsal comminution are consistently reported risk factors for secondary displacement. In some patients, an inability to maintain reduction may justify surgical treatment, especially for those who are functionally active and rely on good wrist function in daily life.<sup>72</sup>

### *Elderly patients and surgery*

VLPs provide stable fixation even in osteoporotic bone and surgical treatment with VLPs has become increasingly common, particularly among women aged 65 years and older.<sup>79</sup>

In the last decade several randomised studies have compared surgical fixation with VLPs to closed reduction and casting (CRC) in elderly.<sup>75,80-86</sup> Most studies define

“elderly” relatively broadly, often including patients aged 60 or 65 years and above.<sup>73,77,87</sup> VLPs allows for earlier mobilisation, faster recovery of grip strength, and a quicker return to daily activities.<sup>77,83,85,86,88,89</sup> In the short term, patients treated with VLPs appear to experience improved functional outcomes compared with those treated non-surgically,<sup>77,83,85-87</sup> while complication rates are similar to conservative treatment.<sup>77,86,88</sup>

In a qualitative study, older patients highlighted the importance of regaining function quickly. Some wanted to recover in time for specific events, such as a holiday, while others aimed to maintain independence in daily activities, including routine tasks like cleaning.<sup>90</sup>

A meta-analysis by Stephens et al. (2020) analysed 6 randomised controlled trials (RCTs) comparing VLP fixation with CRC. 4 trials primarily included older adults, while individual patient data were obtained from 2 mixed-age studies to isolate participants aged  $\geq 60$  years. Using the DASH as the primary outcome, VLPs showed significantly better scores at both final follow-up (12–24 months; mean difference  $-5.9$ , 95% CI  $-8.7$  to  $-3.1$ ) and at 3 months ( $-8.9$ , 95% CI  $-13.0$  to  $-4.8$ ). VLP fixation also resulted in superior palmar tilt, radial inclination, and supination, with no differences in ulnar variance, flexion–extension, pronation, or overall complication rates. However, the between-group differences in DASH did not exceed the predefined minimal clinically important difference (MCID) of 10 points.<sup>77</sup>

A more recent meta-analysis by Yang et al. (2024) focused on long-term outcomes (24 months) in patients aged  $\geq 60$  years. 4 RCTs were included, one of which (Martinez-Mendez et al.<sup>85</sup>) was also part of the 2020 meta-analysis. Using the Patient-Rated Wrist Evaluation (PRWE) as the primary outcome, pooled data from 423 participants showed statistically better results for the VLP group in PRWE, DASH, and grip strength. However, these differences again did not exceed the respective MCID thresholds.<sup>91</sup>

Although the findings are consistent, several methodological limitations make interpretation challenging. In the Stephens et al. meta-analysis, the non-surgical group mostly included fractures that were already well aligned (mean dorsal tilt  $4^\circ$ , ulnar variance 1.2 mm, radial inclination  $16^\circ$ ). This indicates that, for fractures that are initially well reduced, non-surgical treatment can provide long-term functional outcomes comparable to VLP fixation.<sup>77</sup>

In two RCTs, crossover from CRC to VLP fixation was high (41% and 38%, respectively).<sup>82,92</sup> Patients initially treated with CRC were permitted conversion to surgery in the event of significant loss of reduction or pronounced joint incongruence.<sup>82,92</sup>

Across all studies, the overall incidence of complications was low, limiting statistical power to detect between-group differences. In the CROSSFIRE trial, a

combined RCT and observational study of 166 patients aged  $\geq 60$  years, major complications (including deep infection, implant failure, and complex regional pain syndrome), each favoured VLP fixation. Notably, deep infection and implant failure occurred in patients originally allocated to CRC who subsequently crossed over to VLP fixation.<sup>87</sup>

Despite similar PROMs at 24 months, one study found patient-reported treatment success was significantly higher in the VLP group (75% vs 45%), suggesting that subjective satisfaction may be influenced by factors beyond function.<sup>87</sup>

### *Low-demand elderly*

For frail and low-demand elderly patients, conservative or minimal intervention may be most appropriate. Anatomical reduction is often unnecessary, as wrist strength may not be critical for daily activities. Even closed reduction can cause discomfort and complications, particularly in patients with fragile skin. Moreover, reduction is frequently ineffective in this patient group, with one study reporting malunions in 88% of cases, despite attempts at closed reduction.<sup>93</sup> Therefore, primary reduction in low demand elderly patients should be reserved to cases with specific indications, such as median nerve compression.<sup>36,93</sup>

## **Summary**

In summary, according to the Swedish guidelines, chronological age alone should not dictate treatment decisions for DRFs in older adults. Most agree that patient-centred care should be prioritised. Management should be guided by the individual's functional needs and goals, including the ability to resume meaningful activities that promote independence, physical activity, and overall well-being. At the same time, interventions should be avoided when they are unlikely to provide meaningful benefit in the context of the patient's daily life.

Surgical treatment with VLPs is well known to facilitate faster recovery after an acute fracture and does not appear to increase complication rates. Patients also tend to report higher satisfaction following surgical treatment compared with CRC. Although patient-reported outcomes statistically favour VLP fixation in most studies, meta-analyses indicate that these differences are not clinically significant. Surgery is also associated with higher direct hospital-related costs, whereas the societal costs related to prolonged convalescence remain largely unknown.



# Mortality

## Different Ways to Measure Mortality

Mortality can be described in several ways, each with distinct strengths and limitations.

**Table 2.**  
Common epidemiological measures of mortality.

| Measure                                                       | Definition                                                                    | Advantages                                                             | Disadvantages                                                             |
|---------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <b>Crude mortality rate (CMR)</b>                             | Total deaths / number at risk during same period ( $\times 1,000$ )           | Simple to calculate; gives an overall picture                          | Does not adjust for demographic factors (age, sex, etc.)                  |
| <b>Age-specific mortality rate</b>                            | Mortality calculated for a given age group                                    | Provides more detail than CMR; useful for stratification               | Not directly comparable between populations with different age structures |
| <b>Standardised mortality ratio (SMR)</b>                     | SMR = Observed deaths / expected deaths (based on a reference population)     | Can be adjusted for age and/or sex; allows for comparison to reference | Requires reliable reference population data                               |
| <b>Age-standardised mortality rate</b>                        | Mortality recalculated to a standard population (e.g. Statistics Sweden, WHO) | Enables comparison across populations with different age structures    | Requires detailed age-specific data and access to standard population     |
| <b>Cause-specific mortality rate</b>                          | Deaths from a specific cause / population ( $\times 100,000$ )                | Highlights disease-specific burden                                     | May obscure overall mortality patterns                                    |
| <b>Case fatality rate (CFR)</b>                               | CFR = Deaths from a condition / Cases of condition ( $\times 100-1000$ )      | Useful for acute conditions; indicates disease severity                | Does not reflect population-level risk                                    |
| <b>Survival analysis (e.g., Kaplan-Meier, Cox regression)</b> | Time-to-event methods accounting for censored data                            | Captures time dimension; handles incomplete follow-up                  | Requires individual-level longitudinal data; more complex methods         |

Crude mortality rates provide a simple overview but are heavily influenced by the population's age and sex distribution, limiting comparability between cohorts. Age-specific and cause-specific rates offer greater precision, but may be difficult to interpret in isolation.<sup>94</sup> Standardisation methods, such as the age-standardised mortality rate or the standardised mortality ratio (SMR), enable meaningful comparisons across populations by adjusting for demographic differences, although they require detailed reference data.<sup>95</sup> Case fatality rates are clinically intuitive but limited to disease-specific contexts, while survival analysis techniques, including Kaplan–Meier curves and Cox regression, provide the most nuanced assessment by accounting for time-to-event and censored observations, at the expense of greater

statistical complexity. Kaplan–Meier analysis estimates survival probabilities over time, providing a clear visualisation of survival, whereas Cox regression assesses and quantifies the effect of covariates on survival.<sup>96,97</sup>

## **Fragility Fractures and Mortality**

Numerous studies have demonstrated high mortality following fragility fractures, particularly after hip fractures.<sup>98</sup> After a hip fracture, the 30-day mortality risk has been estimated at approximately 3–10%,<sup>99</sup> while contemporary evidence suggests that the 1-year mortality rate is around 22%.<sup>98</sup>

In a large cohort of approximately 13 million Canadian adults aged over 65 years, researchers compared patients with fragility fractures (at any site) to a matched non-fracture cohort. Fragility fractures were associated with reduced survival for up to 6 years post-fracture, with the greatest reduction occurring within the first year, during which mortality risk more than doubled. Interestingly, when fracture types were assessed separately and compared with the matched non-fracture cohort, mortality was elevated following fractures of the hip, humerus, vertebrae, ribs, tibia/fibula or knee, pelvis, combined distal radius and distal ulna, femur, and clavicle or sternum. Mortality was not increased for isolated DRFs.<sup>100</sup>

Although some studies suggest that otherwise healthy and physically fit patients do not experience increased mortality following a hip fracture,<sup>101</sup> patients sustaining fragility fractures are typically older and often present with multiple comorbidities. In addition to age, several factors are associated with higher mortality after hip fracture surgery, including cardiovascular or pulmonary disease, dementia, diabetes, malignancy, and residence in a nursing home.<sup>102</sup>

## **DRFs and Mortality**

Several population-based studies have examined mortality following DRFs. Swedish nationwide data from 23,394 adult patients with DRFs reported an overall 30-day mortality of 0.4% and a 1-year mortality of 2.9%, with similar rates for men and women. Mortality was 4–5 times higher among patients treated non-surgically compared with those undergoing surgical fixation, likely reflecting that non-surgically treated patients were generally older and frailer.<sup>3</sup>

In Korea, a nationwide claims-based study of adults aged 50 years and older showed higher mortality among men, while older women, particularly those aged 70–79 and 90–100 years, exhibited lower-than-expected mortality. When both sexes were combined, individuals aged 60–79 and 90–100 years demonstrated significantly lower-than-expected mortality, suggesting that excess mortality was primarily driven by men in the younger and intermediate age groups.<sup>103</sup> Another Korean

cohort of 27,295 adults, matched 1:4 with controls, found no significant increase in overall mortality (adjusted HR 1.04, 95% CI 0.98–1.11).<sup>104</sup>

A US nationwide cohort of 81,568 Medicare beneficiaries aged 65 years and older with DRFs also demonstrated decreased mortality compared with an age- and sex-matched general population. Female sex, certain racial/ethnic groups, and operative treatment were further associated with lower risk.<sup>105</sup>

However, an earlier US study of 325 elderly patients (mean age 77 years, range 65–106) reported lower survival than expected over 7 years, particularly among men and patients with comorbidities. This study highlights that while many DRF patients may not confer excess mortality, frailty and preexisting disease seem to increase the risk, especially in men.<sup>106</sup>

Norwegian and Polish cohort studies similarly found higher mortality among men, whereas women often experienced lower-than-expected short-term mortality.<sup>107,108</sup> In the Norwegian cohort, women over 70 had 1-year mortality below population expectations, although this difference was not statistically significant (SMR 0.8, 95% CI 0.4–1.2). The long-term mortality at 5 years was elevated (SMR 2.0, 95% CI 1.3–2.7).<sup>107</sup>

A Swedish study from Malmö, including 2,847 patients with low-energy fractures of the distal forearm, hip, shoulder, and spine showed that while hip, vertebral, and shoulder fractures were associated with increased mortality compared with the general population, forearm fractures were not associated with increased mortality in either men or women, even immediately after the fracture.<sup>109</sup>

Across these studies, a consistent pattern emerges. Older women with DRFs often experience lower-than-expected short-term mortality. Differences between studies may reflect variations in patient selection, fracture severity, treatment type, and the use of population-based reference data. Nevertheless, the overarching trend highlights the relative resilience of older female patients following DRFs.

The US study of 325 patients, however, stands out by showing excess mortality. It emphasises that men and those with multiple comorbidities are at highest risk.<sup>106</sup>

## DRFs with Concomitant Distal Ulna Fractures

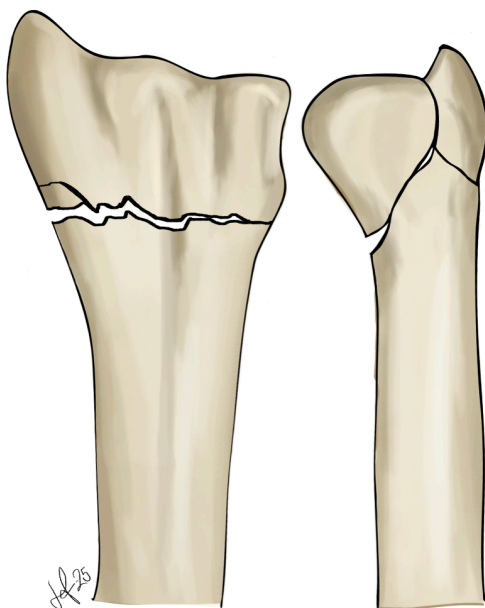
### What Do We Know About DRUFs?

#### *Epidemiology*

Various definitions of DUFs exist, for example those including fractures of the distal third of ulna<sup>110</sup> and the distal fourth of ulna.<sup>111</sup> The term distal metaphyseal ulna

fracture, have previously been defined as a fracture occurring within 5 cm of the distal dome of the ulnar head.<sup>112</sup>

Although DUFs may occur in isolation, it is estimated that 92% are concomitant with DRFs.<sup>110</sup> A large proportion of DRFs (50–58%) are accompanied by DUFs with ulnar styloid fractures accounting for the vast majority (approximately 89–93%).<sup>113,114</sup> While the evidence is not entirely conclusive, most research indicates that nonoperative treatment of ulnar styloid fractures associated with DRFs generally does not worsen outcomes relative to isolated DRFs;<sup>115,116</sup> however, this review will not focus further on ulnar styloid fractures.



**Figure 16.** Illustration of a distal radius fracture (DRF) with a concomitant distal metaphyseal ulna fracture. The term distal metaphyseal ulna fracture has previously been defined as a fracture occurring within 5 cm of the distal dome of the ulnar head. In this thesis, the combination of a DRF and a distal metaphyseal ulna fracture is referred to as a DRUF, as proposed by Liang et al.

In contrast, concomitant distal metaphyseal ulna fractures are relatively uncommon. Varying definitions of DUFs may influence the reported incidence of DRFs accompanied by DUFs. However, when considering only studies focusing on distal metaphyseal ulna fractures, the estimated incidence is approximately 2–9%.<sup>35,113,114,117-119</sup>

In this thesis, the combination of a DRF and a distal metaphyseal ulna fracture is referred to as a DRUF, as proposed by Liang et al.<sup>119</sup>

Although DRUFs can occur at any age, they primarily affect older patients, with a mean age of approximately 65–74 years. A clear predominance of female patients is reported, ranging from 82–100%.<sup>35,119,120</sup>

### *Classifications of DUFs*

Several classification systems for DUFs have been proposed over time. Among the most commonly referenced are the Biyani system<sup>35</sup> and the AO Müller Q-modifier<sup>33</sup>, both of which are described in detail in the Introduction (Figures 12 and 13).

In addition to these, other systems exist, including the updated AO/OTA classification, revised in 2007 and 2018.<sup>34</sup> Within this system, the distal ulna is categorised as 2U3, with subgroups A for extra-articular fractures, B for partial articular fractures, and C for complete articular fractures. The 2U3A category is further divided into three groups: (1) fractures of the styloid process (subclassified into tip or base), (2) simple fractures (spiral, oblique, or transverse), and (3) multifragmentary fractures. Altogether, this framework provides eight distinct classes of DUFs.<sup>34</sup>

Based on a series of 11 DRUF patients, Paksima et al. proposed a classification system for concomitant DUFs comprising four categories. Type A includes simple fractures of the ulnar neck; Type B consists of combined fractures of the neck and styloid; Type C refers to isolated fractures of the ulnar head; and Type D encompasses comminuted fractures involving both the head and neck.<sup>118</sup>

The clinical utility of current classification systems for DRUFs remains limited.<sup>118,121</sup> In a comparative study of 3 classification systems, Moloney et al. concluded that none offered sufficient reliability to be of substantial clinical value. The AO/OTA 2007 classification demonstrated only fair inter-rater agreement (mean  $\kappa = 0.40$ ), while the AO/OTA 2018 and Biyani systems showed moderate agreement ( $\kappa = 0.42$  and  $\kappa = 0.43$ , respectively). Intra-rater reliability was also moderate across all systems.<sup>121</sup> Further evaluations have underscored that the systems are of limited value,<sup>118,122</sup> with even radiologists reporting difficulties applying the AO/OTA 2018 classification consistently.<sup>122</sup>

## **Treatment**

### *To Fix the Ulna or Not — That is the Question*

There are numerous controversies regarding the management of DRUFs.<sup>112,123</sup> Treatment options include closed reduction with nonoperative management, open reduction and internal fixation (ORIF), and distal ulna head resection.<sup>124,125</sup> Most authors agree that the evidence is weak concerning which cases should be managed surgically versus non-surgically, and no clear consensus exists on the optimal

surgical technique.<sup>111,112,118,124,126</sup> Likewise, there are no established guidelines for non-surgical treatment, including the type and duration of immobilisation.<sup>127</sup>

Most studies comparing different surgical treatments for the concomitant DUFs, or surgical versus non-surgical management, are retrospective in nature and based on medical records or registry data. The cohorts are also relatively small with heterogeneous inclusion criteria (Table 3). In the comparative studies, fixation of the DRF is always performed, with the exception of 2 studies that also included small groups of patients (n=15 and n=11) treated with only CRC.<sup>35,119</sup> The fixation method used for the DUFs varies both between and within studies, which further complicates evaluation of outcomes. For example, ORIF of the ulna within a single study may involve 1 pin, multiple pins, a plate with screws, or headless compression screws,<sup>111</sup> and in some cases the specific type of fixation is not described, being referred to only as ORIF.<sup>124</sup>

The common view is that the DRF dictates the initial management. If the DRF requires surgical intervention and the combined DUF remains malaligned or unstable after realignment and fixation of the DRF, surgical treatment of the DUF should also be considered.<sup>111,112,126,128-130</sup>

**Table 3.**

Clinical studies of DRFs with concomitant metaphyseal DUFs aiming to compare surgical and non-surgical methods for the concomitant DUF.

**Retrospective review studies**

| Author             | Year | Treatment groups                                               | N of patients (per group) |
|--------------------|------|----------------------------------------------------------------|---------------------------|
| Glogovac et al.    | 2022 | ORIF DRF only/ORIF DRF+DUF<br>/Ulna Head Resection             | 58 (25/28/5)              |
| Lutsky et al.      | 2020 | ORIF DRF only/ORIF DRF+DUF                                     | 165 (91/74)               |
| Vlček et al.       | 2015 | ORIF DRF only/ORIF DRF+DUF                                     | 27 (15/12)                |
| Liang et al.       | 2015 | Non-surgical/ORIF DRF only/ORIF<br>DRF+DUF/Ulna Head Resection | 24 (11/2/7/4)             |
| Paksima et al.     | 2013 | ORIF DRF only/ORIF DRF+DUF<br>/Ulna Head Resection             | 11 (5/5/1)                |
| Gschwentner et al. | 2008 | ORIF DRF only/ORIF DRF+DUF                                     | 13 (5/8)                  |
| Biyani et al.      | 1995 | Non-surgical/External fixation<br>DRF/ORIF DRF                 | 18 (15/2/1)               |

**Prospective comparative cohort study with sequential allocation**

| Author     | Year | Treatment groups           | N of patients (per group) |
|------------|------|----------------------------|---------------------------|
| Cha et al. | 2012 | ORIF DRF only/ORIF DRF+DUF | 61 (32/29)                |

DRF = Distal radius fracture, DUF = Distal ulna fracture, ORIF = Open reduction and internal fixation.

However, the distal ulna appears to have a high healing potential, and several studies emphasise that DUFs tend to unite regardless of whether surgical fixation is performed.<sup>111,118,131</sup> Most metaphyseal DUFs achieve union within three months, whether they occur in isolation or in conjunction with a surgically treated DRF.<sup>111,122</sup> Furthermore, complication rates are lower in patients managed non-surgically.<sup>124,125</sup>

One prospective study by Cha et al. enrolled 61 patients aged 65 years and older with DRUFs. All included patients had surgically fixed DRFs, after which the stability of the distal ulna was assessed. Only DUFs deemed unstable were included. In the first 29 cases, the DUF was surgically stabilised, whereas in the subsequent 32 cases no fixation was performed. At the 2-year follow-up, outcomes were comparable between the groups. No significant differences were observed in VAS, DASH, grip strength, or range of motion (ROM). Furthermore, no ulnar or radial non-union or malunion was detected. Delayed union of the ulna was observed in 1 patient in the surgically treated group and in 2 patients in the non-surgical group at 12 weeks postoperatively; however, all fractures ultimately achieved union.<sup>130</sup>

### *Plate Fixation*

One of the earliest publications on the surgical management of concomitant DUFs was presented by Ring et al. in 2004, who retrospectively reviewed 24 patients treated with minicondylar blade plates.<sup>132</sup>

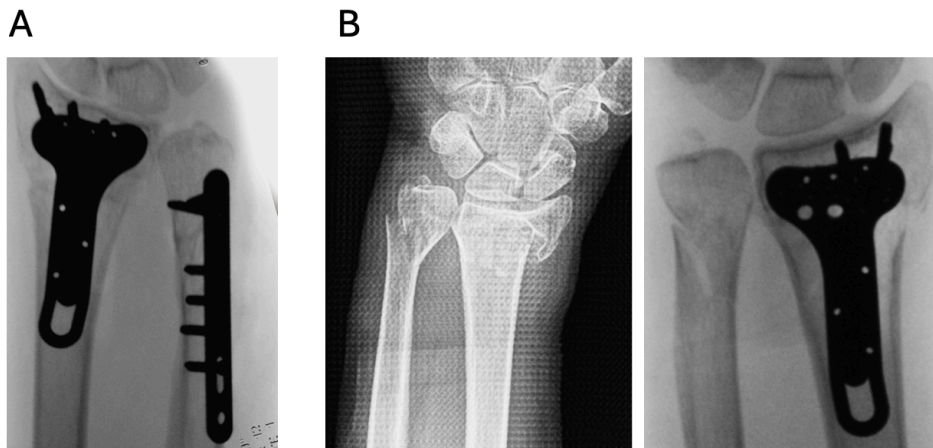
In this study, the DUF was fixed with a minicondylar blade plate when the fracture was deemed unstable following surgical fixation of the DRF (with the decision left to the discretion of the operating surgeon). The ulna was exposed through a separate longitudinal incision using the interval between the extensor carpi ulnaris and flexor carpi ulnaris, with extraperiosteal dissection. Branches of the dorsal cutaneous ulnar nerve were identified and protected. Fractures were reduced and provisionally secured with K-wires before the plate was applied to the medial aspect of the ulna.<sup>133</sup> Fixation maintained alignment and achieved union in all but 1 patient, who had a type III open injury with bone loss. 7 patients (29%) required a second operation for plate removal due to hardware prominence.<sup>132</sup>

Since then, several different plate systems have been developed and used for fixation of DUFs, and more studies have described surgical techniques similar to that reported by Ring et al.<sup>134-136</sup> Nevertheless, the small cohort sizes and study designs limit the ability to identify optimal methods.

In 2012 Lee et al. reported favourable outcomes of distal ulna hook plate fixation in a retrospective study of 25 patients with unstable DUFs. All patients achieved bony union with good ROM and grip strength, and no cases of DRUJ instability.<sup>137</sup> In 2022,

Gauthier et al. also reported good clinical outcomes with distal ulna hook plates; however, the reoperation rate in this study was relatively high (35%). Hardware-

related discomfort led to plate removal in 14 of 48 patients, while 3 patients required secondary ulna head resection (2 due to non-union and 1 for plate dislocation).<sup>138</sup>



**Figure 17.** Radiographs of combined distal radius and distal ulna metaphyseal fractures (DRUFs). (A) a DRUF with plate fixation of both an AO type A distal radius fracture (DRF) and a Biyani type 1 distal ulna fracture; (B) shows a DRUF before and after ORIF of the DRF only.

Dennison et al. reported that fixation of unstable DUFs with locking plates, in the context of an associated DRF, achieved bony union, good to excellent alignment and range of motion, nearly symmetric grip strength, and minimal transient morbidity. However, the series included only 5 patients<sup>136</sup>

The use of intrafocal pin plates has been described in 2 studies from 2012 and 2014, evaluating 5 and 4 patients, respectively. Both studies reported favourable clinical outcomes, although in the series with 5 patients, 2 experienced minor complications, resulting in a complication rate of 40%.<sup>139,140</sup>

### *Intramedullary Nailing*

Plate fixation of the distal ulna has been associated with extensor tendon irritation and secondary procedures due to hardware prominence. Minimally invasive techniques, such as intramedullary (IM) nailing, have been proposed as alternatives. These may provide stable fixation while minimising soft tissue dissection<sup>123,141</sup>

Abboudi et al. suggested that, instead of commercially available IM nails, a 1.6-mm K-wire can be used for the same purpose,<sup>141</sup> and den Hengst et al. have used Steinman pins<sup>142</sup>. Den Hengst et. al. evaluated the use of Steinman pins as IM nails in a case series of 4 elderly female patients with ulnar neck fractures. All showed good radiological and functional outcomes, however 1 Steinman pin required removal.<sup>142</sup> Niemann et al. evaluated retrograde threaded IM pins in a series of 9



patients, reporting good clinical outcomes. 8 patients returned to their pre-fracture activity level, while 1 remained limited due to stiffness<sup>143</sup>.

In a clinical study comparing elastic stable IM nails (n=26) and locking compression plates (LCP) (n=28) in adults with concomitant DUFs, both methods resulted in similar ROM and time to union, with advantages for the elastic stable IM nails in functional outcomes, complication rates, shorter operative time, smaller surgical wounds, and reduced intraoperative fluoroscopy exposure. However, although overall complications were fewer with IM nailing, one patient experienced non-union and required reoperation with bone grafting and plate fixation.<sup>123</sup>

Walz et al. also reported favourable outcomes using antegrade elastic stable IM nailing in a prospective series of 26 patients (mean age 74 years), with all fractures achieving union in anatomical position within 3 months after closed reduction. Aside from 3 cases of asymptomatic nail penetration of the ulnar head, no complications were observed.<sup>144</sup>

### *Ulna Head Resection*

Operative fixation of DUFs can be challenging due to comminution. There is also a risk of hardware impingement on the articular surface of the ulnar head.<sup>145</sup> Furthermore, the thin soft tissue coverage in this region means that osteosynthesis material is often poorly tolerated.<sup>126,145</sup> ORIF of the DUF is associated with a 0-35% reoperation rate.<sup>124,130,132,138,146,147</sup> Fixation of DUFs in elderly patients with osteoporotic bone can be even more technically challenging and may sometimes carry a high risk of complications without achieving particularly stable fixation.<sup>128,130,131,145</sup> In such cases, it may be preferable to leave the fracture unfixed<sup>130,131</sup> or in low demand patients to perform a resection of the ulnar head (also called Darrach procedure).<sup>147-151</sup>

When ulna head resection is compared to plate fixation, the patients undergoing resection are generally older (mean age 73, range 61–80 years) compared with those treated by plate fixation.<sup>124,147,148</sup> In contrast to ulna plate fixation, resection appears to result in substantially fewer complications, without significant differences in VAS, active ROM, or grip strength.

In three retrospective studies evaluating outcomes and function following groups of patients undergoing distal ulna head resection, similar results were observed. The patients demonstrated good ROM and low complication rates.<sup>149-151</sup> Moreover, the procedure enabled the patients to return to their pre-injury level of activity.<sup>149</sup>

These findings suggest that distal ulna head resection may be considered a reasonable first-line treatment in low-demand patients, particularly in those with significant comorbidities who are not suitable candidates for secondary surgery.<sup>125,148</sup>

**Table 4.**

Clinical studies of DRUFs, undergoing primary ulna head resection.

| Author                                                                                                                         | Year | Treatment groups                                                            | N of patients (in groups) |
|--------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------|---------------------------|
| <b>Retrospective studies comparing ulna head resection with other surgical methods</b>                                         |      |                                                                             |                           |
| Shibata et al.                                                                                                                 | 2023 | K-wire fixation/Locking plate fixation/Distal ulna head resection           | 122 (32/48/42)            |
| Boretto et al.                                                                                                                 | 2019 | ORIF Ulna/Distal ulna head resection.                                       | 24 (12/12)                |
| Glogovac et al.                                                                                                                | 2022 | ORIF DRFonly/ORIF DRF+DUF /Distal ulna head resection                       | 58 (25/28/5)              |
| <b>Retrospective studies of cohorts of patients that underwent ulna head resection</b>                                         |      |                                                                             |                           |
| Yoneda et al.                                                                                                                  | 2014 | ORIF of DRFs and distal ulna head resection                                 | 23                        |
| Ruchelsman et al.                                                                                                              | 2009 | ORIF of DRFs and distal ulna head resection                                 | 11                        |
| Seitz et al.                                                                                                                   | 2007 | ORIF of DRFs and distal ulna head resection with soft tissue reconstruction | 15                        |
| DRF = Distal radius fracture, DUF = Distal ulna fracture, K-wire = Kirschner wire, ORIF = Open reduction and internal fixation |      |                                                                             |                           |

## Summary of DRUF-Knowledge

In summary, DRUFs are relatively rare, occurring in approximately 2-9% of DRFs, and are most seen in elderly women. There is currently no high-level evidence guiding their optimal management. Most authors agree that the treatment of the DRF largely determines whether surgical intervention of the DUF is required. If the DUF is deemed stable after fixation of the distal radius, additional fixation of the ulna is generally unnecessary. Conversely, if the ulna fracture remains unstable following radius fixation, surgical stabilisation should be considered. Some evidence suggests that older patients or those with low functional demands may not benefit from ulna fixation. Osteosynthesis of DUFs are associated with a relatively high risk of reoperation, primarily due to hardware-related discomfort. In patients for whom a secondary procedure is considered high-risk, distal ulna head resection may represent a reasonable alternative to ulna fixation.

## COVID-19

In late December 2019, cases of pneumonia of unknown origin were reported in Wuhan, China, and the causative agent was soon identified as a novel coronavirus,

later named SARS-CoV-2, causing coronavirus disease 2019 (COVID-19).<sup>152</sup> The most common symptoms included fever, dry cough, and fatigue, while some patients also experienced shortness of breath and gastrointestinal manifestations.<sup>152</sup>

The rapid global spread of the virus, coupled with uncertainty regarding treatment and outcomes, constituted an unprecedented shock to societies worldwide. In March 2020, the World Health Organization officially declared COVID-19 a global pandemic, highlighting the severity of the crisis. It soon became apparent that many individuals developed severe illness, and global mortality increased as a consequence of the pandemic. Daily reports on rising infection and death counts reinforced the sense of emergency. In response, governments implemented lockdowns, closed public spaces, mandated protective measures such as mask wearing, and promoted social distancing, while households stockpiled food and supplies in anticipation of prolonged restrictions. The scale and speed of these developments represented a modern global health emergency unlike any previously experienced.<sup>152-154</sup>

## **A Catalyst for Development**

The COVID-19 pandemic placed enormous pressure on healthcare systems, which were forced to rapidly reorganise to cope with the influx of patients suffering from COVID-19. Hospitals and clinics had to build an exceptional level of preparedness to manage not only the immediate crisis but also the possibility of an even more severe escalation. Elective surgeries were cancelled as facilities, equipment, and personnel were redirected to treat patients with COVID-19, and many outpatient visits were postponed. At the same time, hospitals and primary care centres reorganised spaces and patient flow in order to reduce the risk of infection for both patients and healthcare staff.<sup>153,154</sup>

The COVID-19 pandemic also accelerated the adoption of telemedicine across healthcare systems worldwide.<sup>153</sup> In orthopaedics, telemedicine had previously been used only to a very limited extent, as clinical assessment and treatment were traditionally dependent on physical examination and in-person interaction.<sup>155</sup> However, when the pandemic restricted in-person consultations and elective surgeries, orthopaedic specialists were also required to implement digital solutions. Video consultations became an essential tool to ensure continuity of care, prevent disease transmission, and maintain patient follow-up. Thus, COVID-19 triggered a substantial shift, marking the first broad introduction of telemedicine into routine orthopaedic practice.<sup>59,154-159</sup>



**Figure 18.** The COVID-19 pandemic represented an exceptional period, imposing substantial demands on healthcare systems to adapt swiftly.

Normally, developing and implementing new healthcare systems is a slow process, partly due to extensive laws and regulations.<sup>160</sup> During the pandemic, however, many of these legal and regulatory barriers were temporarily loosened, which enabled a rapid introduction and scaling of digital solutions. This exceptional situation allowed healthcare providers, including orthopaedic specialists, to adopt and refine telemedicine at a remarkable pace.<sup>158,161</sup>

### **Implementation of Telemedicine after Wrist Fracture Surgery**

At the Orthopaedic Department of Skåne University Hospital, it was initially decided that no DRFs would continue to be treated surgically within the public

healthcare system. As a result, plans were made to enable operative management of DRFs at smaller private facilities, with follow-up conducted remotely. This approach also allowed patients to reduce their risk of infection by avoiding larger hospital wards with higher patient volumes and an increased risk of COVID-19 exposure.

Telephone follow-up after outpatient visits and surgery had been routinely employed prior to the pandemic, whereas video consultations were extremely rare. But now we prepared to conduct postoperative follow-up via video, including both surgeon assessments and physiotherapy sessions. Preparations were also made to guide patients in removing their own sutures via video consultation, in case the situation escalated further; however, this was never required.

The pandemic never escalated to a level that necessitated performing surgery in the private sector; instead, surgical treatment was relocated to a smaller hospital at a different site. However, digital follow-up was implemented. At no cost, we were provided with the opportunity to use a digital video consultation system developed by a private healthcare provider.

Although the elderly were a primary target for infection prevention through remote follow-up, concerns were raised about their ability to engage with digital platforms. Outside the pandemic, studies of elderly patients' experiences with e-health in Swedish primary care had revealed a complex mix of curiosity, hesitation, and the need for support.<sup>162</sup> Study participants described limited familiarity with digital tools, uncertainty about accessing online healthcare, and worries about reduced accessibility of conventional care, increased costs, and unreliable IT systems. Many also reported low confidence in their digital skills, highlighting a perceived generation gap compared with younger users. Nevertheless, they acknowledged potential benefits of video consultations, text messaging, and digital reminders as complementary tools.<sup>162</sup>

Given our limited prior experience with video-based follow-up, we supplemented the video consultations with semi-structured interviews. These were intended both to generate research data and to inform optimisation of follow-up procedures during the ongoing pandemic.

## Augmentation of Fracture Fixation in Osteoporotic Bone

Achieving stable fracture fixation in poor bone quality is challenging and there is an increased risk of fixation failure.<sup>68</sup> DRFs in elderly patients with osteoporosis are expected to become increasingly common.<sup>56</sup> Consequently, there is a growing interest in developing surgical strategies that enable reliable fixation even in osteoporotic bone with reduced quality.<sup>68</sup>

This creates a rationale for the use of augmentation techniques. Such techniques are broadly defined as surgical methods that enhance implant stability, by improving either the mechanical strength of cancellous bone or by reinforcing the bone implant interface.<sup>68,163</sup> There are both biological and synthetic options including the use of autologous mesenchymal stromal cells, bone morphogenic proteins or synthetic materials such as polymethylmethacrylate (PMMA), bone grafts, calcium phosphate-based ceramics (applied as blocks, cements, or coatings), as well as specially designed implants.<sup>68,163</sup> Within the scope of this thesis, we have focused on the use of synthetic materials.

## **Polymethylmethacrylate**

PMMA is an acrylic polymer formed by mixing methyl methacrylate monomer with pre-polymerized PMMA particles, together with initiators, activators, and stabilisers. Clinically, PMMA is used in osteoporotic fracture management, orthopedic oncology, and vertebroplasty, but it is perhaps best known for its widespread use in cemented arthroplasties, owing to its excellent biocompatibility, ease of handling, mechanical strength, and moldability.<sup>164</sup> Meta-analyses have demonstrated that PMMA augmentation in elderly patients with trochanteric femur fractures improves functional outcomes, reduces pain, and shortens hospital stay.<sup>165</sup> It also significantly reduces the number of cut-outs.<sup>166</sup>

Limitations of PMMA include its inability to remodel into living bone and its exothermic polymerization reaction, which can reach temperatures up to 56 °C and cause thermal injury or local tissue necrosis.<sup>167</sup> In addition, there is a risk of cement leakage, and the use of PMMA carries a small but recognized risk of bone cement implantation syndrome. Another important drawback is its susceptibility to bacterial biofilm formation, which can complicate infection management and treatment outcomes.<sup>68,168</sup>

## **Calcium Sulphate/Hydroxyapatite**

Calcium sulphate/hydroxyapatite (CaS/HA) is a biphasic, injectable biomaterial composed of 60:40 CaS to HA by weight. Upon mixing with an aqueous solution, the CaS hemihydrate converts to dihydrate, hardening into a composite with embedded HA particles.<sup>169</sup> CaS/HA is osteoconductive, resorbs gradually, raises local calcium ion concentrations, and creates space for new bone ingrowth. It stimulates osteoblast proliferation and differentiation, promotes apatite precipitation, and encourages cell recruitment, ultimately forming an interlinked, protein-rich apatite matrix that supports bone regeneration.<sup>169,170</sup>

CaS/HA has been evaluated extensively, with over 150 preclinical and clinical studies demonstrating efficacy in both normal and osteoporotic bone,<sup>170</sup> including

in osteotomies of distal radius.<sup>171</sup> When used in vertebroplasty for fragility fractures, it provides comparable pain relief and quality-of-life improvements to PMMA, while reducing the incidence of adjacent-level fractures.<sup>170</sup> Its resorbable nature allows the material to be gradually replaced by living bone, aligning with the host's natural bone turnover. CaS/HA is also an effective carrier for local drug delivery, including antibiotics or other medications.<sup>170</sup>

Safety and feasibility studies in trochanteric hip fractures have confirmed that CaS/HA augmentation is well-tolerated. Stravinskas et al. evaluated CERAMENT G (CaS/HA loaded with gentamicin) and CERAMENT V (loaded with vancomycin) in patients with trochanteric fractures and uncemented hip revisions. Local antibiotic levels were high initially but declined over days without systemic toxicity. Radiographs showed satisfactory fracture healing, minimal screw migration, and no adverse events related to hearing, kidney function, or allergies.<sup>172-174</sup> Augmented proximal femoral nails also demonstrated improved biomechanical stability and functional outcomes in patients with unstable fractures.<sup>175</sup> Comparisons with autologous bone grafts in tibial plateau fracture fixation showed similar radiological and clinical outcomes, supporting the utility of CaS/HA as a bone substitute.<sup>176</sup>

## **Zoledronic Acid**

Zoledronic acid (ZA) is a bisphosphonate (BP) with well-established anti-osteoporotic effects and more than two decades of clinical use. BPs prevent fractures, increase bone mineral density, and confer long-lasting benefits even after discontinuation of therapy, while also reducing morbidity, healthcare costs, and mortality.<sup>177,178</sup> 3-year ZA treatment after hip fracture reduces all-cause mortality by 28%.<sup>177</sup>

BPs are chemically stable derivatives of inorganic pyrophosphate that inhibit bone mineralisation by binding to hydroxyapatite crystals, and their potency is determined by structural modifications. ZA, as a nitrogen-containing bisphosphonate, is among the most potent and effective agents in this class. BPs bind strongly to bone hydroxyapatite, particularly at sites of active remodelling, due to an increased access to HA particles. When osteoclasts attempt to resorb the bone mineral particles, ZA is taken up by the osteoclasts. Intracellular ZA in osteoclasts inhibits the farnesyl pyrophosphate synthase enzyme in the mevalonate pathway causing a defect in ruffled border formation as well as other cytoskeletal perturbations inducing cell death.<sup>178</sup>

Because of their strong affinity to bone, BPs can persist in the skeleton for years, being released and re-incorporated during bone turnover, which explains their prolonged effect even after discontinuation. ZA is typically administered intravenously, avoiding the low gastrointestinal absorption that limits oral

formulations, but it is contraindicated in patients with severe renal impairment (GFR <30 mL/min) due to reduced clearance.<sup>178</sup>

Side effects are generally mild, including fever, myalgia, arthralgia, and influenza-like symptoms, while severe complications such as hypocalcaemia, osteonecrosis of the jaw, or atypical femur fractures are rare.<sup>177,178</sup>

### **Biological Activation of CaS/HA with Zoledronic Acid**

A pilot in vivo study by Širka et al. indicated that when ZA was delivered locally using a CaS/HA carrier, bone formation increased in the femoral neck canal of severely osteoporotic rats. Importantly, this effect was mainly observed in cancellous bone and both in healthy and osteoporotic animals, whereas cortical bone showed little response.<sup>179</sup> Further studies using rat tibial bone defect models confirmed that CaS/HA can act as an effective carrier for local ZA delivery, leading to new bone formation in cancellous bone, also confirmed by micro-CT and histological analyses.<sup>180-182</sup> These findings were later supported in a more clinically relevant implant integration model, where implants combined with CaS/HA and ZA showed significantly greater bone volume around the implant compared to controls.<sup>183</sup>

By exploring new ways of implant augmentation, including the use of CaS/HA biomaterials combined with systemic BP therapy such as ZA, it might be possible to improve the immediate mechanical stability of orthopedic hardware and enhance peri-implant bone formation. These strategies may be particularly valuable in osteoporotic bone, including in the fixation of DRFs.



# Aims

## General Aims of the Thesis

DRFs are the most common type of fracture and predominantly affect older adults, yet much of the current evidence on fracture management is derived from studies in younger populations.

By identifying fracture types in the elderly that warrant particular attention, exploring strategies for individualised treatment and follow-up, and advancing surgical techniques for osteoporotic bone, this thesis aims to improve care for the oldest patients, challenge age-related biases, and contribute to the optimisation of fracture management in older adults.

## Specific Aims of the Individual Publications

### **Study I**

To determine whether a DRUF predicts a worse patient-reported outcomes, measured by DASH, 1 year after injury compared with an isolated DRF.

### **Study II**

To examine the 1- and 5-year SMR in DRF patients aged 80 years or older, and to correlate overall survival with patient-related factors.

### **Study III**

To explore how patients with DRFs experienced video-based follow-up during the COVID-19 pandemic, and to identify the potential benefits and challenges of this digital approach.

### **Study IV**

To evaluate whether the combination of a CaS/HA biomaterial applied at the metaphyseal bone-implant (screw) interface followed by systemic administration of ZA could activate the peri-implant hydroxyapatite particles and thereby enhance bone formation in an osteoporotic rat model of bone-implant integration.

# Methods

## Study I-II

Study I and II are single-site, registry-based cohort studies, using data from The Lund Wrist Fracture Register.

### **The Lund Wrist Fracture Registry**

In 2001, a wrist fracture registry was introduced at the Department of Orthopaedics, Skåne University Hospital in Lund. All patients aged 18 years and older presenting with a DRF to the emergency department in Lund were prospectively and consecutively registered in the Lund Wrist Fracture Registry (also referred to in some studies as the Lund Distal Radius Fracture Register). A secretary has reviewed the medical records of the emergency department weekly to identify cases of wrist fractures. Inclusion was based on the ICD-10 codes S52.50/51 and S52.60/61. An orthopaedic surgeon examined the radiographs of all included patients to make sure the diagnosis and coding were correct. Data collection continued through December 31, 2018, after which the registry was phased out due to the implementation of a national fracture registry.

### **DASH**

All patients in the registry were asked to complete the patient-reported outcome instrument DASH, sent by regular mail at 3 and 12 months after the fracture. Non-responders received a reminder after 2 weeks.

The previous results from the DASH questionnaires in the register were reported for 2001–2002, by Abramo et al.,<sup>50</sup> and for 2003–2012 by Landgren et al.<sup>184</sup>

In 2008, the original 30-item DASH was replaced by the shorter 11-item QuickDASH to improve response rates (the questionnaires are shown in Appendices 1 and 2). Although the questionnaire responses in paper I include both DASH and the QuickDASH results, all are referred to as DASH for simplicity throughout the article.

## **Inclusion**

Inclusion, Study I: All 5,536 patients registered between 2003 and 2018 were included. Data from 2001–2002 were excluded, as the completeness of the registry during its initial implementation phase was uncertain.

Inclusion, Study II: All patients in the registry who were at least 80 years old at the time of injury and sustained a DRF between January 1, 2010, and December 31, 2012, were included. The study years were chosen sufficiently early to allow for a long follow-up period, without including the pandemic period. No exclusion criteria were applied.

## **Data Collection**

Basic data, including date of birth, fracture date, age at the time of fracture, sex, and DASH score, were retrieved from the registry for all included patients.

Additional data were collected through a retrospective review of medical records and radiographs. For Study I, this included all DRUFs and a subset of age- and sex-matched patients with isolated DRFs, with information on comorbidities, medication use, treatment details, fracture classification, and fracture type (open or closed). For Study II, data were collected for all included patients, covering comorbidities, medication use, type of housing, use of walking aids, cognitive impairment, treatment details, and major complications. All comorbidities were classified according to the Charlson Comorbidity Index (CCI).<sup>185</sup> Age was excluded from this index, as it was analysed as a separate variable.

For Study II, dates of death were extracted by linking patients' social security numbers to the Swedish National Cause of Death Register.

## **Data Analyses**

Continuous patient characteristics with symmetrical distributions were reported as mean  $\pm$  standard deviation, and categorical variables as counts and percentages.

Estimates are presented with 95% confidence intervals and two-sided P-values, with  $P < 0.05$  considered statistically significant.

### *Statistical analysis: Study I*

The DASH score was treated as an ordinal variable with a skewed distribution and is presented as median and interquartile range (IQR). For regression analyses, the variable was dichotomised at  $>35$  versus  $\leq 35$ , a threshold previously associated with major disability.<sup>186</sup>

Associations between DRUF status and a DASH >35 were assessed using multivariable logistic regression adjusted for age and sex, with sensitivity analyses using alternative cut-offs (25, 30, 40, 45) confirming robustness.

As it was not possible to retrospectively review the medical records of all 5,536 patients to collect information on potential confounders, a second logistic regression was performed on a smaller, matched dataset. This dataset included all DRUF patients (n = 259) and an equal number of DRF-only controls, matched for age and sex. In this analysis, we were able to adjust for age, sex, CCI, polypharmacy, fracture type (open/closed), treatment (surgical/non-surgical), and the AO classification of the DRF.

Interobserver agreement for fracture classification of the DUFs according to Biyani and AO Q-modifier was evaluated using Cohen's kappa. Trends in the proportions of surgical versus non-surgical treatment from 2003 to 2018 were assessed using linear regression.

Group comparisons were performed using the Mann–Whitney U test for skewed continuous variables, t-tests for normally distributed variables, and chi-square tests for categorical variables. Estimates are presented with 95% confidence intervals (CI) and two-sided P values, with  $P < 0.05$  considered statistically significant.

### *Statistical analysis: Study II*

Mortality outcomes were assessed using Kaplan–Meier estimates to calculate crude 1- and 5-year death rates, and survival differences between groups were compared using log-rank tests.

Age- and sex-standardised mortality was expressed as the standardised mortality ratio (SMR), using the Swedish general population as the reference and age groups 80–84, 85–89, 90–94, and 95–99 years. Information on the reference population was obtained from Statistics Sweden via the Statistical Database.<sup>187</sup>

Prognostic factors for all-cause mortality were evaluated using Cox proportional hazards regression, with independent variables including age, sex, CCI, polypharmacy, cognitive impairment, type of residence, and use of a walking aid.

Multivariable Cox models were used to adjust for potential interactions between prognostic factors. Hazard ratios (HRs) with 95% CI were presented to quantify associations.

## Study III

Study III employed a mixed-methods design, combining qualitative data from semi-structured interviews with quantitative analysis of survey responses.

## Participants

During the study period (April–May 2020), only 12 patients underwent DRF-surgery at our hospital, most likely due to the ongoing pandemic. A convenience sampling approach was used, and all 12 patients were invited to participate. No predetermined exclusion criteria were applied.

## Data Collection

Data were collected through semi-structured telephone interviews 6–8 weeks after surgery. An interview guide was used. The interviews were transcribed verbatim.

In connection with the interview, all participants answered questionnaires regarding functional health literacy (FHL) and functional digital literacy (FDL). The Swedish FHL scale was used. To our knowledge no equivalent questionnaire to measure the patient's functional digital literacy (FDL) existed. Hence, a questionnaire measuring patients' confidence levels and their attitudes towards digital technology was developed (questionnaires are shown in Appendix).

## Data Analysis

For data analysis, we used the qualitative method Systematic text condensation (STC), first described by Malterud.<sup>188</sup> The main steps of STC are:

- 1) Getting an overall impression: All researchers read the semi-structured interview transcripts to gain a general sense of the content and identify preliminary themes.
- 2) Identifying meaning units: The text is divided into small segments, or meaning units, capturing statements, experiences, or other relevant information.
- 3) Condensing meaning units: Each meaning unit is condensed into a more abstract form while preserving its original meaning.
- 4) Grouping into thematic categories: Condensed meaning units are organised into thematic categories, creating a structure that captures the essence of participants' experiences.
- 5) Recontextualisation: The thematic categories are compared with the original material to ensure the analysis accurately reflects the participants' experiences.

Quantitative data were analysed using the recommended transformations for the FHL scale. Scores above 1000 indicated inadequate FHL, scores between 100 and 1000 were classified as problematic, and scores below 100 as sufficient.<sup>189</sup> The same procedure was applied to the FDL scale, with individual scores summed and categorised according to the same recommendations.

| Example: Schematic View of Coding                                                                                           |                       |                            |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------------|
| Units of Meaning                                                                                                            | Units of Significance | Emergence of Key Themes    |
| “It is so nice not having to leave and take the bus to the hospital, I can just stay at home relaxing”                      | Easier not to travel  | Video calls are convenient |
| “It saved me a lot of time when I didn’t need to go to the hospital. I could stay at work and have my follow-up call there” |                       |                            |
| “I didn’t have to take a day off from work”                                                                                 |                       |                            |

**Figure 19.** Schematic view of the coding process, with examples of quotations from Study III.

## Study IV

This study comprises 5 sub-studies forming a translational, stepwise investigation of biomaterial-based strategies to enhance bone repair in osteoporotic conditions. The research progressed from preclinical evaluation in an osteoporotic rat model to clinical feasibility testing in patients with trochanteric femur fractures, to exploration of the generalisability of the concept using alternative ceramic materials.

In this thesis, the focus is solely on sub study 1, a preclinical experimental study using rat models to evaluate whether the combination of a calcium sulphate and hydroxyapatite (CaS/HA) biomaterial applied at the bone-implant interface followed by systemic ZA administration could activate peri-implant HA particles and thereby enhance bone formation in an osteoporotic rat model of bone-implant integration.

### Animals

A total of 38 ovariectomized (OVX) and 4 SHAM-operated female Sprague-Dawley rats (Janvier Labs, France) were used. OVX and SHAM surgeries were performed by the breeder at 12 weeks of age. At the time of the experimental

intervention, all animals were 24 weeks old and weighed  $419 \pm 29$  g. Rats were randomly assigned to 4 groups (G1–G4). Animals were housed 2 in each cage with free access to food and water throughout the study period.

## Experimental Procedures

### *Implant Integration in Osteoporotic Rats*

All OVX rats underwent surgery on the right tibia, approximately 5 mm below the growth plate. Rats were anaesthetised with isoflurane (2–2.5% mixed with oxygen at a flow rate of 0.4 L/min) and received antibiotic prophylaxis (Penicillin-Streptocillin VET, Apoteket AB, Sweden) and preoperative analgesia (buprenorphine, 0.03 mg/kg, subcutaneously).

A 1.8 mm unicortical hole was drilled, and a  $2.3 \times 8$  mm stainless-steel screw (Trimed Ortho, Sweden) was inserted. In G1 and G2 screws were not augmented, in G3 and G4 they were augmented with 50  $\mu$ L of CaS/HA biomaterial (CERAMENT™ BVF, Bone Support AB, Sweden). Two weeks post-surgery, rats in G2 and G3 received a subcutaneous injection of ZA (0.1 mg/kg). 6 weeks after surgery, all animals were sacrificed, and tibiae from both legs were harvested, cleaned, and stored at  $-20$  °C until analysis. SHAM rats were sacrificed at the same time, and their tibiae were collected using the same procedure. A schematic of the surgical model as well as evaluation techniques are described in Figure 20.

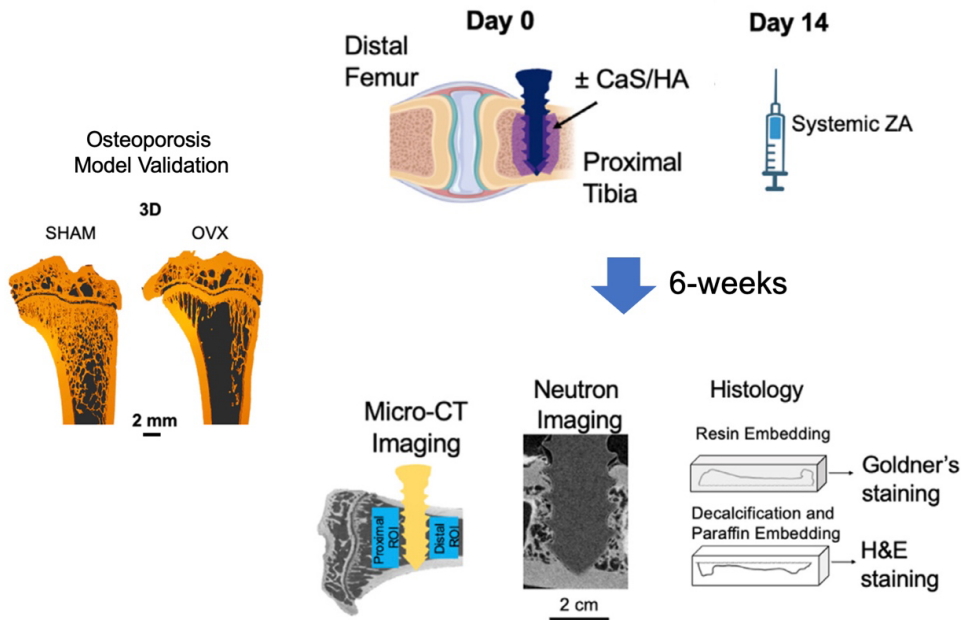
### *Ex Vivo Micro-CT for Peri-implant Bone Quantification*

Harvested tibiae from the operated side were taken out of storage and allowed to reach room temperature prior to scanning with a MI labs U-CT micro-CT scanner. Screws were positioned perpendicular to the X-ray beam to minimise metal artefacts. Scans were performed at 50 kV, 0.21 mA, 75 ms exposure, and  $0.25^\circ$  step angle, and images were reconstructed to 30  $\mu$ m isotropic voxels. To measure the primary outcome bone volume (BV), two regions of interest (ROIs), proximal and distal to the implant, were defined. The ROIs were then used to quantify peri-implant bone formation while avoiding native bone. A global threshold of 0.57 g/cm<sup>3</sup> HA, calibrated using HA phantom standards was applied.

### *Neutron Imaging and Undecalcified Histology*

One representative sample per group (G1–G4) was imaged using neutron imaging at the NeXT beamline at Institut Laue-Langevin, France, to visualise the bone-implant interface with minimal metal artefacts. Samples were fixed in formalin, dried under vacuum, and mounted in Teflon holders for 360° neutron tomography. Images were reconstructed to 7.15  $\mu$ m isotropic voxels. After imaging, samples were processed for undecalcified histology: embedded in Technovit 9100, sectioned to 20  $\mu$ m, and stained with Goldner's Trichrome.

All remaining tibiae were decalcified in an acid-based solution, embedded in paraffin, sectioned to 5  $\mu\text{m}$ , and stained with haematoxylin and eosin (H&E) for standard histological analysis.



**Figure 20.** A schematic of the surgical model and evaluation techniques. Model validation of OVX-rats, Positioning of metaphyseal screw in proximal tibia, ZA injection and CT- and neutron imaging evaluation as well as histology.

### Statistical Analysis

The sample size was based on previous experiments using similar animal models.<sup>183,190</sup> To confirm the osteoporotic status of the animals, micro-CT-based BV was compared between SHAM and OVX groups using a Mann–Whitney U test. The primary outcome variable was micro-CT-derived peri-implant BV. Normality of the data was assessed using the Shapiro–Wilk test, and as the data were not normally distributed, a non-parametric ANOVA (Kruskal–Wallis test) followed by Dunn’s multiple comparison post hoc test was applied. Statistical significance was set at  $P < 0.05$ .

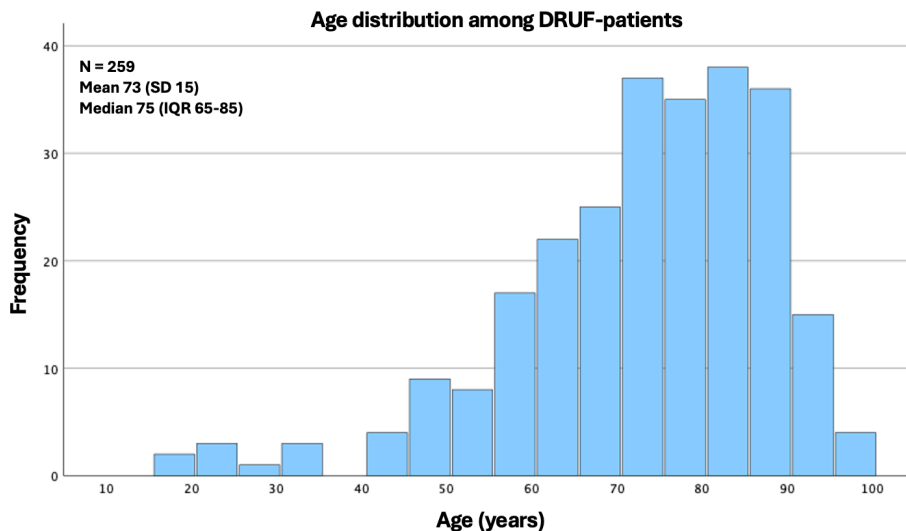


# Main Results

## Study I

### DRUFs Predict Worse Outcome

Of the 5,536 patients with DRFs registered between 2003 and 2018, 259 (5%) had concomitant metaphyseal DUFs.



**Figure 21.** Histogram showing the age distribution of the patients with combined distal radius and distal metaphyseal ulna fractures (DRUFs); 197/259 patients (76%) are 65 years or older.

The DRUF subgroup had a mean age of 73 years (SD 15); 86% (222/259) were women, and 16% (41/259) sustained open fractures.

In the multivariable model, having a DRUF was associated with nearly double the odds of a poor functional outcome (DASH > 35 at 1 year; OR 1.97, 95% CI 1.40–2.75,  $P < 0.001$ ), which remained significant after adjustment (OR 2.35, 95% CI 1.33–4.16,  $P = 0.003$ ).

Other predictors of a poor outcome included comorbidity ( $\text{CCI} \geq 2$ ; OR 2.87, 95% CI 1.78–4.62,  $P < 0.001$ ), polypharmacy (OR 4.60, 95% CI 2.77–7.77,  $P < 0.001$ ), increasing age (OR 1.05 per year, 95% CI 1.03–1.07,  $P < 0.001$ ), and open fracture (OR 2.13, 95% CI 1.03–4.41,  $P = 0.04$ ). Sex and AO classification of the DRF were not associated with outcome.

Surgical treatment of the DRF reduced the odds of a poor outcome (OR 0.44, 95% CI 0.23–0.85,  $P = 0.02$ ). Additional ulna fixation did not improve median 1-year DASH scores (15 [IQR 0–42] vs. 19 [IQR 6–35],  $P = 0.7$ ).

Surgically treated DRUF patients were younger ( $67 \pm 14$  vs.  $78 \pm 15$  years,  $P < 0.001$ ) and had fewer comorbidities ( $\text{CCI } 1.0 \pm 1.4$  vs.  $1.6 \pm 1.6$ ,  $P = 0.004$ ) compared with non-surgically treated patients.

The proportion of surgically treated DRFs ( $P = 0.09$ ) or DRUFs ( $P = 0.40$ ) did not change significantly over time.

## Study II

### **Lower Mortality than Expected in DRF-patients Aged 80 Years or Older**

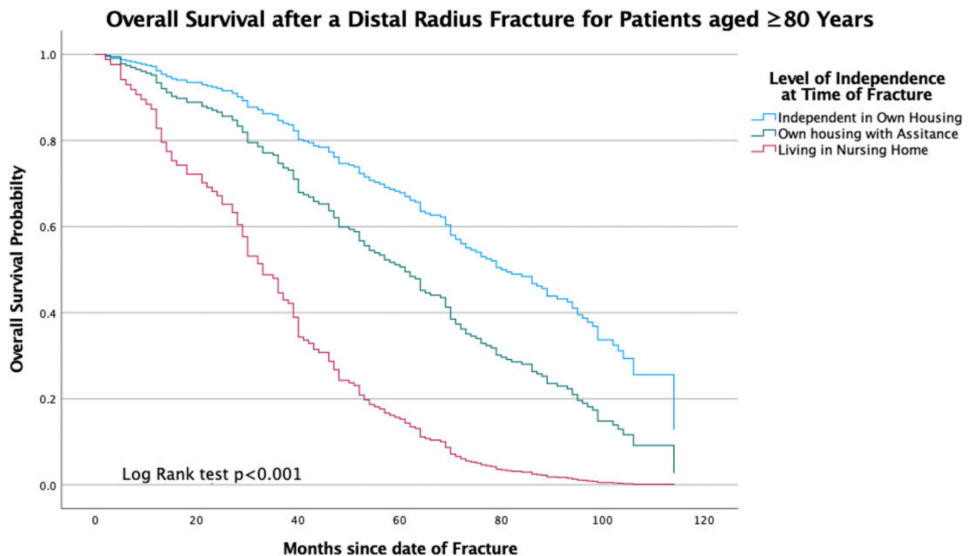
Between 2010 and 2012, 240 of 1,317 (18%) patients with DRFs in the Lund Wrist Fracture Register were aged 80 years or older. Of these, 10% were surgically treated, most with VLPs. 3 of the 240 patients re-attended the clinic due to symptomatic malunions (all non-surgically treated).

Overall, 74% of the patients in this elderly cohort died during follow-up, with a mean survival of 5.2 years (95% CI 4.8–5.6). Mortality was lower than expected compared with the Swedish general population at 1 year (SMR 0.44, 95% CI 0.18–0.69,  $P < 0.01$ ), but similar at 5 years (SMR 0.96, 95% CI 0.78–1.14).

In the multivariable Cox regression analysis, living situation was the strongest predictor of mortality: patients residing in nursing homes had the poorest prognosis (HR 3.2, 95% CI 1.8–5.6,  $P < 0.001$ ), while those receiving home assistance also had an increased risk (HR 1.6, 95% CI 1.0–2.4,  $P < 0.05$ ). Higher comorbidity ( $\text{CCI} \geq 2$ ) was likewise associated with increased mortality (HR 1.5, 95% CI 1.0–2.2,  $P < 0.05$ ).

The mean survival of patients living in their own homes was 6.4 years (95% CI 6.0–6.9), compared with 3.1 years (95% CI 2.5–3.7,  $P < 0.001$ ) for those in nursing homes.

In the univariable Cox regression analysis, cognitive impairment and polypharmacy were also significantly associated with a poorer prognosis; however, these associations did not remain significant in the adjusted model. There were no associations between overall survival and sex, increasing age (analysed as a continuous variable), or use of a walking aid.



**Figure 22.** Kaplan–Meier plot illustrating overall survival among patients aged 80 years or older with a distal radius fracture. Blue line: patients living independently; green line: patients living at home with regular assistance; red line: patients residing in nursing homes or comparable long-term care facilities.

## Study III

### Video Follow-up after DRF Surgery Well Received During the Pandemic

10 out of 12 invited patients (3 men, 7 women; aged 32–85 years) participated in the study. 4 of the 10 did not have Swedish as their native language. Questionnaire data showed that most participants had sufficient levels of FHL, whereas only 4 of 10 had sufficient FDL.

From the interviews, two main thematic categories were identified: “The video call—new, but surprisingly simple” and “The video call—the patient’s choice.” Most participants described the technical solution as easy to use, even among those

with initially low confidence in their digital skills. The user-friendliness of the digital solution was regarded as highly important. Some patients required help from partners or relatives, but overall, the video calls were perceived as manageable and effective for postoperative follow-up.

Nearly all patients stated that they preferred video calls over physical visits, highlighting the convenience, time savings, and reduced need for travel. Additional advantages mentioned included environmental benefits and the flexibility for both patient and clinician. Even patients who needed assistance considered digital follow-up easier than arranging transport to the hospital.

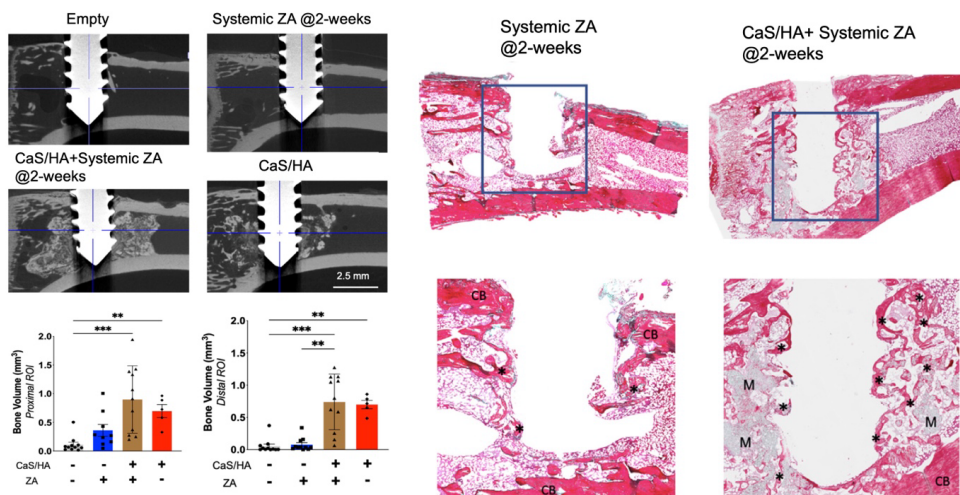
## Study IV

### **CaS/HA plus Systemic ZA Promotes Cancellous Bone Formation**

Osteoporotic status in the rat model was confirmed by micro-CT, showing significantly reduced trabecular BV/TV and increased trabecular separation in the proximal tibia.

At 6 weeks, neither the empty controls (G1) nor the systemic ZA group without biomaterial (G2) demonstrated peri-implant bone formation. The combination of CaS/HA and systemic ZA (G3) resulted in extensive cancellous bone-like formation within and around the screw threads, extending proximally and distally into the marrow cavity. The CaS/HA-only group (G4) showed remnants of biomaterial with limited new bone formation. Selected results from the study are presented in Figure 23.

Micro-CT analysis revealed the highest distal BV in G3, significantly greater than in G1 ( $P < 0.001$ ) and G2 ( $P < 0.01$ ). Proximally, both G3 and G4 had higher BV compared with G1 ( $P < 0.001$  and  $P < 0.01$  respectively). Histological analysis supported these findings, with only G3 showing substantial cancellous bone formation around the implant.



**Figure 23.** Results of bone volume assessment, based on CT imaging and histology.

Advanced imaging confirmed these observations: neutron tomography and histology showed bone-filled screw threads in G3, whereas G1 and G2 mainly contained fibrous tissue or thin bone layers. G4 demonstrated partial trabecular bone formation with residual CaS/HA material.

# Discussion

## Paper I

### Background and Rationale

During the 2000s, surgical management of DRFs advanced considerably, with VLPs and fragment-specific fixation techniques becoming widely established. In contrast, progress in the treatment of concomitant DUFs has been slower. Early studies primarily focused on recognising and classifying these injuries, while later publications began to explore treatment strategies. However, optimal management remains uncertain. DRUFs appear to increase in incidence with age, and reduced bone quality in elderly patients further complicates fixation.

When data collection for Paper I began in 2017, only a few publications on the subject existed. Biyani et al.'s seminal 1995 paper "Fractures of the distal radius and ulna" provided one of the first detailed descriptions of this fracture combination. Although based on only 19 patients (15 with follow-up), it became highly influential and introduced a classification system still used today. In their series, none of the DUFs were surgically treated.<sup>35</sup> Nearly a decade later, Ring et al. (2004) published "Condylar blade plate fixation of unstable fractures of the distal ulna associated with fracture of the distal radius", following 24 patients treated with mini condylar blade plates.<sup>132</sup> Since then, the literature on DRUFs has gradually expanded, though most studies remain small retrospective series.

The establishment of the prospective wrist fracture register in Lund enabled the creation of the largest DRUF cohort to date, providing a unique opportunity to investigate epidemiology, treatment patterns, and outcomes in detail.

### New Additions to the Epidemiology

The incidence of DRUFs among DRFs has been estimated to range between 2% and 9%.<sup>35,114,117-119</sup> By pooling the results of previous studies, 269 DRUFs were identified among 5,277 patients with DRFs only, corresponding to an incidence of 5.1%. In our study, 5,536 patients with DRFs were analysed, more than the combined total of all earlier studies, and 259 of these, corresponding to 4.7%, had a concomitant DUF. When adding the present study to the earlier literature, a total of

528 DRUFs were identified among 10,813 DRF patients, yielding a refined overall incidence estimate of 4.9% (Table 5).

**Table 5.**

Estimated incidence of DRFs with concomitant distal metaphyseal ulna fractures.

| Author           | N DRFs        | N DUFs     | % DRUFs    | Definition of DUF                       |
|------------------|---------------|------------|------------|-----------------------------------------|
| Arvidsson et al. | 5,536         | 259        | 4.7        | AO Q-modifier Q2-Q5                     |
| Huang et al.     | 2,351         | 79         | 3.4        | AO Q-modifier Q2-Q5                     |
| Herzberg et al.  | 1,279         | 116        | 9.0        | Ulnar neck, ulnar head or combined.     |
| Liang et al.     | 1,094         | 35         | 3.2        | AO Q-modifier Q2-Q5                     |
| Paksima et al.   | 512           | 11         | 2.1        | "Metaphyseal distal ulna"               |
| Biyani et al.    | 320           | 19         | 5.6        | "Distal ulna metaphysis"                |
| May et al.       | 166           | 9          | 5.4        | Distal ulna head (not shaft or styloid) |
| <b>Total:</b>    | <b>10,813</b> | <b>528</b> | <b>4.9</b> |                                         |

DRFs = Distal radius fractures, DUFs = Distal metaphyseal ulna fractures (styloid fractures excluded), DRUFs = Distal radius fractures with concomitant distal metaphyseal ulna fractures.

Our findings confirm that DRUFs predominantly affect elderly women, with a mean age of 73 years and 86% of the cohort being female.

The relatively high proportion of open fractures (16%) may be explained by the exposed anatomical position of the ulna just beneath the skin, combined with the fact that these injuries occur mainly in older individuals with thinner, more fragile skin.

## DRUFs and Patient Reported Outcome

Functionally, we observed that DRUF patients reported worse outcomes than DRF-only patients at 1 year, with nearly twice the odds of achieving a DASH score > 35 even after multivariable adjustment. This finding supports the clinical impression that DRUFs represent a distinct and more disabling injury entity than isolated DRFs. Importantly, the presence of a DRUF remained an independent predictor of poorer functional outcome even when accounting for age, comorbidity, fracture type, and treatment modality. This suggests that the additional DUF itself, rather than associated risk factors alone, contributes meaningfully to functional impairment.

In a recent study Jakobsson et al. analysed data from the SFR to examine whether socioeconomic factors, country of birth, and comorbidities predict 1-year patient-

reported outcomes after DRFs, also including a variable for DRUFs. Between April 2012 and December 2018, 48,755 eligible DRFs were registered, of which 17,478 patients (36%) completed the Short Musculoskeletal Function Assessment (SMFA) questionnaire at baseline and one year. Poor outcome was defined as SMFA-Upper Extremity  $\geq 12.5$ . Multivariable logistic regression showed that patients with DRUFs had an adjusted OR of 1.23 (95% CI 1.08–1.41,  $P = 0.002$ ) for poor outcome compared with isolated DRFs (unadjusted OR 1.45, 95% CI 1.27–1.65,  $P < 0.001$ ).<sup>191</sup>

Despite 64% non-response, incomplete SFR coverage (rising from ~50% in 2018 to 69% in 2021), and some uncertainty regarding accurate fracture classification of DRUFs<sup>191</sup>, this large registry study supports our findings that DRUFs are associated with worse 1-year outcomes. Factors most strongly associated with poor outcomes were country of birth outside the EU (OR 2.28), high-energy trauma (OR 1.76), history of anxiety or depression (OR 1.46), and CCI  $\geq 3$  (OR 1.51).<sup>191</sup> Polypharmacy, the strongest predictor in our study, was not included in their analysis.

## Clinical Implications

While the optimal management of these injuries remains debated, most authors agree that the stability of the DUF after fixation of the radius largely determines whether surgical intervention is warranted. Stable ulna fractures can often be managed non-operatively, whereas unstable fractures may require surgical stabilisation. Importantly, osteosynthesis of DUFs has been associated with a relatively high rate of reoperation, mainly due to hardware-related discomfort, and several studies have suggested that older patients with low functional demands may not benefit from ulna fixation.

Interestingly, in our study surgical fixation of the DRF (irrespective of ulna fixation) was associated with a reduced risk of poor functional outcome, suggesting that restoring radial stability is a critical determinant of recovery. By contrast, additional fixation of the ulna did not improve 1-year outcomes compared with DRF fixation alone, lending support to the view that routine ulna fixation may not be necessary unless instability persists after radius fixation.

Taken together, our findings reinforce and extend existing evidence. First, we confirm the relatively low incidence (~5%) of DRUFs among DRFs and that this subgroup constitutes mainly of older women. Second, we provide large-scale support for the notion that treatment decisions should prioritise the radius fracture, with ulna fixation reserved for selected patients with unstable cases.

In line with other research, our findings demonstrate that long-term outcomes after DRFs are influenced not only by fracture characteristics but, to a greater extent, by patient-related factors such as comorbidity burden and polypharmacy. These factors often outweigh traditional fracture classification in predicting recovery,



underscoring the importance of individualised treatment strategies, particularly in elderly and multimorbid patients, to balance surgical risks with functional recovery potential.

## Limitations

This study has several limitations that should be acknowledged. Firstly, the registry-based design inherently relies on the accuracy and completeness of reported data. Importantly, there is no complete registration of all patients presenting to the emergency department in Lund during the study period to compare with our inclusion. Therefore, it cannot be ruled out that some eligible patients were missed. Despite careful efforts to verify radiographs of all patients with ICD-coded DRFs before inclusion in the register, and the additional radiological confirmation that all DRUFs had metaphyseal DUFs in addition to the DRF, the possibility of misclassification or underreporting cannot be completely excluded. Although the dataset for the main analysis was complete, some variables representing potential confounding factors contained missing data. While the extent of missing data is presented, its potential influence on the results cannot be fully determined.

Second, as with all observational studies, the associations identified cannot be interpreted as causal, and despite adjustments for relevant covariates, residual confounding remains possible. For example, variables such as bone quality, handedness, and socioeconomic status were not available in the dataset.

Selection bias is also a concern, since patients who did not complete the DASH questionnaire may differ systematically from responders. An analysis of non-responders was performed by Landgren et al. regarding the patients included 2003–2012<sup>186</sup>, but no updated analysis was presented in paper I. A non-responder analysis performed after publication confirmed the findings of the previously reported analysis. A higher proportion of women and a slightly higher proportion of older patients completed the 1-year DASH questionnaire. However, no significant difference in response rate was observed between patients with DRUFs and those with an isolated DRF (Table 6).

Furthermore, although ulnar styloid fractures were excluded, DUFs remain a heterogeneous group, and treatment strategies varied. Differences in surgical techniques, rehabilitation protocols, and clinical decision-making could have influenced outcomes. Despite the relatively large sample size, the study population was not sufficient to allow meaningful sub-analyses within the DRUF group.

The study period spanned 15 years (2003–2018), during which surgical implants underwent considerable development. Although we found no linear increase in the proportion of surgically treated patients during this period, potential temporal variation in the distribution of surgeons and implant types may also have affected outcomes.

**Table 6.**

1-year DASH non-responder analysis among patients included in the Lund Wrist Fracture Register, 2003–2018 (total patients, n = 5,536, total valid DASH, n = 3819 (69%).

|                                                                                                                                          | <b>DRF-only</b>  | <b>DRUFs</b>   | <b>P-value</b> |
|------------------------------------------------------------------------------------------------------------------------------------------|------------------|----------------|----------------|
| <b>Valid DASH (%)</b>                                                                                                                    | 3653 (69)        | 166 (64)       | 0.09           |
| <b>All DRFs in the register</b>                                                                                                          |                  |                |                |
|                                                                                                                                          | <b>Females</b>   | <b>Males</b>   |                |
| <b>Valid DASH (%)</b>                                                                                                                    | 3078 (71)        | 741 (61)       | <0.001         |
|                                                                                                                                          | <b>Age 18-64</b> | <b>Age 65+</b> |                |
| <b>Valid DASH (%)</b>                                                                                                                    | 1872 (68)        | 1947 (70)      | 0.04           |
| DASH = Disability of the Arm, Shoulder and Hand, DRF = distal radius fracture, DRUF = distal radius and distal metaphyseal ulna fracture |                  |                |                |

Finally, functional outcomes were assessed using the DASH score at a single time point (1 year). While DASH is a validated and widely used patient-reported outcome measure, it is relatively unspecific and can be influenced by comorbidities unrelated to the fracture. In the adjusted regression analysis, where age was included as a covariate, patients with DRUFs fractures still demonstrated worse functional outcomes compared with those with isolated DRFs. However, it is important to note that DASH scores are known to increase with age, which may confound interpretation in an elderly cohort, even after statistical adjustment. The absence of long-term follow-up further limits insight into late complications, functional decline, or implant-related issues.

Taken together, these limitations indicate that, although the findings provide valuable large-scale evidence regarding the impact of DRUFs, they should be interpreted with caution. Future prospective studies with standardised treatment protocols and extended follow-up, or preferably RCTs, are warranted.

## Paper II

### Survival after DRFs in Super-elderly

In Paper II, we examined survival after DRFs in patients aged 80 years and older. The main finding was that super-elderly patients had substantially lower short-term mortality than expected, with a 1-year SMR of 0.44 compared with the general Swedish population. At 5 years, mortality was in line with population expectations (SMR 0.96). Importantly, non-fracture-related factors, particularly type of living,

emerged as the strongest predictors of survival, whereas chronological age (treated as a continuous variable) and sex were not significant determinants.

## **Comparison with Previous Studies**

Our results align with several population-based studies showing that elderly women, and in some cases elderly patients in general, do not experience excess mortality after DRFs.<sup>103-105,109</sup> Korean registry data have consistently demonstrated that older women after sustaining DRFs, particularly in the 70–79 and 90–100 year age groups, have lower-than-expected mortality, while men contribute disproportionately to excess deaths.<sup>103</sup> Similarly, Medicare data from the United States revealed reduced mortality after isolated DRFs compared with an age- and sex-matched general population,<sup>105</sup> and a Swedish Malmö study found no excess mortality after forearm fractures, in contrast to hip, vertebral, and shoulder fractures.<sup>109</sup> The present findings extend these observations by showing that even among the very old ( $\geq 80$  years), short-term survival after DRFs is not compromised but may, in fact, be better than expected.

However, not all studies are concordant. A U.S. cohort of 325 elderly patients reported lower-than-expected survival over seven years, particularly among men and individuals with comorbidities.<sup>106</sup> Our study does not cover that time span, but at the 5-year analysis, survival was no longer better and was instead comparable to that of the general population. Consistent with that study, our multivariable analysis confirmed that frailty-related factors, such as assisted living, nursing home residence, and a higher comorbidity burden, were strongly associated with worse outcomes.

## **Relevance of DRUFs**

Interestingly, in a cohort study of 13 million Canadian adults aged 65 years and older, DRUFs were associated with increased mortality, whereas isolated DRFs were not.<sup>100</sup> This finding supports our hypothesis put forward in Paper I that the subgroup with DRUFs represents an older and more frail population than the patients with a DRF only.

## **Interpretation of Lower-than-expected Mortality**

The observed 1-year SMR of 0.44 may indicate that individuals sustaining DRFs represent a relatively healthier and more active subgroup of the elderly population. Being capable of protecting themselves during a fall by using an outstretched hand indicates preserved reflexes, balance, and mobility. The fracture may also act as a sentinel event, leading to healthcare contact that facilitates detection of underlying

conditions such as osteoporosis, or to the initiation of fall-prevention strategies. Thus, DRFs in the elderly may be more appropriately regarded as a marker of relative robustness rather than a causal protective factor. This appears particularly applicable to independent older women.

## **Clinical Implications**

Clinically, this may be important to consider when assessing elderly patients with DRFs. Treatment should be tailored to functional status and activity level rather than chronological age alone. Moreover, the DRF itself can serve as a trigger for discussion on preventive care: Is there underlying osteoporosis? Should pharmacological treatment be initiated? Can future falls be prevented? In this way, the fracture event may offer an opportunity to protect the individual from subsequent morbidity and mortality.

## **Limitations**

This study has several limitations. First, the relatively small sample size (240 patients aged  $\geq 80$  years with DRFs) limits statistical power.

The cohort consisted predominantly of women, meaning that the findings primarily reflect outcomes in elderly females and should not be directly generalised to men. However, this sex distribution also lends credibility to the results, as several previous studies have similarly reported lower-than-expected mortality particularly among elderly women with DRFs. The consistency across studies supports the likelihood that our findings reflect a true pattern.

However, certain factors may still limit their broader applicability. The study was restricted to patients treated at a single centre in southern Sweden, within the catchment area of Lund University Hospital. Only patients captured in the registry who met inclusion criteria were analysed; individuals with unregistered or undiagnosed fractures may have been missed. Although most patients with an evident fracture are likely to present to the orthopaedic emergency department, at least for cast treatment, it is possible that the very oldest and frailest individuals were managed at home without orthopaedic involvement. As with all registry-based research, the validity of the results also depends on the accuracy and completeness of the recorded data.

Moreover, the study population of elderly residents in Lund may differ systematically from other populations in terms of comorbidity profiles, access to healthcare, ethnicity, and socioeconomic status. While the use of an age- and sex-matched national population provides a reasonable comparator, it does not account for potential differences in comorbidity burden, baseline frailty, functional status, or socioeconomic conditions, and residual confounding is possible. One potential

explanation for the lower mortality observed in our cohort is that Lund municipality is considered to have a relatively high socioeconomic status compared with the Swedish national average. This could theoretically bias the SMR estimate downward. However, when recalculating the SMR using the local Lund population as the reference, results were very similar (SMR 0.46, 95% CI 0.23–0.82,  $P = 0.005$ ), suggesting that socioeconomic differences are unlikely to fully explain the main findings.

## Paper III

### Main Findings

This study provided insight into patients' perceptions of digital, video-based follow-up after DRF surgery. Most patients viewed video follow-up positively, and some even preferred it over traditional in-person visits, despite the majority demonstrating low digital literacy.

### Critical Challenges Fuelling Innovation

During the pandemic there was a sudden demand for remote medical consultations.<sup>161</sup> However, it is interesting to note that “remote follow-up” was treated as a relatively new phenomenon even though telephone-based follow-ups have long been a standard practice in clinical care, and literally is the prime example of telemedicine.<sup>192</sup>

The extraordinary circumstances during the pandemic created a situation in which healthcare systems rapidly adopted digital solutions, deviating from standard regulations. Normally it is hard to implement new systems in health care,<sup>160</sup> but discussions focusing on legal aspects, privacy regulations and how to verify patient identities during digital meetings were set aside, as if operating under a “silent approval”. This catalysed rapid experimentation with video-based follow-ups.<sup>161,192</sup>

### Telemedicine: Access and Acceptance

During the COVID-19 pandemic, previously telehealth-naïve fracture clinics rapidly integrated virtual consultations, even for older patients less familiar with digital technologies. Within weeks, digital meetings accounted for up to half of all appointments at some fracture clinics in the US, without an increase in no-show rates.<sup>193</sup> Virtual fracture clinics proved to enable safe management of selected

injuries, improving efficiency, reducing waiting times, and generating cost savings without compromising patient safety or outcomes.<sup>193-195</sup>

Several studies have reported high patient satisfaction with video consultations during this period, particularly when patients already had established relationships with their clinicians.<sup>196,197</sup> For instance, a French study found that 80% of patients viewed teleconsultations positively and 70% considered them equivalent to in-person visits, though most still said they probably preferred face-to-face encounters once restrictions were lifted.<sup>159</sup> Similarly, over 80% of U.S. arthroplasty patients expressed satisfaction with telemedicine visits, especially younger individuals, those facing long commutes, or those familiar with their providers.<sup>197</sup> Physiotherapists in Ireland also emphasised the flexibility, reduced travel, and lower infection risk offered by telehealth, while noting the limited physical examination as a key drawback.<sup>198</sup>

Consistent with these findings, our study demonstrated that most patients perceived video-based follow-up after DRF surgery positively, appreciating its convenience and the time saved from reduced travel.

Importantly, we observed that the usability of the digital system played a critical role: if the video consultation was straightforward and did not require advanced logins or complicated software, patients, including older individuals and those inexperienced with technology, were generally satisfied. This underscores that the technical design and ease-of-use of telemedicine platforms are essential determinants of acceptance. This finding is also in line with other studies; in a U.S. study involving 253 respondents from both healthcare professionals and the general public agreed that technology not working properly were the main source of frustration with telehealth.<sup>192</sup>

International evidence from the COVID-19 pandemic indicates that access to telehealth was not equal across populations. Rural residents were significantly less likely than urban residents to use video or phone-based medical appointments, and disparities by age and race were also observed, with younger patients and certain racial groups less likely to access video visits. One possible explanation for this is limited access to smartphones and broadband internet.<sup>199,200</sup> In Sweden, however, these barriers are probably smaller, as internet access is widespread (97% of the population) and most people (95%) use BankID for secure identification, providing a strong foundation for broad adoption of digital healthcare.<sup>201,202</sup>



**Figure 24.** Patients, including older and less tech-savvy ones, were satisfied when video consultations were simple and user-friendly.

### **Digital Follow-up – A Temporary Success?**

Overall, healthcare professionals' attitudes toward digital follow-ups improved during the COVID-19 pandemic, and many recognised eHealth as useful for patient monitoring and cost reduction.<sup>158</sup> Telemedicine was generally seen as helpful, but concerns regarding safety, incomplete clinical assessments, and regulatory compliance remained.<sup>158,203</sup> Consequently, after the pandemic, many clinicians returned to in-person visits, particularly for initial consultations.<sup>203</sup> A survey from the US also showed that both clinicians and patients generally favoured standard voice-only telephone visits for remote follow-up care.<sup>192</sup>

Orthopaedic patients' positive attitudes toward digital follow-ups have also been shown to decrease after the pandemic,<sup>204</sup> and even evidence from the time of the pandemic suggests that many patients would prefer traditional in-person visits once the extraordinary circumstances were lifted.<sup>159</sup>

## **Limitations**

The study was conducted during the COVID-19 pandemic, which limits its generalisability. During this period, patients were highly motivated to adapt to the rapid expansion of digital care as part of a collective effort to reduce the risk of infection. This context may have influenced patient attitudes in ways that do not necessarily reflect those in a non-pandemic setting.

It is also important to note that all participants agreed to digital follow-up; this inherently biases the findings, as the study population was already positively inclined toward the intervention.

The questionnaire developed to assess FDL was created specifically for this study. Although it provided an indication of the patients' digital ability, it has not been previously used or validated, which limits the certainty of the interpretation.

Due to the limited number of surgeries performed during the pandemic, patient recruitment was challenging, resulting in a relatively small sample size. Nevertheless, the cohort included a broad range of ages (32–85 years), both sexes, and participants from diverse cultural backgrounds. Instead of extending the recruitment period, the study was intentionally completed within the timeframe it represented, a period that could have rapidly changed or worsened, since we believed the findings to be contextually relevant despite the limited sample.

## **Paper IV**

### **Main Findings**

Our results demonstrate that the combination of CaS/HA augmentation and delayed systemic ZA administration markedly increased peri-implant bone formation compared with either treatment alone. These findings support the concept that synthetic HA particles can function not only as an osteoconductive scaffold but also as a local recruiting matrix for circulating bisphosphonates, thereby enhancing bone regeneration around implants.

### **Clinical Translation to Fragility Fractures**

Beyond the primary aim, the translational potential was also explored in a small cohort of intertrochanteric femur fracture patients, demonstrating increased peri-implant BMD and suggesting feasibility in a clinical setting. Hip fractures represent one of the most clinically relevant challenges in osteoporotic fracture care, where implant anchorage in fragile cancellous bone is associated with high complication rates.<sup>166</sup>



Although the screws used in the rat model are the same as those used in DRF surgery, and the tibial environment could theoretically resemble fixation in metaphyseal bone of the distal radius, the clinical and socioeconomic burden is substantially greater for hip fractures.<sup>205</sup> Hip fracture patients are typically frailer, and the injury is associated with higher morbidity and mortality compared with DRFs.<sup>100</sup> Consequently, from both a clinical and socioeconomic perspective, the incentive to develop effective adjuncts to existing fixation methods is considerably greater in hip fracture patients than in those with wrist fractures.

The translational relevance of the results is considerable. Poor anchorage and fracture fixation failure is a feared complication in fragile cancellous bone. The findings highlight a promising regenerative medicine strategy to improve fracture fixation, which in turn could reduce revision rates and morbidity in elderly fracture patients. Importantly, both CaS/HA biomaterials and ZA are already approved for clinical use, potentially facilitating future clinical translation. While these preliminary results are promising, larger clinical studies are needed to confirm efficacy, optimize ZA timing and dosing.

## **Limitations**

First, each experimental group comprised a relatively small number of rats, which may limit statistical power and render the findings more susceptible to random variability.

Second, the OVX rat model, although widely used, does not fully replicate the structural, metabolic, or biomechanical characteristics of osteoporotic human bone. Furthermore, the tibial implantation site does not fully mimic the challenging mechanical environment of human intertrochanteric femur fractures, the clinical context in which the method was further evaluated. This suggests that, while the model provides valuable insights, which can and have been evaluated in human series, its translational relevance may vary depending on the clinical fracture site considered.

The study relied on radiological and histological assessment of bone volume, without direct evaluation of mechanical fixation strength, such as pull-out or torque testing. This limits conclusions regarding the functional stability of the implants. Bone volume was therefore used as a proxy. Moreover, although rats generally exhibit faster bone healing than humans, a six-week follow-up period does not fully capture long-term remodelling, material resorption, or fixation durability.

Finally, the use of a single ZA dosing regimen at a fixed time point does not account for potential variability in clinical practice or patient pharmacokinetics.

# Conclusion

## Main Conclusions

### **Strong Women and the DRF-spectrum of Fragility**

Findings from our mortality study, supported by previous evidence, suggest that a DRF (particularly an isolated DRF) in an older adult may serve as a marker of better overall health and preserved function. In contrast to those who sustain hip or proximal humerus fractures following a fall, these individuals appear to retain protective reflexes and functional balance.

Our results indicate that when an older patient, particularly an independent woman, sustains this type of fracture, she is likely to have a considerable remaining life expectancy. Treatment should be individualised, with surgical decisions guided by functional status rather than chronological age. Regardless of whether management is surgical or non-surgical, the primary goal should be to promote a rapid return to independence and an active lifestyle, as these patients are expected to live for many years.

In contrast, DRUFs appear to represent the opposite end of the spectrum, a fragility injury more characteristic of the frail elderly. Although we did not observe any significant difference in comorbidity between the DRUF and DRF-only groups in our study, the DRUF group likely represents a more frail population, largely related to their higher age. Much attention has been given to the presence of osteoporosis in these patients, and it is plausible that osteoporosis is both more prevalent and more severe in this group, although, to our knowledge, this has not yet been systematically studied. Many of these patients likely belong to a subgroup with reduced physiological reserve, and their prognosis is correspondingly poorer than that of patients with isolated DRFs; however, our adjusted analysis indicates that the fracture type itself also appears to contribute to the worse outcome.

### **Digital Tools, the Simpler the Better**

The COVID-19 pandemic served as a catalyst for innovation in digital healthcare, including the introduction of digital follow-up after wrist fracture surgery. Under the extraordinary circumstances of the pandemic, this approach proved both feasible

and effective. However, much of the momentum for digital development slowed once pre-pandemic regulatory frameworks returned.

Our study suggests that interest in digital follow-up is high across all age groups, including among patients with low digital literacy, primarily due to its convenience and the considerable time savings achieved by avoiding travel.

Importantly, patients emphasised that digital systems must be intuitive and easy to use in order to be appreciated. When login procedures are complicated or technical issues are frequent, motivation and engagement decline rapidly. Ensuring user-friendly and accessible digital platforms will therefore be essential if virtual follow-up is to remain a sustainable component of postoperative care.

### **Surgery in Elderly: Balancing Benefit, Risk, and Innovation**

Many studies suggest that surgical treatment, even in older adults, leads to a faster recovery. There is also evidence that surgically treated patients are more content, despite functional outcome. However, determining which elderly patients truly benefit from surgery after a DRF remains complex. In the context of limited healthcare resources, treatment strategies must balance costs and surgical risks against potential functional gains. At 1- and 2-year follow-up, functional outcomes after surgery appear comparable to those achieved with conservative management. Furthermore, existing studies often include highly heterogeneous “older” populations, typically those aged 60 years and above, further complicating the interpretation of results<sup>70,77,87,206</sup>.

Our findings strengthen previous evidence suggesting that fixation of a concomitant metaphyseal DUFs does not seem to improve outcomes in elderly DRF-patients, whereas surgical fixation of the DRF is associated with better recovery. These observations emphasise the importance of prioritising restoration of radial stability in DRUF-patients while carefully balancing the risks and benefits of additional procedures in distal ulna, especially in frail or multimorbid individuals.

One of the known challenges of plate osteosynthesis in osteoporotic bone is the risk of implant loosening, which may compromise fixation stability and outcomes. In this context, our experimental and early clinical work introduces a novel method for implant augmentation. The technique has shown promising results both in a preclinical rat model and in a small cohort of patients with pertrochanteric hip fractures. Cas/HA functions as both a bone substitute reinforcing the bone-implant interface and an attractant for systemically administered ZA, leading to enhanced bone formation around screw threads in fragile bone. This approach may represent a step toward improving implant anchorage in osteoporotic bone, potentially expanding the surgical options for elderly patients with high functional aspirations.



**Figure 25.** There is a quote that says: 'Here's to strong women – may we know them, may we be them, may we raise them.' Based on the findings of this thesis, I would like to add: 'may we treat them well'.

## Future Perspective

### **Next Steps: Building on the Findings of This Thesis**

The studies presented in this thesis highlight several possibilities for further research.

The mortality study yielded interesting and partly unexpected findings, but these are based on a relatively small cohort. A natural next step would be to test the hypothesis in a larger population to improve generalisability and robustness of the results.

The current body of evidence regarding whether an unstable DUF should be surgically fixed in elderly patients or those with moderate functional capacity suggests that fixation does not confer clear benefits. However, the available evidence is very limited. A valuable next step would be to conduct an RCT, with the null hypothesis stating no difference in return to pre-injury activity levels, pain, ROM, or complication rates between patients with an unfixed, compared with a surgically stabilised, DUF, alongside DRF fixation. Given the relative rarity of this fracture combination, registry-based randomisation via the Swedish Fracture Register could facilitate patient inclusion.

A natural next step following our study on digital follow-up after wrist surgery is to explore its role in a post-pandemic context. Will the positive perceptions among patients and healthcare providers persist when digital solutions are no longer driven by necessity? Many envision a digital follow-up as a potential future standard, sparing patients unnecessary travel and improving the efficiency of healthcare resource utilisation. However, realising this potential will be challenging unless both clinicians and patients are motivated to embrace these solutions. Understanding current attitudes toward digital follow-up is therefore essential to inform its successful implementation. Furthermore, it must be ensured that the method yields outcomes equivalent to those of conventional in-person visits in our context.

Regarding the novel method for implant augmentation in osteoporotic bone, future studies should first focus on preclinical optimisation, using larger animal cohorts to determine the optimal dosing and timing of ZA for maximal peri-implant bone formation. Subsequently, the approach should be systematically evaluated in clinical settings, ideally through larger RCTs to assess both peri-implant bone response and functional implant integration. Biomechanical testing should also be included to confirm implant stability. These steps will be essential to establish the translational potential and clinical utility of the developed method.

## **The Broader Future of Distal Radius Fracture Care in the Elderly**

The research field of DRF treatment in the elderly has countless opportunities for further exploration. First, the question of whether elderly patients should undergo surgery remains controversial. Although VLP fixation often results in faster recovery and an earlier return to daily activities,<sup>77,81,87,206</sup> many studies suggest that surgery does not lead to long-term functional advantage.<sup>77,87</sup>

The CROSSFIRE study concludes that there is “sufficient evidence” to discourage surgical intervention for displaced type 23A and 23C DRFs in patients aged 60 years and older, yet it also reported higher patient satisfaction among those treated surgically despite no clinically relevant measurable functional differences.<sup>87</sup>

The greater contentment reported by surgically treated patients<sup>87</sup> may reflect a perception of surgery as a more definitive solution or arise from psychosocial factors, such as feeling actively treated, having the reassurance that no available treatment was withheld, or other aspects not captured by conventional outcome measures, highlighting the importance of addressing these dimensions in future research.

“Elderly” patients, often defined as those over 60-65, constitute a highly heterogeneous group, yet most studies treat them as uniform. There is evidence that VLP-fixation leads to a faster return to previous activities<sup>86,207</sup>. While younger seniors might clearly benefit from faster recovery, even very old patients often value early restoration of independence and quality of life. It would be interesting to further investigate what an earlier return to function after surgery truly means from the patients’ perspective. Research is traditionally designed for presentation to physicians, but it would be equally compelling to design studies in ways that make the findings meaningful and understandable to the patients.

Exploring the patient experience of decision-making is another interesting field. What do the elderly consider most important? Person-centred care is a widely cited ideal, but what does it truly entail? And how do patients wish to be involved in their care? Understanding these perspectives could transform both research and clinical practice.

One rationale for avoiding surgical management in older patients is that it consumes healthcare resources without offering substantial additional benefit. However, existing economic evaluations focus primarily on direct hospital costs, such as surgery and inpatient care, while broader societal costs, such as prolonged dependence, need for home assistance, lost productivity and sick leave are rarely considered.<sup>70,75</sup> Incorporating these indirect costs would allow for a more comprehensive assessment of the true economic and societal impact of different treatment strategies for DRF treatment in the elderly.

Moreover, much attention has historically focused on surgical interventions, yet non-surgical management, the most common approach, also deserves evaluation. If

the goal is to maximise clinical impact, research efforts should prioritise the treatment strategy most frequently used in practice. Often, surgical patients receive additional follow-up and attention by default, but what is the best way to monitor and support those treated non-operatively?

The global elderly population is increasing rapidly, bringing both challenges and opportunities for improving care in the face of limited resources. This thesis provides a foundation for continued exploration. My hope is that it will inspire others to approach the care of older adults with DRFs with pride and dedication, to advance research that enhances outcomes, and to meaningfully involve patients in their treatment and in the studies that will shape the care of future generations.



**Figure 26.** My grandmother, 86 years in this picture, a so called “super-elderly”. Quality of life, and the path to it, look different for different people. Photo: Linnea Arvidsson.

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## Use of AI

All original text was written without AI assistance. Artificial intelligence, in the form of ChatGPT, was used for proofreading, language adjustment to British English, formatting in accordance with JAMA style, and the creation of the cover image. Midjourney was used to create the cover picture.

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# Appendix





## Hälsoenkät (arm/axel/hand)

sida 1/3

Denna enkät berör Dina symtom och Din förmåga att utföra vissa aktiviteter.

Svara på **varje fråga**, baserat på hur Du har mått **den senaste veckan**, genom att kryssa för ett svarsalternativ för varje fråga.

Om det är någon aktivitet Du inte har utfört den senaste veckan får Du kryssa för det svar som Du bedömer **stämmer bäst** om Du hade utfört aktiviteten.

Det har ingen betydelse vilken arm eller hand Du använder för att utföra aktiviteten. Svara baserat på Din förmåga oavsett hur Du utför uppgiften.

|                                                                                                                                                       | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt att göra        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Öppna en ny burk, eller hårt sittande lock                                                                                                         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Skriva                                                                                                                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Vrida om en nyckel                                                                                                                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Förbereda en måltid                                                                                                                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Öppna en tung dörr                                                                                                                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Lägga upp något på en hylla över Ditt huvud                                                                                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Utföra tunga hushållssysslor (t ex tvätta golv och väggar, putsa fönster, hänga tvätt)                                                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Trädgårdsarbete                                                                                                                                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Bädda sängen                                                                                                                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Bära matkassar eller portfölj                                                                                                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Bära tunga saker (över fem kilo)                                                                                                                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Byta en glödlampa ovanför Ditt huvud                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Tvätta eller föna håret                                                                                                                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Tvätta Din rygg                                                                                                                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Ta på en tröja                                                                                                                                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Använda en kniv för att skära upp maten                                                                                                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Fritidsaktiviteter som kräver liten ansträngning (t ex spela kort, sticka, boule)                                                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Fritidsaktiviteter som tar upp viss kraft eller stöt genom arm, axel eller hand (t ex spela golf, använda hammare, spela tennis, skytte, bowling) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Fritidsaktiviteter där Du rör på armen fritt (t ex spela badminton, simma, gympa)                                                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 20. Färdas från en plats till en annan                                                                                                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 21. Sexuella aktiviteter                                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

22. Under **de senaste sju dagarna**, i vilken utsträckning har Dina arm-, axel- eller handproblem störst  
Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?

☐ Inte alls      ☐ Lite      ☐ Måttligt      ☐ Mycket      ☐ Världigt mycket

23. Under **de senaste sju dagarna**, i vilken utsträckning har Dina arm-, axel- eller handproblem störst  
Ditt vanliga arbete eller andra dagliga aktiviteter?

☐ Inte alls      ☐ Lite      ☐ Måttligt      ☐ Mycket      ☐ Världigt mycket

Ange svårighetsgraden på Dina symtom **de senaste sju dagarna**:

|                                                                | Ingen                    | Lätt                     | Måttlig                  | Svår                     | Mycket<br>svår           |
|----------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 24. Värk/smärta i arm, axel eller hand                         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 25. Värk/smärta i arm, axel eller hand i samband med aktivitet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 26. Stickningar (sockerdricks känsla) i arm, axel eller hand   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 27. Svaghet i arm, axel eller hand                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 28. Stelhet i arm, axel eller hand                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

29. Har Du haft svårt att sova, under **de senaste sju dagarna**, på grund av värk/smärta i arm, axel eller hand?

☐ Inte alls    ☐ Viss svårighet    ☐ Måttlig svårighet    ☐ Stor svårighet    ☐ Mycket stor svårighet

30. Jag känner mig mindre kapabel, har sämre självförtroende eller känner mig mindre behövd på grund av mina arm-, axel- eller handproblem.

☐ Instämmer absolut inte    ☐ Instämmer inte    ☐ Vet inte    ☐ Instämmer    ☐ Instämmer absolut

Följande frågor rör hur mycket Dina arm-, axel- eller handproblem påverkat Din förmåga att arbeta (inklusive hushållsarbete om detta är Ditt huvudsakliga arbete).

Arbetar Du? ☐ Ja ☐ Nej

Om Du inte arbetar kan Du hoppa över de följande fyra frågorna

Ange här Ditt arbete

Kryssa för det påstående som bäst stämmer in på Din kroppsliga förmåga **de senaste sju dagarna**.

| Hade Du någon svårighet att:                                                    | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt                 |
|---------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. använda Din vanliga teknik för att arbeta?                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. utföra Ditt ordinarie arbete på grund av värk/smärta i arm, axel eller hand? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. utföra Ditt arbete så bra som Du skulle vilja?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. utföra Ditt arbete på den tid Du brukar använda?                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Följande frågor rör hur mycket Dina arm-, axel- eller handproblem påverkat Din förmåga att spela musikinstrument och/eller utöva idrott.

Spelar Du något musikinstrument eller utövar någon idrott? ☐ Ja ☐ Nej

Om Du inte spelar något musikinstrument eller utövar någon idrott kan Du hoppa över resterande frågor

Om Du spelar mer än ett musikinstrument eller utövar mer än en idrott ska Du svara med avseende på den aktivitet som är viktigast för Dig.

Ange här det musikinstrument eller den idrott som är viktigast för Dig

Kryssa för det påstående som bäst stämmer in på Din kroppsliga förmåga **de senaste sju dagarna**.

| Hade Du någon svårighet att:                                                | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt                 |
|-----------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. använda Din vanliga teknik för att spela instrument/idrotta?             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. spela instrument/idrotta på grund av värk/smärta i arm, axel eller hand? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. spela instrument/idrotta så bra som Du skulle vilja?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. använda lika mycket tid som vanligt för att spela instrument/idrotta?    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |





## Hälsoenkät (arm/axel/hand)

Denna enkät berör Dina symtom och Din förmåga att utföra vissa aktiviteter.

Svara på **varje fråga**, baserat på hur Du har mått **den senaste veckan**, genom att kryssa för ett svarsalternativ för varje fråga.

Om det är någon aktivitet Du inte har utfört den senaste veckan får Du kryssa för det svar som Du bedömer **stämmer bäst** om Du hade utfört aktiviteten.

Det har ingen betydelse vilken arm eller hand Du använder för att utföra aktiviteten. Svara baserat på Din förmåga oavsett hur Du utför uppgiften.

|                                                                                   | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt att göra        |
|-----------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Öppna en ny burk eller hårt sittande lock                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Utföra tunga hushållssysslor (t ex tvätta golv, putsa fönster, hänga tvätt)    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Bära matkassar eller portfölj                                                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Tvätta Din rygg                                                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Använda en kniv för att skära upp maten                                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Fritidsaktiviteter där Du rör armen fritt (t ex spela badminton, simma, gympa) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

7. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?

☐ Inte alls      ☐ Lite      ☐ Måttligt      ☐ Mycket      ☐ Väldigt mycket

8. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga arbete eller andra dagliga aktiviteter?

☐ Inte alls      ☐ Lite      ☐ Måttligt      ☐ Mycket      ☐ Väldigt mycket

Ange svårighetsgraden på Dina symtom **den senaste veckan**:

|                                                              | Ingen                    | Lätt                     | Måttlig                  | Svår                     | Mycket svår              |
|--------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 9. Värk/smärta i arm, axel eller hand                        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Stickningar (sockerdricks känsla) i arm, axel eller hand | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

11. Har Du haft svårt att sova, under **den senaste veckan**, på grund av värk/smärta i arm, axel eller hand?

☐ Inte alls    ☐ Viss svårighet    ☐ Måttlig svårighet    ☐ Stor svårighet    ☐ Mycket stor svårighet

Följande frågor rör hur mycket Dina arm-, axel- eller handproblem påverkat Din förmåga att arbeta (inklusive hushållsarbete om detta är Ditt huvudsakliga arbete).

Arbetar Du? ☐ Ja ☐ Nej

Om Du inte arbetar kan Du hoppa över de följande fyra frågorna

Ange här Ditt arbete

Kryssa för det påstående som bäst stämmer in på Din kroppsliga förmåga **den senaste veckan**.

| Hade Du någon svårighet att:                                                    | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt                 |
|---------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. använda Din vanliga teknik för att arbeta?                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. utföra Ditt ordinarie arbete på grund av värk/smärta i arm, axel eller hand? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. utföra Ditt arbete så bra som Du skulle vilja?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. utföra Ditt arbete på den tid Du brukar använda?                             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Följande frågor rör hur mycket Dina arm-, axel- eller handproblem påverkat Din förmåga att spela musikinstrument och/eller utöva idrott.

Spelar Du något musikinstrument eller utövar någon idrott? ☐ Ja ☐ Nej

Om Du inte spelar något musikinstrument eller utövar någon idrott kan Du hoppa över resterande frågor

Om Du spelar mer än ett musikinstrument eller utövar mer än en idrott ska Du svara med avseende på den aktivitet som är viktigast för Dig.

Ange här det musikinstrument eller den idrott som är viktigast för Dig

Kryssa för det påstående som bäst stämmer in på Din kroppsliga förmåga **den senaste veckan**.

| Hade Du någon svårighet att:                                                | Ingen svårighet          | Viss svårighet           | Måttlig svårighet        | Stor svårighet           | Omöjligt                 |
|-----------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. använda Din vanliga teknik för att spela instrument/idrotta?             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. spela instrument/idrotta på grund av värk/smärta i arm, axel eller hand? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. spela instrument/idrotta så bra som Du skulle vilja?                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. använda lika mycket tid som vanligt för att spela instrument/idrotta?    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

| <b>Questionnaire: Functional Digital Literacy (FDL)</b>                                                                                                               |        |           |       |        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|-------|--------|
| A. Do you find it difficult to use digital devices (eg computer, smartphone, tablet) because you do not understand how they work?                                     |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| B. Do you find it difficult to keep up with the digital development that is taking place in society?                                                                  |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| C. Do you find it difficult to learn how to use new applications or programs (such as applications on your computer, smartphone or tablet)?                           |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| D. Do you find it difficult to solve problems that may arise around programs or applications on digital devices (programs on the computer or apps on the smartphone)? |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| E. Do you sometimes ask another person to help you with (or explain how to use) new programs or applications for a computer, phone or tablet?                         |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| <b>Questionnaire: Functional Health Literacy (FHL)</b>                                                                                                                |        |           |       |        |
| A. Do you think that it is difficult to read health information because the text is difficult to see (even if you have glasses or contact lenses)?                    |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| B. Do you think that it is difficult to understand word or numbers in health information?                                                                             |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| C. Do you think that it is difficult to understand the message in health information?                                                                                 |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| D. Do you think that it takes a long time to read health information?                                                                                                 |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| E. Do you ever ask someone else to read and explain health information?                                                                                               |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| Score system: Never = 1, Seldom = 2, Sometimes = 3, Often = 4, Always = 5                                                                                             |        |           |       |        |



# Paper I





## Double trouble! Concomitant distal ulna fractures predict worse 1-year outcome in distal radius fractures: a registry-based cohort study of 5,536 patients

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**Background and purpose** — Data on distal radius fractures (DRFs) with concomitant metaphyseal distal ulna fractures is limited. We aimed to determine whether a combined DRF and distal ulna fracture (DRUF) predicts a worse patient-reported outcome, measured by the Disabilities of the Arm, Shoulder, and Hand (DASH) score, 1 year after injury.

**Methods** — This prospective registry-based cohort study included 5,536 adult patients with a DRF between 2003 and 2018. The 1-year DASH scores were recorded. All DRUFs were identified. Multivariable binary logistic regression assessed whether the presence of a distal ulna fracture predicted a 1-year DASH score > 35, indicating severe upper-extremity symptoms.

**Results** — 259 of 5,536 patients (4.7%) had a DRUF. Their mean age was 73 years (SD 15), and 86% were women. The median 1-year DASH score was higher in the combined fracture group compared with those with a DRF only (23, interquartile range [IQR] 5–45] vs 9, IQR 2–27,  $P < 0.001$ ). A DRUF increased the odds of a 1-year DASH > 35 by 97% (OR 1.97, 95% confidence interval [CI] 1.40–2.75,  $P < 0.001$ ). Surgical fixation of the DRF in DRUF patients was associated with lower odds of a worse outcome (OR 0.44, CI 0.23–0.85,  $P = 0.02$ ). Distal ulna fracture fixation did not affect 1-year DASH ( $P = 0.7$ ).

**Conclusion** — The odds of having a DASH > 35, indicating severe symptoms, almost doubled at 1 year in patients with a DRUF compared with those with a DRF only.

A distal radius fracture (DRF) is often accompanied by an ulnar styloid fracture [1,2]. A concomitant metaphyseal fracture of the distal ulna is less common, occurring in only 2–9% of DRFs [3–5], and there is limited evidence regarding patients with combined distal radius and distal metaphyseal ulna fractures, here termed DRUFs [2].

The distal ulnar metaphysis is important for DRF stability. However, distal ulna fracture management is rarely discussed, and optimal treatment remains unclear [2,6–8]. In the few published studies of DRUFs, most authors recommend surgical fixation of the distal ulna in young and active patients if the fracture remains unstable after DRF fixation [2,9]. Yet, most patients with DRUFs are elderly with poor bone quality [2]. When DRUFs are treated surgically, standard techniques are used for fixation of the DRF. However, osteosynthesis of the distal ulna fracture, particularly in osteoporotic bone, can be technically challenging, and no consensus exists regarding the preferred ulnar fixation method [2,10,11]. In an elderly patient with severe osteoporosis, resection of a highly comminuted ulnar head is an alternative [2,8]. Comparable clinical and radiological results have been reported in elderly patients following both surgical and non-surgical treatment [8,12–15]. However, all series are small, and most often highlight the knowledge gap.

Radiographic healing is a limited indicator of successful treatment. Even with fracture union, the patient's functional level may decline, and larger studies incorporating patient-reported outcomes are needed [16].

Our primary aim was to investigate whether a DRUF was a predictor of a worse 1-year DASH score compared with a DRF only.

## Methods

### Design

This was a single-site, registry-based cohort study assessing whether a combined DRF and distal ulna fracture, i.e., the DRUF, affects patient-reported outcomes, as measured by DASH, 1 year after injury. The study is reported according to STROBE guidelines.

### The Lund Distal Radius Fracture Registry

Since 2003, all patients aged 18 years and older presenting with a metaphyseal DRF to the emergency department at Skåne University Hospital in Lund have been prospectively and consecutively registered in the Lund Distal Radius Fracture Registry. One secretary has reviewed the medical records of the emergency department weekly to identify cases of wrist fractures. All patients aged 18 years or older with a DRF are included, with no exclusion criteria applied. Patients were included in the registry based on the ICD-10 codes S52.50/51 and S52.60/61. Data collection continued through December 31, 2018, after which the registry was phased out due to the implementation of a national fracture registry. The present study was designed and conducted retrospectively using data from the registry.

According to local clinical guidelines at the time [17,18], non-displaced DRFs were treated with a forearm cast for 4–5 weeks. Displaced DRFs were reduced and immobilized in a cast. If reduction failed or secondary displacement occurred by the time of the 10-day follow-up, surgical treatment was recommended. The proportion of surgical vs non-surgical treatment of the DRFs remained constant during the years 2003–2012 [17]. There were no guidelines regarding treatment of a concomitant distal metaphyseal ulnar fracture and these were treated according to the surgeon's preference, either conservatively or using closed pinning of the ulna fracture or open surgery using wire forms or ulnar plates.

### Outcome measures

The primary outcome was the DASH score, a patient-reported outcome measure, assessing disabilities and symptoms related to the upper extremity. Scores range from 0 to 100, with higher scores indicating higher disabilities.

As part of the registry protocol, the DASH questionnaire was sent to all patients 12 months after their injury. Non-responders received a reminder 2 weeks later. In 2008, the original 30-item DASH was replaced by the shorter 11-item QuickDASH to improve response rates. The 2 versions are strongly correlated (Spearman's  $\rho = 0.97$ ,  $P < 0.001$ ) [18]. Both versions have been validated in Swedish [19,20]. When comparing QuickDASH and DASH scores, QuickDASH tended to show slightly higher values. This difference was statistically significant, but not considered clinically relevant [19]. As the 2 scores are generally regarded as interchangeable [19], the term

“DASH” will be used throughout this article, despite the data including both versions.

### Study participants and variables

All 5,536 patients in the registry were included. To avoid the impact of coding errors and to ensure differentiation between ulnar styloid and distal metaphyseal ulnar fractures, the emergency department radiographs were retrospectively reviewed by an orthopedic surgeon. Patients with a DRF and a concomitant metaphyseal distal ulna fracture were classified as DRUFs. Those with a DRF, with or without an ulnar styloid fracture, were classified as DRF-only.

Age, sex, fracture type, and DASH were recorded in the registry. Additional variables, such as comorbidity, polypharmacy, fracture classification, open vs closed fracture, and type of treatment, were retrieved through medical record review. Due to resource constraints, this manual review was performed only for the DRUF patients and an equally sized, randomly selected, age- and sex-matched subset of DRF-only patients. Matching was performed to reduce imbalance, as the age and sex distribution of the DRUF group differed from that of the full cohort. For each patient with a DRUF, a patient with an isolated DRF matched by sex and age at time of injury was randomly selected. In the youngest and oldest age groups, the number of patients was limited and sex was prioritized over age, and an age difference of less than 3 years was accepted. No additional exclusion criteria were applied.

Comorbidity was assessed using the Charlson Comorbidity Index (CCI), which scores chronic conditions using weights of 1, 2, 3, or 6 based on severity and mortality risk [21]. For analysis, the CCI was dichotomized into  $< 2$  vs  $\geq 2$ . Age, although part of the original CCI, was not included in the score in this study, as it was analyzed separately. Polypharmacy was defined as 5 or more prescribed medications.

All DRUFs were classified by an orthopedic surgeon using the AO Q-modifier and the Biyani classification for distal ulna fractures [3,22] (classification systems are illustrated in Figure 1). To assess intra- and interobserver reliability, 10% of DRUF radiographs were independently reviewed twice (6 months apart) by a hand surgery specialist and an orthopedic resident. Interobserver agreement was substantial for both the Biyani classification ( $\kappa = 0.78$ ) and the AO Müller classification ( $\kappa = 0.67$ ).

### Sample size

No power analysis was performed prior to the study. All cases from the registry were included in the main analyses.

### Statistics

DASH is an ordinal variable with a skewed distribution and was dichotomized into  $> 35$  vs  $\leq 35$ . A 1-year DASH  $> 35$  has previously been associated with major disability [17]. A multivariable binary logistic regression model was used to assess the association between DRUF status and a DASH  $>$



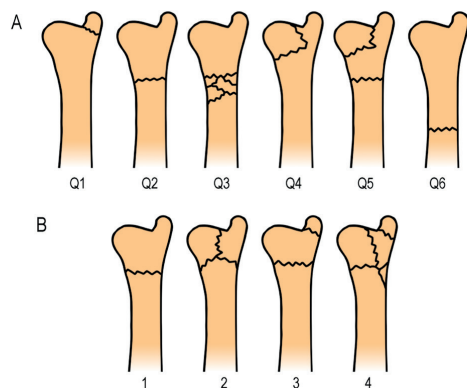


Figure 1. Classification of distal ulna fractures. AO Q-modifier subclassification, Q1–Q6 (Q1 = ulnar styloid base fracture, Q2 = simple neck fracture, Q3 = comminuted neck fracture, Q4 = ulnar head fracture, Q5 = ulnar head and neck fracture, and Q6 = fracture of ulnar diaphysis).

Biyani classification system for ulnar metaphyseal fractures in the setting of DRFs (1 = simple extraarticular fracture with minimal comminution, 2 = inverted T- or Y-shaped fracture with an ulnar styloid fragment including a portion of the metaphysis, 3 = fractures of the lower end of the ulna with avulsion fracture of the ulnar styloid, and 4 = comminuted fractures of the lower ulnar metaphysis, with or without styloid fracture).

35, adjusting for age and sex. To assess the robustness of the chosen cut-off, a post-hoc sensitivity analysis was performed using alternative DASH thresholds (25, 30, 40, and 45), and findings were consistent (see Supplementary Table 1).

A second logistic regression was performed on the smaller dataset (DRUF patients and matched DRF-only patients), adjusting for age, sex, CCI score, polypharmacy, open vs closed fracture, treatment type (surgical or non-surgical), and AO classification. Variables with a  $P$  value  $< 0.25$  in univariable analysis were included in the multivariable model.

DASH scores were reported as median and interquartile range (IQR), and group comparisons were made using the Mann–Whitney  $U$  test. Normally distributed continuous variables were reported as mean and standard deviation (SD), with group differences analyzed using a 2-sample  $t$ -test. Categorical variables were presented as counts and percentages, and differences in distribution were tested using the chi-square test. Interobserver agreement for fracture classification was assessed using Cohen's kappa.

Trends in the proportion of surgically treated DRFs (2003–2018) were assessed using linear regression analysis, both for all DRFs and separately for DRUFs.

To describe the uncertainty of each estimate, 95% confidence intervals (CIs) are presented alongside  $P$  values. A 2-sided  $P$  value  $< 0.05$  was considered statistically significant. Data was analyzed using SPSS version 29 (IBM Corp, Armonk, NY, USA).

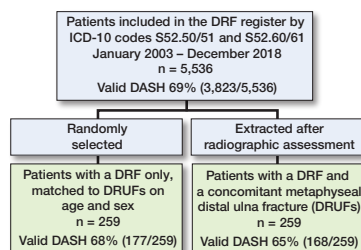


Figure 2. Flowchart of patients included in the study.

### Ethics, data sharing plan, funding, and disclosures

The study adhered to the principles of the Declaration of Helsinki. Approval was obtained from the Regional Ethical Review Board in Lund, which waived the need for informed consent (ETIK 2009/318). Data is available upon reasonable request. The study was supported by the Swedish Government Grant for Clinical Research (ALF), Region Skåne Research Funds, and the Maggie Stephens, Erik and Angelica Sparre, Greta and Johan Kock, and Alfred Österlund Foundations. The authors report no conflict of interests. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2025.44352

## Results

### Patients

Between January 2003 and December 2018, 5,536 patients were included in the register. Among these, 259 patients (4.7%) had a concomitant distal ulna fracture (a flowchart of the inclusion process is shown in Figure 2).

The overall response rate for the DASH questionnaires in the registry was 69% (3,823/5,536) and for the DRUF subgroup 65% (169/259). Baseline patient characteristics are summarized in Table 1. For the secondary analysis including additional covariates, characteristics of the matched subset of DRF-only patients are listed in Supplementary Table 2.

### Fracture classifications and treatment

There was no statistically significant linear trend in the proportion of DRFs ( $P = 0.09$ ) or DRUFs ( $P = 0.4$ ) treated surgically over time. Fracture classifications for DRUFs are set out in Table 2. Details of surgical and non-surgical treatment for DRUFs are provided in Table 3.

### Patient-reported outcome

In the DRUF group, the DASH score at 1 year was inferior to the DRF-only group (23 [IQR 5–45] vs 9 [IQR 2–27];  $P < 0.001$ ) (Figure 3). A greater proportion of patients with DRUFs reported a 1-year DASH  $> 35$ : 36% vs 18% in the DRF-only group ( $P = 0.01$ ).

Table 1. Baseline characteristics for all 5,536 DRF and DRUF patients. Values are count (%) unless otherwise specified

| Item            | DRF        | DRUF                 | P value |
|-----------------|------------|----------------------|---------|
| No. of patients | 5,277      | 259                  |         |
| Male            | 1,176 (22) | 37 (14)              | < 0.001 |
| Female          | 4,101 (78) | 222 (86)             | < 0.001 |
| Mean age (SD)   | 62 (18)    | 73 (15)              | < 0.001 |
| CCI ≥ 2         |            | 94 (36) <sup>a</sup> |         |
| Polypharmacy    |            | 75 (29) <sup>b</sup> |         |

DRF = distal radius fracture; DRUF = distal radius and distal metaphyseal ulna fracture; CCI = Charlson Comorbidity Index.  
<sup>a</sup> Missing data for 2 patients.  
<sup>b</sup> Missing data for 15 patients.

Table 4. Univariable and multivariable binary logistic regression analyses assessing the association between predictor variables and a 1-year DASH of > 35 in 5,536 patients

| Predictor of 1-year DASH > 35 | OR (CI)          | P value |
|-------------------------------|------------------|---------|
| Univariable analyses          |                  |         |
| Age (continuous)              | 1.03 (1.03–1.04) | < 0.001 |
| Sex (female vs male)          | 1.90 (1.50–2.41) | < 0.001 |
| Fracture (DRUF vs DRF-only)   | 2.56 (1.84–3.55) | < 0.001 |
| Multivariable analyses        |                  |         |
| Age (continuous)              | 1.03 (1.03–1.04) | < 0.001 |
| Sex (female vs male)          | 1.42 (1.11–1.82) | 0.005   |
| Fracture (DRUF vs DRF-only)   | 1.97 (1.40–2.75) | < 0.001 |

CI = 95% confidence interval; DASH = Disabilities of the Arm and Shoulder and Hand; DRF = distal radius fracture; DRUF = distal radius and distal ulnar metaphyseal fracture; OR = odds ratio.

In the multivariable logistic regression model, the presence of a DRUF was associated with a 97% increase in the odds of having a DASH > 35 at 1 year (OR 1.97, CI 1.40–2.75,  $P < 0.001$ ) (Table 4).

In the secondary regression analysis (with DRUF patients and the matched DRF-only subset) several additional covariates were included (CCI, polypharmacy, fracture type, surgical vs non-surgical treatment, open vs closed fracture, and AO classification). Univariable analyses for these variables showed that each additional year of age increased the odds of a poor DASH outcome by 5% (OR 1.05, CI 1.03–1.07,  $P < 0.001$ ). Patients with DRUFs had higher odds of a 1-year DASH score > 35 (OR 1.82, CI 1.14–2.90,  $P = 0.03$ ), as did patients with open fractures (OR 2.13, CI 1.03–4.41,  $P = 0.04$ ). Comorbidity (CCI ≥ 2) (OR 2.87, CI 1.78–4.62,  $P < 0.001$ ) and polypharmacy (OR 4.60, CI 2.77–7.77,  $P < 0.001$ ) were the strongest predictors of poor outcome. Sex and AO classification of the DRF were not associated with the 1-year DASH outcome (Supplementary Table 3). After adjustment, having a DRUF remained a significant predictor of a worse

Table 2. Fracture classifications of DRUF patients (n = 259)

| Item                               | n (%)    |
|------------------------------------|----------|
| DRF AO                             |          |
| AO – A                             | 127 (49) |
| AO – B                             | 4 (1.5)  |
| AO – C                             | 128 (49) |
| Distal ulna fracture Biyani        |          |
| Biyani 1                           | 82 (32)  |
| Biyani 2                           | 60 (23)  |
| Biyani 3                           | 62 (24)  |
| Biyani 4                           | 55 (21)  |
| Distal ulna fracture AO Q-modifier |          |
| AO-Q 1                             | N/A      |
| AO-Q 2                             | 88 (34)  |
| AO-Q 3                             | 13 (5.0) |
| AO-Q 4                             | 29 (11)  |
| AO-Q 5                             | 127 (49) |
| AO-Q 6                             | 2 (0.4)  |
| Open fractures                     | 41 (16)  |

For abbreviations, see Table 1 and AO-Q = the classification for ulnar styloid fractures, N/A = not applicable.

Table 3. Treatment of DRUF patients (n = 259)

|                                  |     |
|----------------------------------|-----|
| Surgically                       | 111 |
| Fixation of DRF                  | 111 |
| Volar plate                      | 73  |
| Fragment-specific fixation       | 18  |
| External fixation                | 13  |
| Combination/other method         | 7   |
| Fixation of distal ulna fracture | 49  |
| Ulnar sledge                     | 11  |
| Ulnar pin plate                  | 14  |
| Other ulnar plate                | 11  |
| Cerclage                         | 7   |
| K-wire                           | 1   |
| Combination                      | 5   |
| Non-surgically                   | 148 |
| Weeks in cast <sup>a</sup>       |     |
| 1–5 weeks                        | 123 |
| > 5 weeks                        | 11  |
| Type of cast <sup>b</sup>        |     |
| Non-circulated                   | 123 |
| Below elbow                      | 136 |

For abbreviations, see Table 1.  
<sup>a</sup> Missing data for 14 patients.  
<sup>b</sup> Missing data for 2 patients.

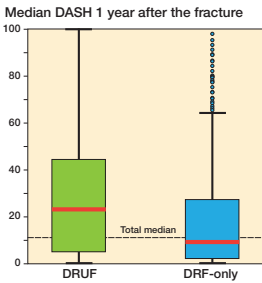


Figure 3. Box plot of median DASH 1 year after fracture, comparing median DASH for patients with a distal radius and distal metaphyseal ulna fracture (DRUF) with patients who have only a distal radius fracture (DRF).

outcome (DASH > 35) at 1 year (OR 2.35, CI 1.33–4.16,  $P = 0.003$ ) (Supplementary Table 4).

A secondary finding in this model was that surgical treatment of the DRF (with or without fixation of the distal ulna fracture) was associated with significantly lower odds of a worse outcome (OR 0.44, CI 0.23–0.85,  $P = 0.02$ ). Addition of distal ulna fixation alongside DRF fixation did not affect the median 1-year DASH score in the DRUF group (15 [IQR 0–42] after DRF fixation only vs 19 [IQR 6–35] for both DRF and DUF fixation;  $P = 0.7$ ).

Surgically treated DRUF patients were younger (mean age 67 years, SD 14) than those treated non-surgically (mean age 78 years, SD 15;  $P < 0.001$ ) and had fewer comorbidities (mean CCI 1.0, SD 1.4 vs 1.6, SD 1.6;  $P = 0.004$ ).

## Discussion

We aimed to determine whether a DRUF predicts a worse patient-reported outcome, measured by the Disabilities of the Arm, Shoulder, and Hand (DASH) score, 1 year after injury. We found that patients with a DRUF had significantly higher odds of major disability at 1 year than patients with a DRF only. This association remained significant even after adjusting for age, sex, comorbidity, polypharmacy, and fracture characteristics. Although DRUFs are relatively uncommon (5% in our cohort), this finding highlights their potential clinical impact.

In line with previous studies, our results show that DRUFs primarily affect older women [2,4] and most often are associated with AO type A or C DRFs, but rarely with type B fractures [4]. Both the AO-Q and Biyani classification systems demonstrated only substantial interobserver reliability, which aligns with previous studies [23]. Notably, the rate of open fractures among DRUFs was unexpectedly high at 16%.

Sweden's national guidelines for DRFs emphasize that there is a lack of evidence-based treatment recommendations regarding concomitant distal ulna fractures [24]. It is up to each treating physician to determine the appropriate method for further treatment. In our cohort, both surgical techniques and nonoperative management strategies (including type and duration of immobilization) differed widely, reflecting the absence of standardized treatment protocols in the department.

Our data showed that surgically treated DRUF patients had better outcomes than those treated non-surgically. While this may partly be explained by confounding factors—such as the surgically treated group being younger and having fewer comorbidities—surgery remained significantly associated with better outcomes even after adjustment.

While our results suggest that fixation of the distal ulna fracture may not significantly influence the 1-year DASH outcome, these findings should be interpreted cautiously. The sample size was limited, with only 34 patients undergoing surgical fixation of the distal ulna fracture and completing the DASH questionnaire.

Given the rarity of DRUFs, a registry-based randomized controlled trial comparing surgical and non-surgical treatment could be a feasible approach for future research.

## Strengths

A major strength of this study is the use of a large prospective registry, which enabled us to analyze an uncommon but potentially important fracture combination.

## Limitations

Although patients were registered and DASH collected prospectively, additional clinical variables, including comorbidities

and treatment details, were collected retrospectively from the medical records, which may have affected data quality and contributed to missing values.

Nonetheless, the primary regression analysis was performed using a complete dataset for the independent variables.

DASH measures function and symptoms across the entire upper extremity. Other conditions affecting the shoulder, elbow, and hand may influence the DASH independently of the wrist fracture. Moreover, while the DASH response rate was relatively high (69%), we did not perform a non-responder analysis for this study. However, a previous analysis of a subset of this register cohort found that non-response was more common among patients younger than 40 or older than 80 years, men, and those treated nonoperatively [17].

Due to resource constraints, not all covariates were available for the entire cohort. To address this, we conducted a secondary regression analysis using all DRUF patients and a subset of age- and sex-matched DRF-only patients. Analyzing only this subset introduces a loss of power and potential selection bias, and analyzing the full cohort would be preferable. However, the similar effect estimates in both analyses support the assumption that there is a true correlation.

Although this study includes a relatively large number of cases, it was conducted at a single center, which may limit the external validity of the findings. As the patient group consists almost exclusively of elderly patients, the findings may not be transferable to a younger patient population.

## Conclusion

The odds of having a DASH > 35, indicating severe symptoms, almost doubled at 1 year in patients with a DRUF compared with those with a DRF only.

*In perspective*, the finding that combined distal radius and distal ulna fractures predict poorer outcomes can be valuable knowledge for both the treating physician and the patient, as it may aid in shared decision-making and justify closer follow-up.

There is a need for better treatment strategies to enhance patient outcomes.

## Supplementary data

Supplementary Tables 1–4 are available as supplementary data on the article page, doi: 10.2340/17453674.2025.44352

LA: methodology, investigation, formal analysis including statistical analysis, writing—original draft. ML: investigation, data curation, writing—review and editing. AKH: investigation, writing—review and editing. AA: software, writing—review and editing. MT: supervision, project administration, validation, writing—review and editing.

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## Paper II





# Patients Aged 80 or More With Distal Radius Fractures Have a Lower One-Year Mortality Rate Than Age- and Gender-Matched Controls: A Register-Based Study

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## Abstract

**Introduction:** With a rapidly ageing population, the number of distal radius fractures (DRFs) in the elderly will increase dramatically. The aim of this retrospective register study was to examine the 1- and 5-year mortality in DRF patients aged 80 years or more and correlate the overall survival to factors not related to the fracture itself. **Material and Methods:** Patients aged  $\geq 80$  diagnosed with DRFs in Lund University Hospital in Sweden in the period 2010-2012 were extracted from the prospective Lund Distal Radius Fracture register. One- and 5-year standardised mortality rates (SMRs) were calculated using the Swedish standard population as a reference. Medical records were searched for non-fracture-related factors including comorbidity, medications, cognitive impairment and type of living. Cox proportional hazard regression models were used to identify prognostic factors for all-cause mortality. **Results:** The study cohort included 240 patients, with a mean age of 86. The overall 1-year mortality was 5% ( $n = 11/240$ ) and the 5-year mortality was 44% ( $n = 105/240$ ). The 1-year SMR was .44 (CI .18-.69,  $P < .01$ ) when indirectly adjusted for age and gender and compared to the Swedish standard population. The 5-year SMR was .96 (CI .78-1.14). The patients' ability to live independently in their own home had the highest impact on survival. **Discussion:** The 1-year mortality rate among the super-elderly DRF patients was only 44% of that expected. Possibly, a DRF at this age could be a sign of a healthier and more active patient. **Conclusions:** The DRF patients aged 80 or more had a substantially lower mortality rate 1 year after fracture compared to the age- and gender-matched standard population. Patients living independently in their own homes had the longest life expectancy. Treatment should not be limited solely because of old age, but individualised according to the patient's ability and activity level.

## Keywords

distal radius fracture, fragility fractures, geriatric trauma, mortality, trauma surgery, upper extremity surgery

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## Introduction

The distal radius fracture (DRF) is the most common fracture of the upper extremities.<sup>1</sup> Advanced age is one of the most important risk factors for DRF and the elderly constitute the largest group of patients with DRFs. In the published studies about DRFs in the elderly, a wide age span is typically presented. Usually, in published series and guidelines, the threshold for being elderly is set to somewhere between 50 and 70 years.<sup>2</sup> However, defining the elderly as a group this way is imprecise and differences do exist between a 60 and an 80-year-old patient regarding both expectations and needs as determinants of successful outcome.

The number of patients aged 80 years or more is calculated to rise by 50% in Sweden between 2023 and 2030.<sup>3</sup> With an increasing life expectancy, an exponential increase of osteoporosis with age<sup>4</sup> and the fact that more people live very active lives even in old age,<sup>5-7</sup> the number of DRFs in the elderly can be expected to rise. Therefore, we face a major challenge regarding how to optimize both the use of resources and the outcome for our oldest patients with a DRF.

The mortality rates are found to be increased after hip fractures. In a register study of 55 716 patients, the 1-year mortality after a hip fracture was estimated to be 26%.<sup>8</sup> In a study of patients aged 65 years or older, a fragility fracture occurring at any site, was associated with increased mortality up to 6 years post-fracture. The mortality rate was mainly affected by a hip or a vertebral fracture.<sup>9</sup> In DRF patients, the results are less clear and the mortality has been shown to be both increased,<sup>10,11</sup> decreased,<sup>12,13</sup> or without difference.<sup>14-16</sup>

Previously, the mortality rate in Sweden after a DRF was calculated in 23 394 patients aged 18 years or more in the Swedish fracture register, and the overall 1-year mortality was 2.9%.<sup>17</sup> However, this study includes patients from all adult age categories. To our knowledge the survival rates after a DRF in patients aged over 80 in Sweden is unknown and is speculatively related to factors other than the fracture.

## Aim of this Study

Our aim was to calculate the one- and 5-year mortality rate for DRF-patients aged 80 years or older, by using a large local DRF register and to correlating the overall survival to non-fracture-related factors.

## Material and Methods

### *The Lund Distal Radius Fracture Register*

The Department of Orthopaedics, at Skåne University Hospital in Lund, Sweden, serves a population of

300 000 inhabitants from both urban and rural areas. In the prospective Lund Distal Radius Fracture Register, all patients aged 18 years or older with a DRF have been prospectively registered and followed since 2002.<sup>18,19</sup> Weekly, a secretary scrutinises the medical records from the emergency department for wrist fractures coded as s52.50 and s52.60 according to the International Classification of Diseases 10th Revision (ICD-10). An orthopaedic surgeon examines the X-rays of all included patients to make sure the diagnosis and coding are correct, and then they are included in the register.

### *Options for Treatment*

Non-displaced fractures are treated in a forearm cast for 4 to 5 weeks. Displaced fractures are reduced and casted. If impossible to reduce primarily, or if secondary loss of reduction occurred at the 7-10 day follow-up, surgical treatment is recommended. However, the final decision lies with the responsible surgeon and the patient. In most surgically treated, a volar locking plate (VLP) is used for osteosynthesis. The treatment protocol has remained the same for all ages during the whole period.<sup>18</sup>

### *Patients*

In the present study we extracted a subset of patients from the Lund distal fracture register. All patients in the register who were at least 80 years old at the time of injury and had their DRF between January 1, 2010 and December 31, 2012 were included. We had no exclusion criteria. Patients were followed from the incidence date (time of fracture) to the date of death or the closing date of the study, which was set to January 1, 2020.

The inclusion years were set to 2010-2012 to enable a long follow up for all patients. The closing date was set to before the outbreak of the COVID-19 pandemic to minimize the risk of our results being affected by the potential excess mortality during this period.

Data regarding age, gender, date of injury, treatment date and type of surgery was extracted from the register. The medical records were reviewed for comorbidity, use of medication, cognitive impairment, type of living and use of walking aids. If the information was missing in the medical records at the date of injury, notes up to 1 year back in time were read in order to retrieve the data. To see if the patients suffered from major complications, all medical records were reviewed to discover whether the patient had visited the orthopaedic, hand surgery or radiology unit again, due to complaints from the same wrist that had suffered the DRF. We did not look for minor complications.



## The Non-fracture Related Factors

The Charlson Comorbidity Index (CCI) was used to classify comorbidity. In this index a number of common chronic conditions are scored with weighed values of 1, 2, 3 or 6, depending on severity and influence on mortality. A weighed value of 1 represents a slightly elevated mortality rate and 6 a very high mortality rate.<sup>20</sup> Due to the relatively limited cohort, the patients in our study were dichotomised into Charlson index “less than 2” or “2 or more”. In the original CCI, age is also taken into account when calculating points; in this study we have only given points for comorbidities. Cognitive impairment was also analysed as a separate variable (apart from “dementia” as one of the categories in the Charlson index) and included both patients with a dementia diagnosis as well as patients reported in the medical records as having a cognitive impairment without having a neurodegenerative diagnosis. The number of prescribed drugs was dichotomised into “5 or less” or “polypharmacy” (more than 5). Type of living was categorised as “Independent living”, “Living with assistance” or “nursing home” (this also including dementia care facilities). Information on the use of walking aids (cane, crutches, walker) was taken from the medical record and coded as yes or no.

## Statistical Analysis

All statistical analyses were made using IBM SPSS statistics for Mac V.28.0.0. The authors performed the statistical analysis. A two-sided  $P$ -value  $< .05$  was considered significant. Scale variables for patient characteristics had a symmetrical distribution and are presented as mean with standard deviation. Categorical data is presented with count and proportions (%).

Dates of death were extracted by linking the social security number for each patient to their death certificates in the Swedish National Cause of Death register. The crude 1- and 5-year death rates were calculated by the Kaplan-Meier method. The standardised mortality ratio (SMR) is expressed as a percentage quantifying the decrease or increase in mortality of a study cohort compared to the general population. If lower than 1, there is a lower number of deaths than expected. The SMR also constitutes an indirect form of standardisation. In this study, age and sex standardised SMRs were calculated. The mortality rates of the standard Swedish population for the same period of time was used as a reference population.<sup>21</sup> Age groups used in the indirect standardisation were 80-84, 85-89, 90-94 and 95-99. Cox proportional hazard regression models were used to identify prognostic factors of all-cause mortality, presented as hazard ratio (HR) with 95% confidence intervals (CI). Analyses were based on time-to-event, where time is the time from the date of fracture and

event is defined as all-cause mortality. The primary analysis aimed to determine the risk factors associated with all-cause mortality. The potential prognostic factors in the analysis were the independent variables: age, gender, comorbidities according to the CCI, polypharmacy, cognitive impairment, type of living and use of a walking aid. Multivariate Cox proportional hazard models were used to adjust for interactions between prognostic factors of mortality. Kaplan-Meier estimates with log rank tests were used to plot survival and compare survival between stratified groups.

## Results

### Patients and Treatment

Between January 1, 2010, and December 31, 2012, in total 240/1317 (18.2%) DRF patients in the register were 80 years or older at the time of their fracture. See patient characteristics in Table 1. During the time period, 308/1317 (23.4%) of all the DRF patients in the register (age 18-96) were treated surgically, compared to 25/240 (10.4%) in the subset of patients aged 80 years or more. Among the subset of elderly, the majority of the surgically treated patients underwent open reduction and internal fixation using VLPs ( $n = 18$ ). Other methods used were fragment-specific fixation ( $n = 2$ ) and external fixation ( $n = 3$ ). After completion of treatment, three of the patients sought care again due to pain from the injured wrist. All three had been treated non-surgically, and all three suffered from malunion with more than 30 degrees of dorsal angulation. One of the patients underwent an osteotomy.

### Mortality

During the study period, 74% (178/240) of the patients in the cohort died. No difference was found in overall survival between men and women. From the date of fracture, the mean survival time of the patients was 5.2 years (95% CI 4.8-5.6). The crude overall 1-year mortality was 5% ( $n = 11/240$ ) in the study cohort and 11% ( $n = 54/309/496/904$ ) in the standard population. The crude 5-year mortality was 44% (105/240) in the study cohort and 55% ( $n = 271/886/496/904$ ) in the standard population.

The 1-year age and sex standardised SMR for the DRF patients aged 80 or more was .44 (95% CI .18-.69,  $P < .01$ ); thus, in the short term, the mortality rate was only 44% of that expected when compared to the Swedish general population and weighted for both age and gender. The 5-year age and sex standardised SMR was the same as expected in the general population: SMR .96 (95% CI .78-1.14).

In the univariate Cox regression analysis, assisted living or living in a nursery home, a high rate of comorbidity,

**Table 1.** Patient Characteristics.

| Characteristics                | Patients n = 240 (%) | Missing Values |
|--------------------------------|----------------------|----------------|
| Age                            |                      |                |
| Mean                           | 86 (SD 4.2)          |                |
| Range                          | 80-97                |                |
| Gender                         |                      |                |
| Males                          | 26 (11)              |                |
| Females                        | 214 (89)             |                |
| Charlson comorbidity index     |                      |                |
| 0                              | 56 (23)              | 1              |
| 1                              | 82 (34)              |                |
| 2-3                            | 86 (36)              |                |
| 4+                             | 15 (6)               |                |
| Polypharmacy                   |                      |                |
| Yes                            | 127 (53)             | 26             |
| No                             | 87 (36)              |                |
| Cognitive impairment           |                      |                |
| Yes                            | 43 (18)              | 43             |
| No                             | 191 (82)             |                |
| Type of living                 |                      |                |
| Own housing with no assistance | 136 (57)             | 18             |
| Own housing with assistance    | 45 (19)              |                |
| Nursing home                   | 41 (17)              |                |
| Walking aid                    |                      |                |
| Yes                            | 81 (38)              | 29             |
| No                             | 130 (62)             |                |

Baseline characteristics of the patients in the study cohort.

cognitive impairment and polypharmacy were significantly associated with a poorer prognosis. There were no significant associations between overall survival and gender, increasing age or use of a walking aid.

In the adjusted multivariate Cox regression model, the best predictor of mortality was the type of living. Patients with some type of regular assistance at home had a poorer prognosis compared to fully independent patients living in their own home (HR 1.6, 95% CI 1.0–2.4,  $P < .05$ ). Patients living in a nursing home had the poorest prognosis (HR 3.2 95% CI 1.8–5.6,  $P < .001$ ). The mean survival of patients living in their own home was 6.4 years (95% CI 6.0–6.9) compared to patients in nursing homes with a mean survival of 3.1 years (95% CI 2.5–3.7,  $P < .001$ ). The difference in survival expectancy of patients with different living situations is displayed in a Kaplan-Meier estimation; see [Figure 1](#). In the adjusted multivariate Cox regression model, a CCI score of 2 or more also affected the prognosis (HR1.5 95% CI 1.0–2.2,  $P < .05$ ). Cognitive impairment and polypharmacy showed no significant impact on survival in the adjusted model.

## Discussion

Our main finding was, somewhat surprisingly, that patients 80 years or older had a substantially lower mortality one year after a DRF compared to the age- and gender-matched standard population. This finding differs from several previous reports. However, since the majority of previous studies analysed a wider range of age categories it is difficult to accurately compare the results.

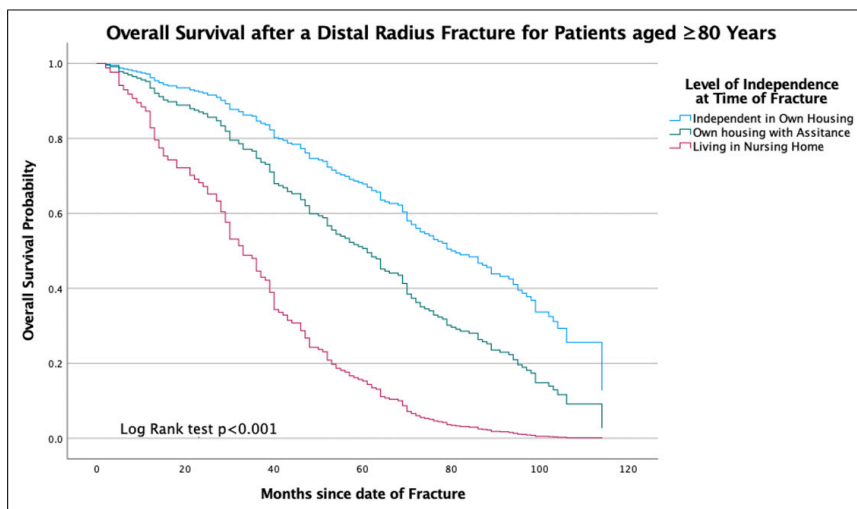
In an American cohort of 325 patients aged 65 years or older, the mortality rate was significantly higher after a DRF than in the standard US elderly population. The estimated survival was 57% 7 years after the fracture, i.e., less than the expected 71% for elderly US residents.<sup>10</sup> In a Norwegian cohort, 883 patients with a DRF were stratified for age, and an increased mortality was seen, but only in female patients aged 70 years or older.<sup>11</sup> When analysing patients aged more than 80 in subgroups Kwon et al found a subtle decrease in 1-year mortality (SMR .88) after a DRF-fracture among patients over 90 in a Korean cohort. However, the mortality was unaffected for patients 80–89 years.<sup>12</sup>

Chung et al found lower mortality rates in DRF patients when analysing standardised mortality rates in 81 568 patients aged 65 years or older in the US Medicare population. The authors suggested that regular visits to a healthcare provider after a DRF could be a possible explanation, allowing diagnosis and treatment of other conditions contributing to mortality.<sup>13</sup> In our cohort, 90% of the patients were treated non-surgically with casts and received only 1 or 2 return visits without further investigation regarding medical conditions, so in our series we find it difficult to see this as an explanation.

One can speculate that a DRF in our cohort was simply an indirect sign of a healthier patient. A DRF could be an indicator of a better balance and a functioning reflex system enabling the patient to fall on the outstretched hand instead of landing on for example the hip. A DRF could also indicate a relatively active lifestyle as it is necessary for the patient to be reasonably mobile in order to sustain a fracture.

In our study, the difference between the mortality in the cohort and the reference population decreased over time. Even though the patients aged 80 or more had a great chance of living another year, the chance of living many more years decreases significantly per year in higher age. This could explain the fact that the differences no longer appear in the 5-year analysis, i.e., this may happen because the expected average survival is evened out over time among the oldest in the population.

The best marker of expected survival was type of accommodation which could be seen as an indirect indication of the patient's level of autonomy. The low mortality in this study was not explained by a lower proportion of patients



**Figure 1.** Kaplan-Meier plot for overall survival, for patients aged 80 years or more with distal radius fracture. Time (months) from fracture date. Blue line: patients living in own housing, green line: patients living in own housing with some type of regular assistance, red line: patients living in nursing home or equivalent care facility.

living in their own homes. In the same geographic area as the hospital serves, statistics from the National Board of Health and Welfare show that 15% of those over 80 lived in nursing homes or residential care facilities in 2014,<sup>22</sup> while that number was 17% in this study.

With limited resources in healthcare and a large and increasing number of patients, we should consider how we allocate resources and which patients benefit best from surgical treatment. For a long time, the perception has been that the oldest patients do not benefit from advanced care for DRFs, and that their recovery will be “good enough” regardless of the type of treatment, but is this really true? In recent years, opinions seem to have shifted as more and more studies demonstrate that elderly patients benefit from surgical treatment.

In elderly DRF patients, anatomically pre-contoured VLPs are the most commonly used implant for osteosynthesis.<sup>23,24</sup> Elderly patients treated with VLPs have a better functional outcome than the conservatively treated<sup>25,26</sup> and a similar early complication rate as in younger patients.<sup>25,27</sup> It has been shown that surgery can lead to a faster start of range of motion training and an earlier increase in grip strength,<sup>25</sup> leading to a quicker return to regular activities.<sup>2</sup> For an old patient, time is a scarce commodity and early activation and return of hand function could allow the patient to maintain independence, probably resulting in a lower overall cost for the health care and society. The high mortality following a hip fracture has created an interest in improving the care for these patients

with multidisciplinary care.<sup>28–30</sup> Perhaps this could also benefit the group of frail elderly with DRFs.

Maybe the treatment of DRFs, like other diagnoses in elderly, should be more individualised, and should reflect functional needs as well as physical capacity to go through an operation. Possibly, we should consider surgical treatment of more elderly to enable those who are active with high demands on their wrist function, to continue to live independent lives. Depending on the functional level, different types of rehabilitation and follow-up may also be relevant<sup>31</sup> regardless of whether surgical treatment is provided or not. It is obvious, particularly in patients aged 80 or more, that health-related factors such as comorbidity and level of independence are more relevant for assessing future needs for good wrist function, than the number of years previously lived.

## Limitations

A limitation of the study is the relatively small cohort size and the low number of male patients. Even if the standardised mortality rate is adjusted for gender, the tendency is that survival mostly reflects the survival of women since they constitute 89% of the patients. The study has not taken into account possible differences in socio-economics. However, the hospital’s catchment area spans both cities and rural areas, and the facility is the only one in the area that treats acute DRFs. The socio-economics are therefore expected to be varied and at least relatively comparable to

the entire country. No power analysis was conducted before the study. To describe the uncertainty of each estimate the CIs are presented with each *P*-value. There are some missing data concerning patient characteristics that could affect the HRs in the Cox regression estimations; this was due to missing information in the medical records. However, our main aim in the study was to calculate the mortality rates of the patients and for this the dataset is complete.

## Conclusions

This study is the first to evaluate both short- and long-term survival among DRF patients aged 80 or more. Our main finding was that these elderly patients had a substantially lower mortality one year after the fracture compared to the age- and gender-matched standard population. The best predictor of mortality was the patient's type of living, where living in a nursery home had the worst prognosis.

In conclusion, age alone appeared inappropriate for triaging the patients aged 80 or more to best possible treatment. In fact, the patients in this study seemed to have passed a threshold where age no longer affected mortality on an annual basis. The patients ranged from healthy independent patients with high demands and high expectations to dependent patients with dementia, unlikely to cooperate in a strenuous rehabilitation. However, a high percentage of the patients seemed to have many years left to live, where a functional and pain-free wrist could be decisive for the quality of life.

## Author's Contribution

Linnea Arvidsson: Methodology, Investigation, Formal analysis including statistical analysis, Writing – Original Draft. Marcus Landgren: Investigation, Data Curation, Writing – Review & Editing. Anna Kajsa Harding: Investigation, Writing – Review & Editing. Antonio Abramo: Software, Writing – Review & Editing. Magnus Tägil: Supervision, Project administration, Validation.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical Statement

### Ethical Approval

The study was approved by the Research Ethics Committee of Lund University (ETIK 2009/318). According to the ethical committee no verbal or written consent was needed from the patients for this register study. The study conforms to the principles outlined in the Declaration of Helsinki.<sup>32</sup>

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## Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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## Paper III







# Virtual Follow up After Distal Radius Fracture Surgery—Patient Experiences During the COVID-19 Pandemic

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## Abstract

The majority of patients with a distal radius fracture (DRF) are elderly, a group known to experience difficulties with new technology, partly due to a low level of digital literacy. At the beginning of the coronavirus disease 2019 pandemic, during the spring 2020, patients that underwent DRF surgery had regular follow-ups replaced by video calls from their surgeon and physiotherapist. Afterward, patients answered questionnaires regarding health and digital literacy and took part in semi-structured interviews regarding the experience of the virtual follow-up. By systemic text condensation, 2 major categories were identified: (1) The video call—new, but surprisingly simple: All but 1 found it easier than expected, and (2) Video calls—the patient's choice: All but 1 patient preferred video calls to physical visits for follow-up. This is the first mixed methods study to assess patients' experiences of digital follow-up after DRF surgery. This study indicates that digital follow-up was highly appreciated, even among patients with low levels of digital literacy. Digital technologies must be made suitable even for patients with inadequate levels of digital literacy.

## Keywords

access to care, COVID-19, health literacy, patient satisfaction, qualitative methods, telemedicine, orthopedics, surgery

## Introduction

Recent studies have indicated that telemedicine systems appear to be safe for postoperative visits, saving time and money, and resulting in high satisfaction among patients and surgeons.<sup>1-3</sup> Younger patients are more confident in using digital health tools.<sup>4,5</sup> The distal radius fracture (DRF) is the most common fracture<sup>6</sup>, and phone applications used to assist with rehabilitation have been studied.<sup>7,8</sup> Patients who suffer a DRF are of mixed ages, but the majority are elderly, a group known to experience difficulties with new technology.<sup>9</sup> The elderly as a group may, on the other hand, benefit substantially from telemedicine, something that became obvious during the pandemic.

To study the use of telemedicine by the elderly, the concept of functional digital literacy (FDL) has been introduced, similar to functional health literacy (FHL). FHL is a health literacy concept that covers basic skills in understanding and using health information.<sup>10</sup> FDL, in a similar way, measures the ability to engage practically with new technology and requires operational, social, and creative skills.<sup>11,12</sup>

Studies of health literacy and digital literacy in the clinical setting are scarce.<sup>12</sup> To the best of our knowledge, no mixed method studies, which use both interviews and surveys, have been performed to investigate the patient's experience of telemedicine after a surgically treated wrist fracture. Furthermore, knowledge about the feasibility of telemedicine, eg, video meetings for patients with DRFs, is lacking. Since the patients are expected to take part and be engaged in their own rehabilitation, health instructions need to be

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accessible and easy to understand.<sup>11</sup> Thus, both FDL and FHL are important tools to study telemedicine, particularly in patients undergoing surgery.

Our aim was to study how patients with a DRF experienced video-based follow-up. We aimed to identify advantages as well as challenges with new digital technology. Since the approach included both digital technology and active participation by patients, we measured FDL and FHL in a mixed methods study.

## Method

In spring 2020, the coronavirus pandemic was escalating in our neighboring countries, and we prepared for a similar situation. We decided to follow all surgically-treated wrist fracture patients remotely, by video calls instead of face-to-face meetings. The patients received a video call via a secure link from the surgeon the day after surgery and from the physiotherapist 5 to 7 days after surgery. The video call started automatically when the patient pressed the link in a text message

### Participant Recruitment

At the Skane University Hospital in Lund, Sweden, about 250 patients with a DRF are operated on annually. During the study period of April and May 2020, only 12 patients underwent surgery at our hospital, due to limited surgical resources during the pandemic. For the study, the primary researcher invited all 12 patients during the hospital visit. Once verbal consent was provided, a time was arranged. To reduce the risk of having a homogeneous sample, there were no predetermined exclusion criteria.

### The Interviews

An interview guide was developed by the research team. The interview questions were concerned about (1) the experience of video calls as follow-up, and (2) the patients' view on an "optimal follow-up." The questions were open-ended and designed to allow the patients to provide their own experiences.

Semistructured interviews, 1 per patient, were conducted by telephone 6 to 8 weeks after surgery at the end of May and the beginning of June 2020 by an orthopedic resident (LA) with experience in the treatment of DRFs. The resident did not treat the participating patients. The interviews were 30 min long on average. All patients were at home during the interviews. The interviews were held in Swedish (the native language of the researchers and most of the patients) and are translated into English in this article. The interviews were transcribed verbatim.

### Analysis of the Interviews

The analytical steps were guided by systematic text condensation<sup>13</sup>, a method that is common in medical qualitative

research in Scandinavia because it is transparent and has a methodological approach. Three authors participated in the analysis: 1 specialist in orthopedic and hand surgery (MT), 1 resident in orthopedics (LA), and 1 physiotherapist specializing in rehabilitation after wrist trauma (BH). All read the transcripts individually, thoroughly, and repeatedly to get a sense of the full content. Each researcher listed their preliminary thoughts and themes using an inductive analytic approach eg, deriving primary themes directly from the raw data.<sup>13,14</sup>

Discussions were held on how to interpret the content and the meaning of the preliminary themes. In the next step, the authors independently condensed the text, line-by-line, into meaning units, and labeled the units with a code. Subsequently, codes with similar content were sorted into code groups developed from the preliminary themes. The researchers' meaning units, codes, and code groups were then compared and discussed within the whole research group, until consensus on relevant coding and code groups was reached (see examples of coding in Figure 1).

Next, the code groups were interpreted by the authors and developed into descriptions and concepts, and labeled with category headings. The categories were discussed between the researchers to ensure the consistency of the findings (triangulation). Finally, all 4 of the authors agreed upon the 2 "main categories" in the results.

### Questionnaire Data

In connection with the interview, all participants answered questionnaires regarding FHL and FDL.

The Swedish FHL scale was used (Figure 2). The scale's first item focused on visual ability, related to the design of text and its accessibility. The following 2 items focused on the understanding of words and concepts, the fourth on perseverance in reading, and the fifth on the need for help in reading and understanding information. Responses were on a 5-point ordinal scale (1 = never to 5 = always), with lower scores indicating lower health literacy.<sup>15</sup>

To the best of our knowledge, there is no equivalent questionnaire to measure the patient's FDL. Hence, a questionnaire measuring patients' confidence levels and their attitudes toward digital technology was developed (Figure 2). The first question focused on general digital competence regarding the use of digital tools. The second question focused on the attitude to digital transformation in society. The third question focused on the ability to learn how to use new software, and the last 2 questions focused on the ability to solve problems concerning the software.

### Analysis of the Questionnaires

The Swedish FHL scale does not provide an initial summary score. Instead, reported variables are recategorized into 3

| Example: Schematic View of Coding                                                                                           |                       |                            |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------------|
| Units of Meaning                                                                                                            | Units of Significance | Emerge of Key Categories   |
| "It is so nice not to have to leave and take the bus to the hospital, I can just stay at home relaxing"                     | Easier not to travel  | Video calls are convenient |
| "It saved me a lot of time when I didn't need to go to the hospital. I could stay at work and have my follow-up call there" |                       |                            |
| "I didn't have to take a day off from work"                                                                                 |                       |                            |

**Figure 1.** Schematic view of coding.

| Questionnaire: Functional Digital Literacy (FDL)                                                                                                                      |        |           |       |        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|-------|--------|
| A. Do you find it difficult to use digital devices (eg computer, smartphone, tablet) because you do not understand how they work?                                     |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| B. Do you find it difficult to keep up with the digital development that is taking place in society?                                                                  |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| C. Do you find it difficult to learn how to use new applications or programs (such as applications on your computer, smartphone or tablet)?                           |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| D. Do you find it difficult to solve problems that may arise around programs or applications on digital devices (programs on the computer or apps on the smartphone)? |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| E. Do you sometimes ask another person to help you with (or explain how to use) new programs or applications for a computer, phone or tablet?                         |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| Questionnaire: Functional Health Literacy (FHL)                                                                                                                       |        |           |       |        |
| A. Do you think that it is difficult to read health information because the text is difficult to see (even if you have glasses or contact lenses)?                    |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| B. Do you think that it is difficult to understand word or numbers in health information?                                                                             |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| C. Do you think that it is difficult to understand the message in health information?                                                                                 |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| D. Do you think that it takes a long time to read health information?                                                                                                 |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| E. Do you ever ask someone else to read and explain health information?                                                                                               |        |           |       |        |
| Never                                                                                                                                                                 | Seldom | Sometimes | Often | Always |
| Score system: Never = 1, Seldom = 2, Sometimes = 3, Often = 4, Always = 5                                                                                             |        |           |       |        |

**Figure 2.** Functional digital literacy and health literacy questionnaires.

different levels (inadequate, problematic, or sufficient health literacy). Thus, FHL was categorized using the recommended transformations: 1 and 2 became 1; 3 became 100; and 4 and 5 became 1000. All values were summed. Scores exceeding 1000 were interpreted as an inadequate FHL, values between 100 and 1000 as problematic, and values below 100 as sufficient.<sup>15</sup> The same analytics procedure was used for the FDL scale.

## Reporting

To ensure clear reporting of the study, we have followed the COREQ checklist for reporting qualitative research.<sup>16</sup>

## Results

Ten out of 12 invited patients participated in the study. One patient was unable to participate due to cognitive impairment, and 1 due to language issues. Of the participants, 3 were men and 7 were women, and the age ranged from 32 to 85 years. Two patients were in their thirties, 2 in their forties, 4 in their fifties, 1 in her 60s, and 1 patient was over 80 years old. Four patients did not have Swedish as their native language.

The questionnaires showed that a majority of the participants had sufficient levels of FHL. However, only 4 of the 10 patients had sufficient levels of FDL, 3 had inadequate levels, and 3 had problematic levels. The levels of FHL and FDL are presented in Table 1.

In the interviews, the 2 main categories were identified: “The video call—new, but surprisingly simple” and “The video call—The patient’s choice”.

### The Video Call—new, but Surprisingly Simple

The majority expressed no problems participating in a video call.

The video call was very easy. Usually you have to download something, but here it was, just press a link and it just worked! It was really good.—Participant 9

Some patients with inadequate FDL worried whether they would be able to cope with the technology. However, all but one of these found it easier than expected to connect.

At first I thought: I will never be able to do this. I thought it would be really hard. But it went just fine!—Participant 5

My husband was home, so I asked him to connect. It seemed easy, I’m 100% sure I could do it on my own if I had to, but since he was home I didn’t—Participant 8

The patients described that it was easy to show the physiotherapist and surgeon, through the video, how they performed their hand exercises.

**Table 1.** Results: Functional Digital and Health Literacy Questionnaires.

| Results: Questionnaire for self-reported digital literacy |           |   |   |   |   |       |
|-----------------------------------------------------------|-----------|---|---|---|---|-------|
| Participants                                              | Questions |   |   |   |   | Score |
|                                                           | A         | B | C | D | E |       |
| P1                                                        | 1         | 3 | 2 | 3 | 3 | 302   |
| P2                                                        | 1         | 1 | 1 | 1 | 1 | 5     |
| P3                                                        | 1         | 1 | 1 | 2 | 1 | 5     |
| P4                                                        | 1         | 1 | 2 | 2 | 2 | 5     |
| P5                                                        | 4         | 4 | 5 | 3 | 4 | 4100  |
| P6                                                        | 1         | 1 | 3 | 3 | 3 | 302   |
| P7                                                        | 1         | 3 | 1 | 4 | 3 | 1202  |
| P8                                                        | 3         | 1 | 3 | 1 | 4 | 1202  |
| P9                                                        | 1         | 1 | 1 | 1 | 1 | 5     |
| P10                                                       | 1         | 3 | 2 | 2 | 1 | 104   |

| Results: Questionnaire for self-reported health literacy |           |   |   |   |    |       |
|----------------------------------------------------------|-----------|---|---|---|----|-------|
| Participants                                             | Questions |   |   |   |    | Score |
|                                                          | A         | B | C | D | E  |       |
| P1                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P2                                                       | 1         | 3 | 3 | 1 | 1  | 203   |
| P3                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P4                                                       | 1         | 1 | 2 | 1 | 2  | 5     |
| P5                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P6                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P7                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P8                                                       | 1         | 1 | 1 | 1 | 1  | 5     |
| P9                                                       | 1         | 1 | 1 | 1 | 3* | 104   |
| P10                                                      | 1         | 1 | 1 | 3 | 1  | 104   |

\*The patient comments that since Swedish is not his first language, he sometimes has trouble understanding certain words.

The doctor sort of carefully checked the exercises I did and pushed me to do the finger exercises properly. It went very well.—Participant 2

The oldest patient mentioned that she received help to connect from her partner of the same age. She said she could not manage on her own.

Well, of course it is good if you know how to handle it. I could never connect and do all of it on my own. But I went to my partner, so we could do it on his phone. And he managed to connect. And then I thought it worked really well actually. But you must know how to handle it ... I’m 85 years old! I wasn’t born with all these technical things.—Participant 7

Many patients emphasized the fact that the technical solution for the video call itself must be simple. Yet even simple technical solutions can be experienced as difficult, both for the patient and the clinician.

It was very easy since I just had to press a link in a text message. Sometimes you must install new programs and applications, I don't like that.—Participant 2

The first call went technically fine. The discussion with the physiotherapist and the content of the meeting were very good, but we had some technical difficulties. It just went off. But to start it again just took a minute. I could just press the link again ... so we had some issues, but since it was very easy to connect again, I wasn't bothered. But for someone who is not technically oriented it would have been confusing.—Participant 9

### *The Video Call—The Patient's Choice*

All but 1 patient preferred video calls over physical visits as the first follow-up after surgery. The participants emphasized how comfortable and easy it was to not travel and not take time off from work.

I really liked the video call; it saves a lot, especially the travel to the hospital. Maybe it's a benefit that the doctor can also be anywhere. It provides freedom for both the doctor and the patient.—Participant 2

The video call is the best! I thought: Oh excellent, now I don't need to go to the hospital again just to talk ... to be able to sit in peace and quiet at home, it works just as well as to be in a room at the hospital.—Participant 6

For me, the video call is absolutely the best, I didn't have to take a day off from work.—Participant 1

The patients also mentioned the advantages of environmental benefits of not traveling.

I would really like the follow-ups to be like this, with digital video calls. Because if we think about the environment and, depending on where you live, take into account the time it takes to travel to the hospital. It was a very positive experience.—Participant 3

One participant emphasized that even if she needed assistance, it was easier for her to get help with making the video call than to get help with transportation to the hospital and back.

I could not handle the technique. But I would not manage to go to the hospital by myself either; I would have to ask someone for help. People don't have time to help me get to the hospital, but to help me with the phone is easy for someone who knows how to do it.—Participant 7

## **Discussion**

Earlier studies on telemedicine in orthopedics are diverse, using various methods and outcome measures, and the findings are

sometimes difficult to interpret and generalize.<sup>17</sup> In a systematic review, 41 studies on telemedicine in orthopedics were included, and a trend was shown toward high patient satisfaction using digital follow-up.<sup>17</sup> There are, however, limitations to telemedicine. The physical proximity between doctor and the patient, emphasized as helping to create trust and reassurance,<sup>18</sup> is absent in teleconsultations. Even if advanced virtual examination techniques are being developed,<sup>19</sup> telemedicine does not allow ordinary physical examination of the patient, which is usually considered an essential component of an orthopedic assessment.<sup>20</sup> In order to still benefit from the many unique advantages of digital care, a hybrid model of care can be used. For example, return visits can be carried out digitally. According to surgeons, the postoperative patient is the most suitable for digital follow-up, with a 79% surgeon satisfaction rate, whereas first-time visits are considered the least suitable.<sup>3</sup>

The first visit after wrist surgery mainly addresses the postoperative swelling and emphasizing correct hand exercises; for this, the digital video meeting is ideal. The patient's mobility can be visually examined and misunderstandings in technique easily corrected. In our study, the early rehabilitation result was visually checked once again by the physiotherapist, giving a second opportunity to intervene if the result was unsatisfactory.

By using mixed methods, we aimed to achieve a deeper understanding of patients' experiences of digital follow-up. In 2020, the safety and efficacy of telemedicine were studied in general surgery<sup>1</sup> and the authors concluded that their telemedicine program was safe, timesaving, and had extremely high patient satisfaction. Interestingly, quotes from the patients were included, although they were anecdotal and not relevant to the study analysis and aim. To us, this indicates an interest in describing the patients' true and deeper personal opinions and experiences of telemedicine rather than a focus on just measuring the results in scores and questionnaires.

We were able to show that the benefits of video meetings are many, but we also identified clear challenges that require careful consideration to enable the digital health transition. From the interviews, we learned that half of the study participants expressed a fear or some degree of worry beforehand of not being able to handle the technology. In general, the FHL level was high, whereas the FDL was lower. The patients expressed relief once the technology turned out to work. In hindsight, the patients (including the patients who scored low on the FDL scale) concluded that the technology was relatively simple to use.

In general, elderly people are considered more resistant to using new technologies, but maybe that is a myth. It has also been suggested that the elderly are underrepresented in studies of digital health research.<sup>21</sup> In an emergency department-based, telemedicine program, the satisfaction scores among the older patients were similar to those of the younger patients.<sup>22</sup> In Sweden, high Internet use is reported in general. Declining use is seen with increasing age, but still, 93% of people aged 62–71 use the internet daily, 83%

in the age group 72–81, and 50% in the groups aged 82 or older.<sup>4</sup> With a high number of nonusers in the super elderly, a challenge exists for the digital transition in health-care, in particular in diagnoses such as DRF with patients ranging from the young to the super elderly.

The coronavirus pandemic served as a catalyst for the rapid development of tools to conduct digital care. The acute state of emergency, and the urge to reduce the risk of infection for patients and clinicians, made it possible to temporarily overlook several legal and security aspects when implementing telemedicine.<sup>23,24</sup> Now that the situation is not as acute, in order to continue the use of digital care, there is an urgent need to develop rules of application to ensure quality, safety, liability, and confidentiality.<sup>23–26</sup> The patients in our study emphasized the importance of easy-to-use technology, but this will become a balancing act when IT-security is of the highest priority.

## Limitations

Our study had limitations. Although all available patients were asked to participate, the study was small and single site, and the findings may be difficult to generalize to a larger patient group or another setting. All patients participating in the study accepted follow-up by video consultation. It would have added to the study to interview someone who was initially more skeptical or negative about telemedicine. Two patients declined to be interviewed due to cognitive impairment and/or language difficulties, which highlights the limitations of the follow-up method.

## Conclusions

In the transition into telemedicine, the needs and capabilities of heterogeneous groups of patients must be considered. The technology needs to be adapted to patients with inadequate or problematic FDL. In our study, the patients managed to handle the new technology, despite a low FDL. This study also indicates that digital follow-up after DRF surgery is highly appreciated even among patients with low FDL.

We conclude that the technology was well adapted for our audience. In the future, we hypothesize that digital follow-up will be the new standard, at least partly. In our society, the aim is to provide equal care. We, therefore, need to ensure that digital technologies are made suitable for people with inadequate levels of FDL. The patients are ready for the change, but healthcare needs to optimize the tools for digital meetings. Patients, as well as medical staff, deserve tools with intuitive design and high levels of usability.

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## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval

The regional ethics committee approved the study (ETIK 2009/318). The study confirms to the principles outlined in the Declaration of Helsinki.<sup>23,27</sup>

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## Paper IV







## Full length article

# Systemically administered zoledronic acid activates locally implanted synthetic hydroxyapatite particles enhancing peri-implant bone formation: A regenerative medicine approach to improve fracture fixation

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## ABSTRACT

Fracture fixation in an ageing population is challenging and fixation failure increases mortality and societal costs. We report a novel fracture fixation treatment by applying a hydroxyapatite (HA) based biomaterial at the bone-implant interface and biologically activating the biomaterial by systemic administration of a bisphosphonate (zoledronic acid, ZA). We first used an animal model of implant integration and applied a calcium sulphate (CaS)/HA biomaterial around a metallic screw in the tibia of osteoporotic rats. Using systemic ZA administration at 2-weeks post-surgery, we demonstrated that the implant surrounded by HA particles showed significantly higher peri-implant bone formation compared to the unaugmented implants at 6-weeks. We then evaluated the optimal timing (day 1, 3, 7 and 14) of ZA administration to achieve a robust effect on peri-implant bone formation. Using fluorescent ZA, we demonstrated that the uptake of ZA in the CaS/HA material was the highest at 3- and 7-days post-implantation and the uptake kinetics had a profound effect on the eventual peri-implant bone formation. We furthered our concept in a feasibility study on trochanteric fracture patients randomized to either CaS/HA augmentation or no augmentation followed by systemic ZA treatment. Radiographically, the CaS/HA group showed signs of increased peri-implant bone formation compared with the controls. Finally, apart from HA, we demonstrated that the concept of biologically activating a ceramic material by ZA could also be applied to  $\beta$ -tricalcium phosphate. This novel approach for fracture treatment that enhances immediate and long-term fracture fixation in osteoporotic bone could potentially reduce reoperations, morbidity and mortality.

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### Statement of significance

• Fracture fixation in an ageing population is challenging. Biomaterial-based augmentation of fracture fixation devices has been attempted but lack of satisfactory biological response limits their widespread use. • We report the biological activation of locally implanted microparticulate hydroxyapatite (HA) particles placed around an implant by systemic administration of the bisphosphonate zoledronic acid (ZA). The biological activation of HA by ZA enhances peri-implant bone formation. • Timing of ZA administration after HA implantation is critical for optimal ZA uptake and consequently determines the extent of peri-implant bone formation. • We translate the developed concept from small animal models of implant integration to a proof-of-concept clinical study on osteoporotic trochanteric fracture patients. • ZA based biological activation can also be applied to other calcium phosphate biomaterials.

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## 1. Introduction

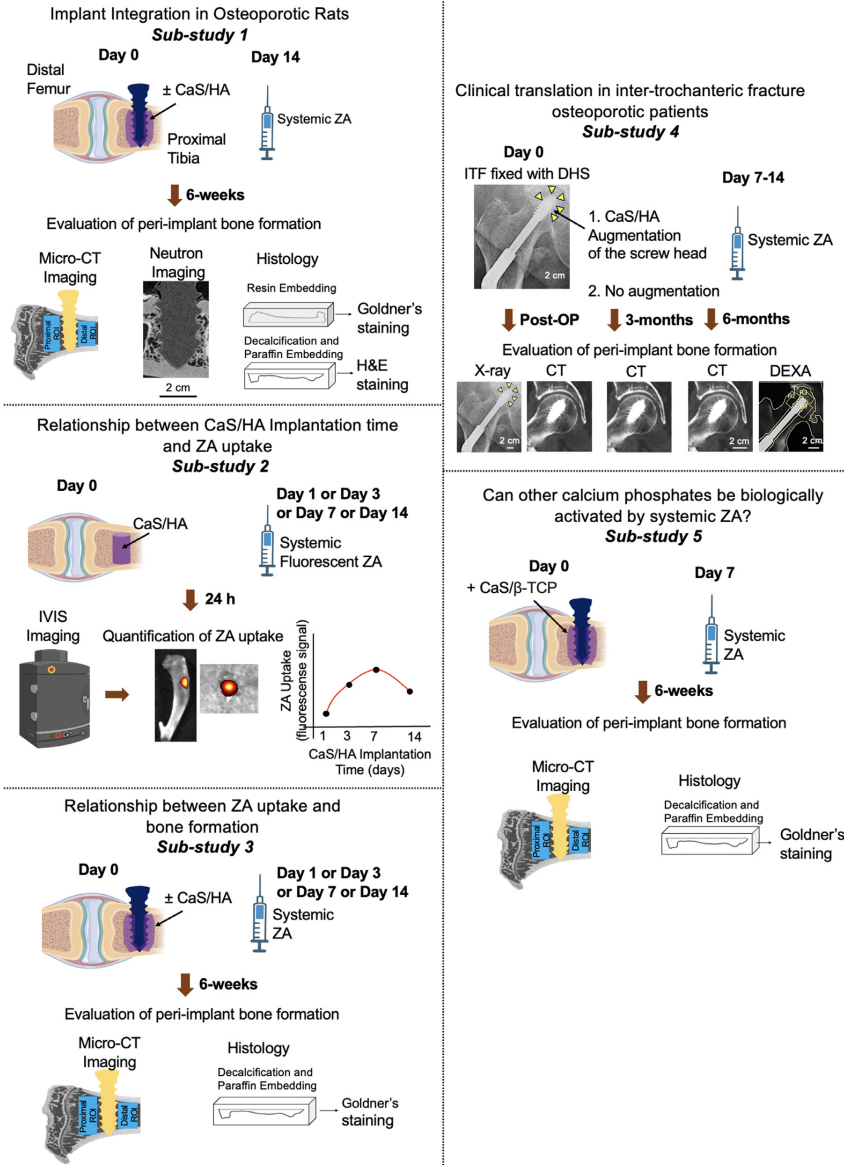
Osteoporosis affects more than 200 million people worldwide, and by 2050, that figure is anticipated to double [1]. A noticeable decline in bone mineral density (BMD) and an increase in trabecular bone porosity are typical symptoms of the condition. Osteoporosis makes it difficult to securely fix fractures in the fragile cancellous bone. Osteoporosis is a “silent” disease and very often doesn’t show symptoms until a fracture occurs, which makes it even more difficult for the healthcare system to manage [2,3]. Fragility fractures account for 75 % of all trauma cases operated in the US and Europe. More than half of hip fractures are intertrochanteric fractures (ITF), routinely treated surgically using a dynamic hip screw (DHS) or a proximal femoral nail (PFN) fixation system depending on fracture type/stability [4,5]. About 3–7 % of ITF require revision surgery [6,7]. In addition, around 2 % of the cases are reported to have a postoperative infection [8,9]. A reoperation in an already fragile patient reduces quality of life and increases the risk of premature death [10]. As failure of internal fixation of fractures in osteoporotic bone typically occurs through breakage of the bone that surrounds the implant, rather than the implant itself, augmentation of the bone could be considered in patients with trochanteric fractures.

To improve screw anchorage in osteoporotic bone, attempts have been made to apply polymer-based injectable materials at the screw-bone interface. Methods to reinforce the bone-implant interface using bone cement (PMMA) in ITFs have been described earlier [11,12] but the clinical evidence of the advantage is weak as data from large-scale randomized controlled trials (RCTs) is not available. The disadvantage of using bone cement in augmenting screws in ITFs is the inert nature of the PMMA material, which fails to induce new bone formation. Although mechanical augmentation can be beneficial initially, an ideal biomaterial that transforms into the patient’s own bone over time would be a significant leap forward towards reducing implant failures and reoperations. Apart from PMMA, the only ceramic materials that have been used in the augmentation of screws in load bearing locations have comprised of either injectable calcium phosphate (Norian SRS, Norian Corporation) [13,14] or a solid HA cylinder (Neobrace®) [15]. While both studies indicated a positive effect of the biomaterial augmentation on hip fracture fixation and eventual implant anchorage, both studies comprised of a small patient group making it difficult to draw robust statistical conclusions regarding the benefit of the approach in reducing revision surgery. Calcium sulphate/hydroxyapatite (CaS/HA) is an alternative to PMMA with initial mechanical properties similar to calcium phosphates (CaP) [16]. Owing to a balanced material degradation-osteoconduction rate of the CaS/HA biomaterial, it has previously been demonstrated that the CaS/HA biomaterial can promote efficient bone healing [17,18]. Furthermore, CaS/HA biomaterial has been used for

local and controlled delivery of various pro-osteogenic molecules to promote bone formation [19]. An example of one such molecule is the bisphosphonate zoledronic acid (ZA), originally considered to only act on osteoclasts [20]. Reports have shown that controlled local delivery of ZA not only acts to dampen the osteoclast effect but also promotes cancellous bone formation in several animal models [20–22]. However, the addition of a pharmaceutical agent like ZA to a CaS/HA material causes a significant change in the setting time of the CaS/HA material and requires difficult and costly regulatory approvals increasing the clinical translational time of the proposed approach. Interestingly, the HA phase in the CaS/HA material not only aids in delivering drugs locally but also acts as a recruiting moiety for systemically administered drugs including bisphosphonates. Raina et al. recently demonstrated that systemically administered bisphosphonate ZA seeks pre-implanted CaS/HA both ectopically and orthotopically [20,23]. Some experimental studies have indicated that ZA plays a pseudo-anabolic role on mesenchymal stromal cells (MSCs) by rendering a pro-osteogenic effect on the cells when used at low-doses [24]. Low dose bisphosphonate treatment enhances the osteogenic differentiation of MSCs by up-regulating key genes including runt-related transcription factor-2 (Runx-2), alkaline phosphatase (ALP) and osteocalcin (OCN). The exact molecular mechanism for this upregulation is not clear but early studies have indicated that bisphosphonates may act as a substrate for ALP, which would in-turn lead to increased mineralization [25]. Therefore, the approach of combining a resorbable CaS/HA biomaterial to augment the immediate mechanical properties of an implant [26] followed by pharmaceutical activation of the biomaterial by systemically administering ZA to promote bone regeneration would be desirable in overcoming the drawbacks associated with inert biomaterials including PMMA. Even more important is the possibility to test this new indication and concept clinically as both CaS/HA material and ZA are already approved by the respective regulatory bodies.

The primary aim of this study was to evaluate whether the combination of a CaS/HA biomaterial applied at the bone-implant interface followed by systemic administration of ZA could activate the peri-implant HA particles and thereby enhance bone formation in an osteoporotic rat model of bone-implant integration. The secondary aims were to:

- 1) Evaluate the relationship between the timing of ZA administration and its effect on the uptake of ZA in the CaS/HA material and consequently the effect of ZA administration time on eventual peri-implant bone formation,
- 2) Test the feasibility of using the method in a clinical setting on osteoporotic patients undergoing treatment of a trochanteric fracture using internal fixation and
- 3) Whether other calcium phosphate materials such as tricalcium phosphate could also be biologically activated by systemically administered ZA.



**Schematic 1.** Study overview outlining the experimental set-up used in the five sub-studies described in this study.

**2. Methods**

**2.1. Study overview**

This study consists of five sub-studies as shown in [Schematic 1](#) below.

In the first part of this study (sub-study 1), using an osteoporotic rat model, we investigated implant integration and peri-implant bone formation around a clinically used stainless steel screw in the proximal tibia of rats. The screw was augmented with CaS/HA or left untreated and subsequently the effect of systemically administered ZA on peri-implant bone was investigated. In

the second part of the study (sub-study 2), we evaluated the differences in ZA accumulation around a CaS/HA biomaterial as a function of CaS/HA implantation time post-surgery. To study this phenomenon, fluorescently marked ZA and in-vivo imaging system (IVIS) based fluorescence imaging was employed. In the third sub-study (sub-study 3) we elucidated the role ZA uptake in the CaS/HA material plays on the eventual peri-implant bone formation in a model similar to the one described in sub-study 1. To translate the pre-clinical results in a clinical setting, a proof-of-concept, clinical study (sub-study 4) was initiated to highlight the role of CaS/HA augmentation and subsequent treatment with systemic ZA in trochanteric fracture patients undergoing surgical treatment with a dynamic hip screw (DHS). The control group of patients received surgical treatment with a DHS but without CaS/HA augmentation. Both groups were treated with systemic ZA. Finally, in the last pre-clinical study (sub-study 5) we aimed to investigate whether peri-implant bone formation could only be modulated in the presence of HA or whether other calcium phosphate materials, particularly  $\beta$ -tricalcium phosphate could also be used. A detailed description of the experimental groups and the total number of animals used in each animal study (sub-study 1, 2, 3 and 5) is provided in supplementary Table 2.

## 2.2. Implant integration in osteoporotic rats (Sub-study 1)

The effect of HA application and systemic ZA treatment on peri-implant bone formation was assessed using an ovariectomized (OVX) rat model of implant integration. We used 38 ovariectomized (OVX) and four SHAM-operated Sprague-Dawley female rats, which were bought from Janvier Labs (France). OVX and SHAM surgeries were performed by the breeder when the rats were 12-weeks old. At the time of surgical intervention, the animals were 24-weeks old and weighed  $419 \pm 29$  g. The animals were randomly assigned to four groups (G1, G2, G3 and G4). All OVX animals underwent surgery in their right tibia approximately 5 mm below the tibial growth plate based on well-established protocols [20,23]. Animals were anesthetized using isoflurane anaesthesia (2–2.5 % mixed with oxygen). Antibiotic prophylaxis (Penicillin-Streptocillin VET, Apoteket AB, Sweden) was administered 15 min prior surgery via an intramuscular injection in the hind leg. Perioperative pain management was achieved using one single subcutaneous injection of buprenorphine (Temgesic®, 0.03 mg/kg) 15 min prior to surgery. After shaving the right tibia, the skin was disinfected with chlorhexidine alcohol and a 1 cm incision was made on the medial aspect of the proximal tibia. A 1.8 mm unicortical hole was drilled in the medial aspect of the tibia parallel to the insertion of the medial collateral ligament (MCL) without harming the MCL. A sterile gauze was inserted into the drill-hole to clean the remnants of the bone as well as to reduce bleeding. A stainless-steel screw (Trimed Ortho, Sweden) with a diameter of 2.3 mm and a length of 8 mm was inserted into the drilled hole until resistance from the posterolateral cortex was felt. At this point the screw was deemed fully-inserted. Approximately 2–3 mm of the screw remained outside the bone on the anteromedial aspect. Depending on the treatment groups, the screw was either augmented or left unaugmented. Screw augmentation was performed using a CaS/HA biomaterial (purchased as CERAMENT™ BVF from Bone Support AB, Sweden), which comprises of 60 % alpha calcium sulphate hemihydrate (CaS) and 40 % hydroxyapatite (HA) by weight [18]. Each 1 g of the CaS/HA powder was mixed with 0.43 mL radiographic contrast agent (C-TRU, Bone Support AB, Sweden) which is an iodine-based non-ionic contrast agent. This leads to the formation of a paste, which is injectable up to 5 min post mixing and mouldable after 7 min. In groups G1 and G2, the screws were left unaugmented and each group comprised of  $n = 11$  rats. In groups G3 and G4, after cleaning the drilled hole,

50  $\mu$ L of the CaS/HA material was inserted into the bone using a spatula 7 min post the initiation of mixing. In group G3, a total of  $n = 11$  rats were used, while group G4 comprised of  $n = 5$  rats. After completion of the screw placement, the muscle and the skin were closed using resorbable and non-resorbable sutures, respectively. Two weeks after surgery, all animals in groups G2 and G3 received a subcutaneous injection of bisphosphonate ZA (Novartis, Switzerland) at a dose of 0.1 mg/kg. ZA dosage and timing were based on prior studies performed by us and others [23,27,28]. During the experimental period, all animals were provided access to regular food pellets and water ad libitum. 6-weeks post-surgery, all animals were sacrificed by CO<sub>2</sub> asphyxiation and both right (defect side) and left (healthy side) tibiae were removed, cleaned of all soft tissue, wrapped in saline-soaked gauze and stored at  $-20$  °C until further analysis. The SHAM animals, which were neither ovariectomized nor surgically treated, were also sacrificed at the same time as the OVX animals. The tibiae were harvested and stored as described above.

### 2.2.1. Ex-vivo micro-CT for quantification of peri-implant bone volume

Harvested tibiae from the defect side were thawed at room temperature and subjected to a micro-CT scan using a MI labs U-CT micro-CT scanner (MI Labs, Netherlands). In order to minimize X-ray interference with the metal implant (scattering artefacts), care was taken in mounting the implant perpendicular to the X-ray beam, which restricted the artefacts in one direction i.e., in the direction parallel to the long axis of the screw. The bones were scanned using following settings; scan mode: full 360-degree scan in ultra-focus mode, X-ray energy: 50 kV, exposure time: 75 ms, current: 0.21 mA and step angle: 0.25°. After image acquisition, raw images were reconstructed to an isotropic voxel size of 30  $\mu$ m using manufacturer's software suite. All images were exported as DICOMs and saved as bitmap files. The bitmap files were realigned with Dataviewer (Bruker, Belgium) and the coronal plane images were analyzed with CTAn (Bruker, Belgium). In order to quantify peri-implant bone formation, two separate regions of interest (ROIs), one proximal and one distal to the implant surface, were used. The proximal ROI, which was close to the knee joint, comprised of a cube with a width of 1 mm, a height of 2.25 mm and a depth of 0.75 mm. The distal ROI comprised a cube with a width of 1 mm, a height of 1.5 mm and a depth of 0.75 mm. The dimensions of the ROIs were carefully chosen in order to exclude native bone and yet achieve a robust quantification of the peri-implant bone formation. Furthermore, ROIs were placed carefully in close proximity (without overlap) to the implant threads. A global thresholding corresponding to a density of 0.57 g/cm<sup>3</sup> HA was applied after calibrating the images against a phantom material comprising two HA phantoms (densities: 0.25 and 0.75 g/cm<sup>3</sup>) and water. Bone volume (BV) was used as the outcome variable of the CT analysis.

### 2.2.2. Neutron imaging and undecalcified histology

One representative sample from each of the groups G1–G4 was chosen for a more detailed imaging of the bone-implant interface using neutron imaging at the Institut Laue-Langevin (nEUT beamline, Grenoble, France). We have previously shown that neutron imaging provides more detailed insights at the interface of metallic implants and bone when compared with X-ray based imaging by significantly reducing artefacts at the bone-implant interface [29,30]. The samples were first fixed in formalin for 48 h before being dried in vacuum at ambient temperature for 12 h to remove moisture and improve tissue differentiation in the neutron images [31]. At the beamline, the samples were placed in a vertical position inside a bespoke, 0.5 mm thick, cylindrical Teflon sample holder with an inner diameter of 9.5 mm. A Teflon lid

was put on the cylinder to retain moisture and pressed slightly on the specimen to reduce movement during imaging. Neutron tomographic images were acquired using a 20  $\mu\text{m}$  Gadolinium scintillator and a 30 mm pinhole at 10 m, yielding a field-of-view of 13.5  $\times$  13.5 mm. The specimen was rotated 360° while acquiring 1792 images, each using an exposure time of 7 s and averaging 3 images to reduce noise. The tomographic images were reconstructed in absorption mode using RX Solutions X-Act Software yielding an isotropic voxel size of 7.15  $\mu\text{m}$ , corresponding to a true resolution of approximately 14  $\mu\text{m}$ . The samples were frozen at  $-20^\circ\text{C}$  immediately after imaging before being transferred into formalin for one week before processing for undecalcified histology.

Formalin-fixed tissue was embedded in Technovit9100 using standard resin embedding protocols. Samples were then cut to a thickness of 100  $\mu\text{m}$  using a high-precision saw and ground to 20  $\mu\text{m}$  thickness followed by staining with Goldner's Trichrome.

### 2.2.3. Decalcified histology

All remaining samples (except those used in 2.2.2) were decalcified using an acid-based rapid decalcification medium (Decalcification Solution Lite, Sigma Aldrich, Germany) by immersing the entire tibia in 50 mL of the solution. After decalcification, samples were embedded in paraffin, cut to a thickness of 5  $\mu\text{m}$  using a semi-automatic microtome (Thermo Scientific, USA), and stained with hematoxylin and eosin (H&E) (Thermo Scientific, Richard Allen and Shandon series).

### 2.3. Relationship between CaS/HA implantation time and ZA uptake in the CaS/HA material (Sub-study 2)

In the first study, we chose to inject ZA systemically, at a time-point of two weeks based on prior literature, particularly from pre-clinical studies [27,28]. However, our next aim was to understand this CaS/HA seeking property of ZA as a function of CaS/HA implantation time. To address this aim, we used Alexa-fluor 647 conjugated ZA (BioVinc, USA), which is a fluorescently labelled variant of ZA that has similar bone seeking properties as unconjugated ZA [32]. A total of 25 male Sprague-Dawley rats (average weight =  $442 \pm 23$  g) were operated in the proximal tibia as described in Section 2.2 above, with a difference that the drilled hole was 2.3 mm. In  $n = 20$  rats, the drilled hole was filled with 50  $\mu\text{L}$  of the CaS/HA material, while the remaining  $n = 5$  rats did not receive any CaS/HA material. The  $n = 20$  rats implanted with the CaS/HA material were divided into 4 groups; 1) injection with fluorescent ZA (FZA) on day 1, 2) injection with FZA on day 3, 3) injection with FZA on day 7 and 4) injection with FZA on day 14. The remaining  $n = 5$  rats, which did not receive the CaS/HA material, were also injected with FZA on day 14. FZA was administered subcutaneously at a dose of 0.1 mg/kg. In order to optimize the signal-to-noise ratio during imaging, 10 wt% of AF647 labelled ZA was first mixed with 90 wt% of unconjugated ZA. 24 h after the FZA injection, animals were sacrificed using  $\text{CO}_2$  asphyxiation, and their operated as well as contralateral tibiae were harvested and frozen at  $-20^\circ\text{C}$  until further analysis. The defect and the contralateral tibiae from each animal were scanned on an In-Vivo Imaging System (IVIS Spectrum, Perkin Elmer, USA). The fluorescence signal in the drilled region and an anatomically similar region on the contralateral tibia was quantified by applying a rectangular ROI using manufacturer's software suite (Living Image 4.0, Perkin Elmer, USA). The ROIs were carefully placed in order to avoid any interference from ZA uptake in the growth zones. In order to understand the relationship between CaS/HA implantation time and the consequent ZA uptake, the mean fluorescence signal on the defect side for all groups was compared with each other. Furthermore, to elucidate the CaS/HA seeking property of ZA, the fluorescence signal

of the defect leg was compared with the contralateral healthy leg in a pairwise fashion.

### 2.4. Effect of CaS/HA implantation time and ZA uptake on peri-implant bone formation (Sub-study 3)

In the experiment in Section 2.3, we could determine the biodistribution of ZA around HA particles as a function of CaS/HA implantation time but we could not elucidate whether the timing of ZA administration affects the consequent peri-implant bone formation at the 6-week time point since the animals were sacrificed 24 h after ZA administration. In this sub-study, we repeated the implant integration model described in Section 2.2 on male Sprague-Dawley rats (average weight =  $429 \pm 50$  g). A total of 35 rats were divided into five experimental groups ( $n = 7/\text{group}$ ) as follows: G1) CaS/HA, G2) CaS/HA+ systemic ZA on day 1, G3) CaS/HA+ systemic ZA on day 3, G4) CaS/HA+ systemic ZA on day 7 and G5) CaS/HA+ systemic ZA on day 14. During surgery, 50  $\mu\text{L}$  of the CaS/HA material was first inserted in a 1.8 mm diameter hole in the proximal tibia followed by inserting a stainless-steel screw of 2.3 mm diameter and 8 mm length. In groups G2–G5, all animals received one subcutaneous injection of ZA (0.1 mg/kg) at the designated time points. All animals were sacrificed 6-weeks post-surgery. Tibiae implanted with the metal screw were harvested and subjected to micro-CT imaging and histological analysis as described in Sections 2.2.1 and 2.2.3. CT and histology-based peri-implant bone formation was used as the outcome variable and compared between different treatment groups and the control group. Samples for histology were prepared using EDTA decalcification (10% w/v, pH 7.2). Histological sections were stained with Goldner's Trichrome and the area of bone tissue was quantified using ImageJ.

### 2.5. Effect of CaS/HA augmentation and systemic ZA treatment on peri-implant bone mineral density in trochanteric fracture patients (Sub-study 4)

So far, we could demonstrate the role of peri-implant CaS/HA material in recruiting systemically administered ZA and the biological activation of the material thereof. Our next aim was to translate the pre-clinical results into a clinical setting and elucidate the role of the developed approach on peri-implant bone formation in patients undergoing treatment for a low-energy trochanteric fracture using a dynamic hip screw (DHS)-based fixation system.

The surgical method of introducing the CaS/HA material at the interface of the lag-screw and osteoporotic bone has been described in an earlier study [26]. Briefly, the CaS/HA material was injected through the cannulated DHS as described below: 1) preparing a screw canal using an 8-mm drill, 2) partially inserting the DHS into the proximal femur (2.5–3 cm from its final position), 3) insertion of a long cannula connected to a syringe containing the CaS/HA paste, 4) injecting the CaS/HA paste in front of the DHS, 5) inserting the DHS to its final position and 5) connecting the femoral plate to the DHS. This proof-of-concept study aimed to determine the changes in peri-implant bone mineral density (BMD) in two randomly assigned treatment groups; G1) No CaS/HA material and G2) CaS/HA augmentation of lag-screw in a total of 21 patients with  $n = 11$  assigned to G1 and  $n = 10$  assigned to G2. Patient demographics are available in Supplementary Table 1. After a period of 7–14 days, all patients received an intravenous infusion of ZA (4 mg/patient) mixed with normal saline. Patient follow-up comprised of the following regimen: 1) X-ray and pelvic CT within 1–3 days post-operatively in order to confirm the outcome of the surgical procedure as well as the presence of CaS/HA material at the screw-bone interface, 2) an interim CT evaluation at 3-months and 3) a final evaluation comprising of X-ray, pelvic CT

and dual energy absorptiometry (DEXA) at 6-months. The primary outcome variable of our study was to compare the BMD measured by DEXA in the two patient groups after 6-months. DEXA images (both treatment and contralateral hip) were acquired on a GE Hologic DEXA machine (GE Healthcare) and three regions of interest around the screw threads (one at the screw tip, one inferior to the screw threads and one superior to the screw threads) were drawn manually by a trained orthopaedic surgeon. All patients who completed the final follow-up at 6-months were included in the quantification of BMD. This study was a proof-of-concept feasibility study to evaluate whether the developed method could safely be implemented in a clinical setting. No statistical conclusions were drawn from this clinical study due to a low sample size.

## 2.6. Elucidating the role of other calcium phosphate materials and ZA administration on peri-implant bone formation (Sub-study 5)

In all of our experiments so far, we used a CaS/HA biomaterial, and therefore the goal of this sub-study was to evaluate whether other calcium phosphate materials, more specifically  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) could also be biologically activated by systemically circulating ZA. Thus, we replaced the HA component within the CaS/HA with  $\beta$ -TCP. We pre-mixed 60 wt% CaS (VWR, Sweden) and 40 wt%  $\beta$ -TCP (Sigma Aldrich, Germany) both having a purity of >98 %. To this pre-mixed powder, 0.43 mL of Iohexol (Omnipaque, 180 mg I/mL, Apoteket AB, Sweden) was mixed to form a paste. 50  $\mu$ L of the paste was then implanted in a 1.8 mm drilled hole in the proximal tibia of six male Sprague-Dawley rats (average weight = 573  $\pm$  19 g) followed by insertion of a stainless-steel screw (TriMed Ortho, Sweden) of 2.3 mm diameter and 8 mm length. One-week post-surgery, all six animals were injected with ZA (dose 0.1 mg/kg) subcutaneously. The animals were sacrificed six weeks post-surgery and the tibiae were harvested for the analysis of peri-implant bone formation using micro-CT and histology as described in Sections 2.2.1 and 2.4.

## 2.7. Ethics

### 2.7.1. Animal experiments

All animal experiments were approved by the Swedish Board of Agriculture (Permit number: 152888/2019). All personnel involved in animal experimentation were trained as per FELASA guidelines and ARRIVE guidelines were followed in reporting the animal experiments. Animals had free access to regular food pellets and water during the entire course of the experiment. Animals were always housed at least 2/cage and were maintained in temperature and humidity-controlled rooms with 12 h light/dark cycles.

### 2.7.2. Clinical study

Informed patient consent was obtained prior to patient randomization. The clinical study was approved by the Institute Review Board of the Kaunas University Hospital, Lithuanian University of Health Sciences, Kaunas, Lithuania (permit number: P1 BE-2-76/2019). More details of the study can be obtained at [www.clinicaltrials.org](http://www.clinicaltrials.org) (identifier number: NCT04498715). All patients planned to be included in the study have been recruited and DXA data for all available patients is included in this study.

## 2.8. Statistics

Sample size in the pre-clinical studies (sub-studies 1, 2, 3 and 5) was based on our previous experiments using similar animal models [20,23]. Study 4 was a clinical feasibility and safety study.

**Sub-study 1:** In order to confirm the osteoporotic status of the animals micro-CT based BV was compared between SHAM and OVX animals using a Mann-Whitney U test.

The primary outcome variable in the experiment was micro-CT based peri-implant bone volume. The normality of data was tested using the Shapiro-Wilk normality test. Data was further analyzed using a non-parametric ANOVA (Kruskal-Wallis test) with a Dunn's multiple comparison post-hoc test.

**Sub-study 2:** The uptake of FZA in the CaS/HA implanted leg was compared with the contralateral (non CaS/HA) leg using a paired sample *t*-test. The fluorescence signal in the CaS/HA treated legs followed by ZA injection at days 1, 3, 7, and 14 was then compared with the control group (i.e. animals that did not receive CaS/HA but were administered FZA systemically) using Dunnett's ANOVA. The uptake of FZA in the remaining CaS/HA groups was compared using an ordinary one-way ANOVA with Tukey's post-hoc. Similar was done to evaluate the ZA uptake in the contralateral limbs that did not receive the CaS/HA material.

**Sub-study 3:** In the 3rd experiment involving the study of the effect of CaS/HA implantation time and eventual ZA uptake on peri-implant bone formation at a later time point, micro-CT based analysis of bone volume was used as a primary outcome variable. A total of 5 experimental groups were used and CaS/HA group without ZA administration was used as a control. Therefore, the groups that received ZA (2–5) were compared with group 1 using a Dunnett's ANOVA. The remaining groups (2–5) that received both CaS/HA and systemic ZA were compared to each other using an ordinary one-way ANOVA with Tukey's post-hoc test.

**Sub-study 4:** No statistical analysis was performed due to the small sample size.

**Sub-study 5:** No statistical analysis was performed as this was a single-group study.

Statistical significance was set at  $p < 0.05$ .

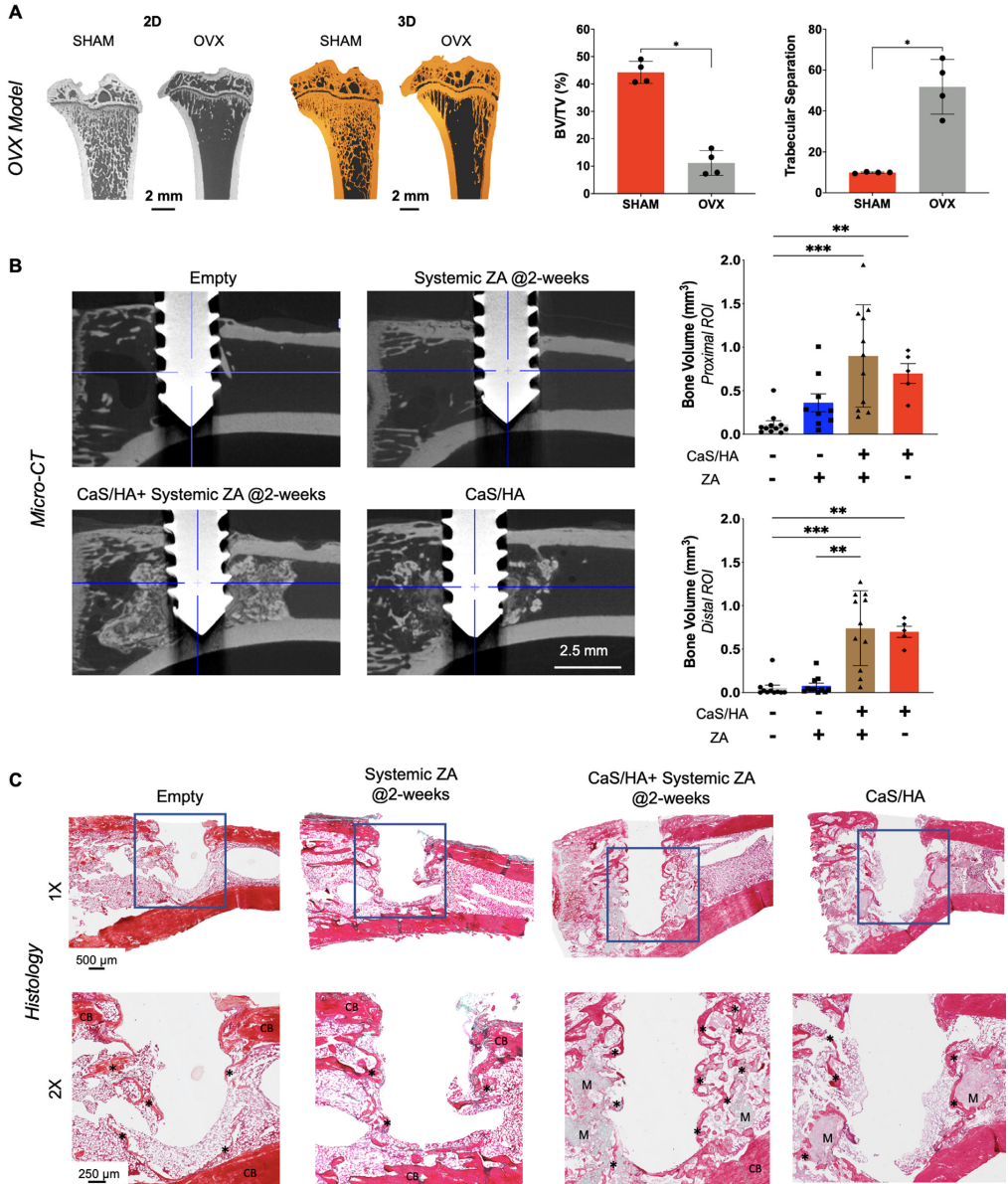
## 3. Results

### 3.1. Implant integration in osteoporotic rats (Sub-study 1)

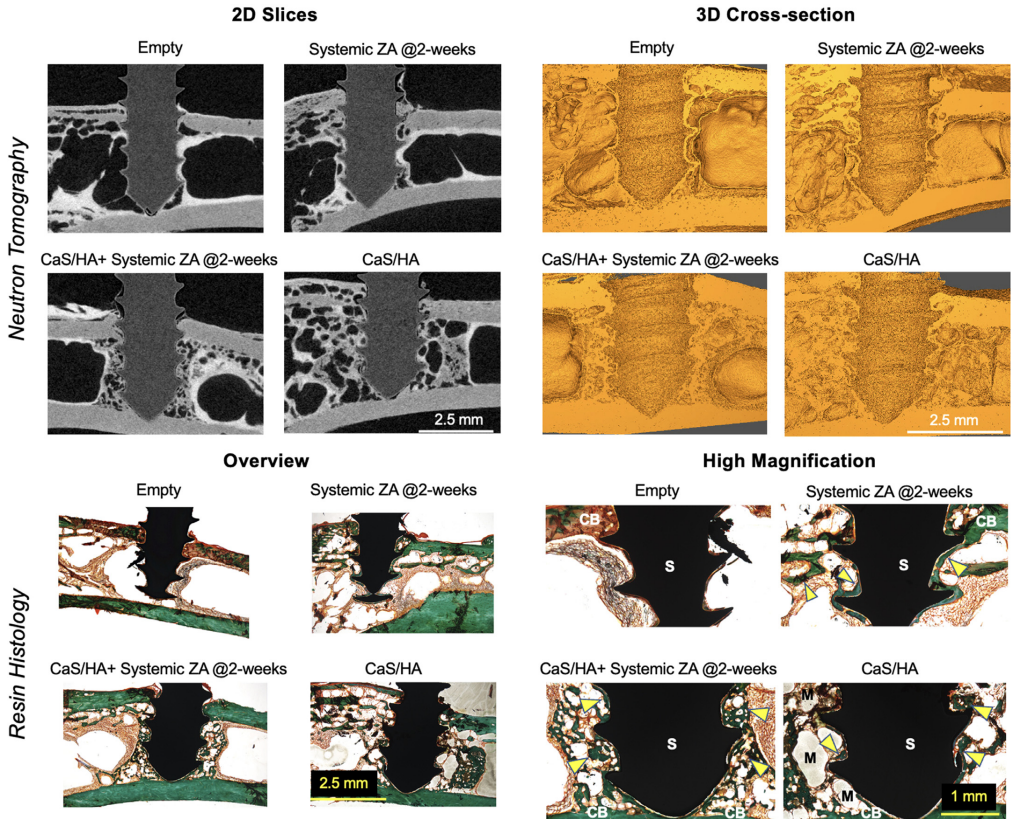
Firstly, the osteoporotic status of the experimental animals was confirmed using micro-CT (Fig. 1A). A severe loss of cancellous bone was observed in the proximal tibial metaphysis with a statistically significant reduction in the trabecular bone volume/tissue volume (BV/TV) fraction as well as an increased trabecular separation, both of which are hallmarks of osteoporosis in this model [33].

At the end of the experimental period at 6-weeks, the empty group (G1) as well as the unaugmented systemic ZA group (G2) showed no signs of peri-implant bone formation (Fig. 1B). In the experimental group with CaS/HA and systemic ZA administration at 2-weeks, cancellous bone-like structures could be observed throughout the length of the screw threads extending 2 mm into the marrow cavity, both proximally and distally. In the CaS/HA group without ZA (G4), remnants of the CaS/HA material could be seen as aggregated clumps without signs of obvious new bone formation around the implant. In terms of micro-CT based bone volume (BV), the BV in the distal region of interest (ROI) was the highest in G3 (CaS/HA+ systemic ZA at 2-weeks), which was significantly higher than the BV in groups G1 ( $p < 0.001$ ) and G2 ( $p < 0.01$ ). Only CaS/HA (G4) showed a significantly higher BV than G1 ( $p < 0.01$ ) but no differences could be observed between G3 and G4. In the proximal ROI, both G3 and G4 had a higher BV when compared with G1 ( $p < 0.001$  and  $p < 0.01$ , respectively). Histology results corroborated well with the representative CT slices. Groups G1, G2 and G4 demonstrated a thin layer of bone formation close to the screw while group G3 demonstrated extensive cancellous bone formation. Remnants of the CaS/HA material could be observed in both group G3 and G4. Although both micro-CT and decalcified histological analysis provided a robust estimate of peri-implant new bone formation, it was not possible to observe





**Fig. 1.** Implant integration in an osteoporotic rat model. (A) Representative micro-CT based 2D and 3D slices of SHAM vs. OVX rats show a significant loss of cancellous bone in the proximal tibial metaphysis, verifying the osteoporotic status of the animals. The graphs on the right show the changes in the BV/TV fraction as well as Trabecular Separation ( $n = 4$ ). (B) Shows the representative 2D micro-CT slices from the experimental animals at 6-weeks post screw implantation. The scatter plots on panel B, right show the micro-CT based BV quantified both proximally (top) and distally (bottom) to the screw. A detailed description of the statistical tests used is provided in Section 2.8 above. \* indicates  $p < 0.05$ , \*\* indicates  $p < 0.01$  and \*\*\* indicates  $p < 0.001$ . (C) Shows the representative histology images (at 6-weeks post-implantation) stained with H&E for all experimental groups both at overview (1X) magnification and a more magnified (2X) snapshot of the immediate bone-implant interface. CB indicates cortical bone, \* indicates new bone around the implant and M indicates material.



**Fig. 2.** Detailed analysis of screw-bone interface using neutron imaging (top) and resin-embedded histology sections stained with Goldner Trichrome (bottom). Images in the top panel show representative 2D (left) and 3D (right) pictures from the neutron imaging experiment 6-weeks after in-vivo implantation. Images in the bottom panel shows resin embedded Goldner's Trichrome stained sections from the 4 experimental groups 6-weeks after in-vivo implantation. Histology images on the left were captured at 2X magnification while the images on the right were captured at 4X magnification. Yellow arrowheads indicate new bone observed in the screw threads and the marrow canal, S indicates the screw, CB indicates cortical bone and M indicates the remnants of the CaS/HA material.

the tissue characteristics and bone ingrowth into the screw threads using these methods due to X-ray induced artefacts as well as removal of the screws during histological analysis, respectively.

In order to get a representative snapshot of the tissue reaction in the screw threads, two important imaging techniques were employed. Neutron imaging revealed that the screw interface was covered with a high contrast water-rich material in groups G1 and G2 (Fig. 2, top). Histologically, the empty group G1, the screw threads were filled with a thin layer of fibrous tissue while group G2 demonstrated a very thin layer of cancellous bone within the screw threads (Fig. 2, bottom). Both G1 and G2 did not show bone formation extending outwards from the screw threads and into the marrow canal.

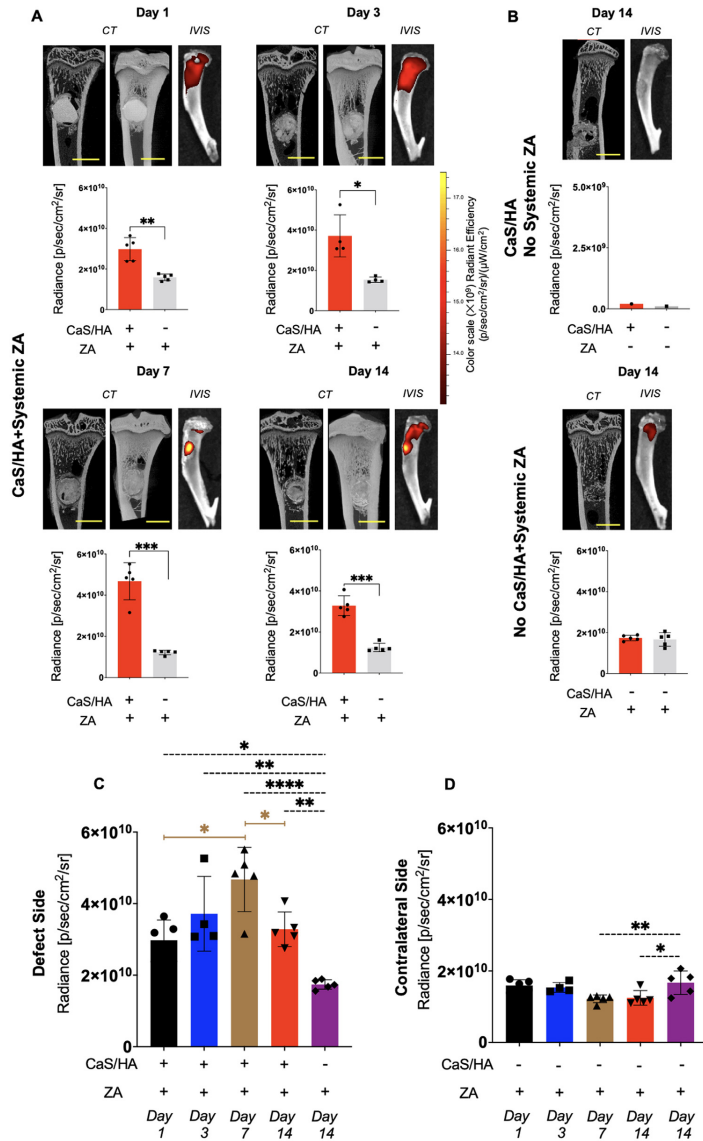
All the screw threads in the medullary canal in G3 were filled with bone tissue with trabecular bone-like structure within the threads as well as in close proximity of the implant both proximally and distally (Fig. 2, top). In agreement with the neutron tomography imaging, the histological analysis of the threads and peri-implant areas in G3 revealed cancellous bone formation in all

the threads of the screw and the bone extended outwards both proximally and distally (Fig. 2, bottom). G4 demonstrated distribution of a high contrast tissue in the screw threads while the regions outside the screw threads were a mixture of both high and low-contrast tissues, however, the micro-structural distribution of the tissue including porosity of the structures was too large to be cancellous bone. Histology showed that the threads in G4 were also covered with a thin layer of trabecular bone. Moreover, remnants of the CaS/HA material mixed with some cancellous bone were also observed in the marrow canal.

### 3.2. Relationship between CaS/HA implantation time and ZA uptake in the CaS/HA material (Sub-study 2)

Micro-CT imaging revealed the presence of the CaS/HA material in the drill hole under the metaphyseal bone in the proximal tibia at all time points (Fig. 3).

The density of the material gradually reduced with the passage of time, which is a typical characteristic of the fast-resorbing CaS



**Fig. 3.** CaS/HA implantation time determines the uptake of systemically administered ZA. (A) Shows representative micro-CT images (both 2D (left) and 3D (middle)), as well as the IVIS image (right) of the operated tibia, acquired 24 h after ZA administration. In order to study the relationship between CaS/HA implantation time and the eventual ZA uptake in the material, the in-vivo implantation time for the CaS/HA material was varied (days 1, 3, 7 and 14) while ZA was always injected 24 h before imaging. The graphs in panel A provide a quantification of the FZA in the area where CaS/HA was implanted and the uptake was compared to an anatomically similar region in the contralateral tibia that did not receive the CaS/HA material. Statistical analysis was performed with a paired sample *t*-test. \* Indicates *p* < 0.05, \*\* indicates *p* < 0.01 and \*\*\* indicates *p* < 0.001. (B, top) shows the representative micro-CT and IVIS images from a control animal that received the CaS/HA material but was never injected with FZA. (B, bottom) shows the micro-CT and IVIS images from another control animal that did not receive the CaS/HA material but was injected with FZA, 14-days after defect creation. (C) Quantification of FZA uptake in the CaS/HA material (in the animals with different CaS/HA implantation times) as well as in the defect area of the control animal without the CaS/HA material. \* Indicates, *p* < 0.05, \*\* indicates *p* < 0.01 and \*\*\*\* indicates *p* < 0.001. (D) Quantification of FZA uptake in the contralateral tibia of animals that are presented in panel C. Black bars in the statistical comparisons indicate a comparison of the treatment group with the control group (Dunnett's post-hoc) while the brown bars indicate a comparison between the experimental groups (Tukey's post-hoc). Scale bar in the CT images = 3 mm.

phase in the CaS/HA material. IVIS imaging showed no fluorescence signal in the control animal that received the CaS/HA material without FZA injection (Fig. 3B, top). Animals that were injected with FZA without the presence of CaS/HA showed a clear uptake of FZA in the growth plate region, while no uptake could be observed in the drilled hole (Fig. 3B, bottom). In the animals that received the CaS/HA followed by a systemic injection of FZA, a strong uptake of FZA in the growth zones could be observed in animals that were injected with FZA on day 1 and day 3. On the contrary, a marked reduction in the FZA uptake in the growth zones was observed in animals that were injected with FZA on days 7 and 14. Irrespective of the time point of ZA administration, all animals that were treated with CaS/HA biomaterial had a significantly higher uptake of FZA in the drill-hole region (ROI) of the CaS/HA implanted side when compared with the untreated contralateral leg indicating that ZA specifically seeks the implanted ceramic biomaterial. This increased uptake was more prominent for animals that received ZA on days 7 and 14. Upon quantifying the total uptake of FZA in a defined ROI in the CaS/HA treated leg (i.e. FZA uptake in the drilled hole), the uptake of FZA was significantly higher compared to the animals that did not receive the CaS/HA material (Fig. 3C). Among the CaS/HA treated animals that received ZA, the uptake of ZA was the highest in day 7 animals with a significantly higher uptake in day 7 animals compared with both day 1 and day 14 ( $p < 0.05$ ). No differences could be observed between day 3 and day 7 animals. Looking at the contralateral, nontreated side, the uptake of FZA was lower in the CaS/HA groups with FZA injections on day 7 ( $p < 0.01$ ) and day 14 ( $p < 0.05$ ), when compared with the control group without CaS/HA. This finding is in line with the FZA uptake on the defect side and shows that the groups with a higher FZA uptake (particularly the day 7 group) accumulate a large amount of the circulating ZA in the material and therefore leads to lesser ZA binding at other anatomical sites.

### 3.3. Effect of CaS/HA implantation time and ZA injection timing on peri-implant bone formation (Sub-study 3)

In the previous experiment, we could demonstrate that the total uptake of ZA in the implanted CaS/HA material is affected by the timing of ZA administration but we could not establish the relationship between total ZA uptake and its eventual effect on peri-implant bone formation. To do so, we repeated the implant integration model and followed the animals for a total period of 6-weeks before the analysis of peri-implant bone formation was performed. Using micro-CT, we observed that the use of CaS/HA material alone did not significantly impact the new bone formation around the implant (Fig. 4).

When ZA was injected on day 1, a mixture of cancellous bone and resorbing CaS/HA material in the marrow cavity could be observed with loosely packed cancellous bone. This reaction however changed from day 3 onwards and the cancellous bone was more compact and denser. Upon quantifying the BV in defined ROI's proximally, we could observe that the BV in CaS/HA groups that received ZA on day 7 ( $p < 0.001$ ) and 14 ( $p < 0.01$ ) was significantly higher than the BV in CaS/HA group without ZA. Furthermore, the BV in the day 7 group was also significantly higher than the BV in the day 1 and day 3 groups ( $p < 0.05$ ), which was in line with the results from the previous experiment pertaining to the ZA uptake in the CaS/HA material. Micro-CT findings were also verified using decalcified histology in order to both separate bone from the CaS/HA material as well as to quantify the total bone area both proximal and distal to the implant (Fig. 5).

Histologically, both the CaS/HA group without ZA and the group that received ZA on day 1 after implantation presented with the lowest amount of new bone formation and remnants of the CaS/HA material were clearly visible at 6-weeks. Animals that

were injected with ZA at days 3, 7 and 14 demonstrated robust peri-implant bone formation although the trabecular islands were closely packed in the day 7 group when compared with day 3 and day 14 animals. All threads in the medullary canal were covered in cancellous bone. Quantification of bone area demonstrated that the bone area/tissue area was significantly higher in all CaS/HA treated groups that received systemic ZA when compared with the control group without ZA (Fig. 5, bottom). Therefore, the results from this experiment demonstrate that the timing of ZA administration can play an important role on the overall peri-implant bone formation when synthetic HA particles are applied around a metallic screw.

### 3.4. Effect of CaS/HA augmentation and systemic ZA treatment on peri-implant bone mineral density in trochanteric fracture patients (Sub-study 4)

A total of  $n = 5$  patients in group 1 (no CaS/HA) and  $n = 2$  in the treatment group 2 (CaS/HA augmented) did not complete the follow-up. CaS/HA material could radiographically be observed around the screw threads in the patient group treated with CaS/HA immediately post-surgery (Fig. 6).

No adverse effects due to CaS/HA application prior to screw positioning were reported post-operatively and neither could the material or the radiographic contrast agent be observed in the surrounding vasculature. X-ray and CT images post-operatively confirmed the presence of a ceramic material around the screw head. At 3-months post-surgery, the ceramic biomaterial had remodelled into cancellous bone, which densified at the terminal time-point of 6-months. CT-based cancellous bone formation in the treatment group was more prominent at the tip of the screw. No major peri-implant changes could be observed in the control group. At 6-months, the BMD quantified using DXA measurements revealed an increase of 5.4 % in the R1 ROI, 5.2 % in the R2 ROI and 17.7 % in the R3 ROI of CaS/HA augmented patients compared with the control group.

### 3.5. Elucidating the role of other calcium phosphate materials and ZA administration on peri-implant bone formation

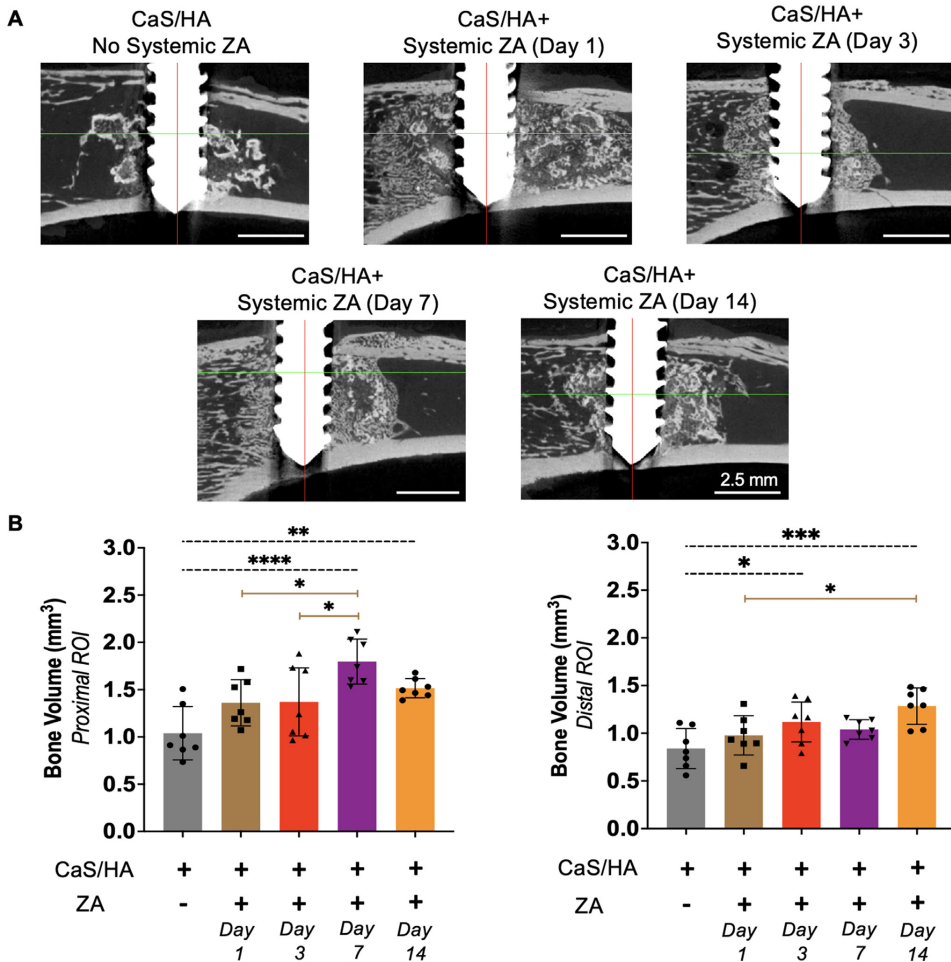
The aim of this sub-study was to demonstrate that systemic biomodulation with ZA is not limited to the combination of CaS/HA and that other calcium phosphate materials such as tricalcium phosphate can be used to achieve similar results. Using micro-CT, we could observe a dense network of cancellous bone around the threads of the stainless-steel screw similar to what was observed for the CaS/HA combination (Fig. 7).

The new bone observed using CT was viable and comprised mainly of cancellous bone, as seen using histology. All threads in the medullary bone were covered with cancellous bone and remnants of the biomaterial could be observed in all specimens.

## 4. Discussion

The goal of this study was to evaluate the possibility of activating peri-implant HA by systemic administration of ZA and thereby improve peri-implant bone formation in osteoporotic bone with a long-term goal of reducing re-operations and mortality in patients undergoing treatment for ITFs. In this study, we successfully showed that systemically administered ZA seeks and biologically activates the peri-implant synthetic HA microparticles. The combination of local delivery of a CaS/HA material followed by systemic administration of ZA led to significantly higher bone formation than when either of the two constituents were applied alone. Importantly, we show that the timing of ZA administration is critical for both achieving a sufficient uptake of ZA in the CaS/HA ma-



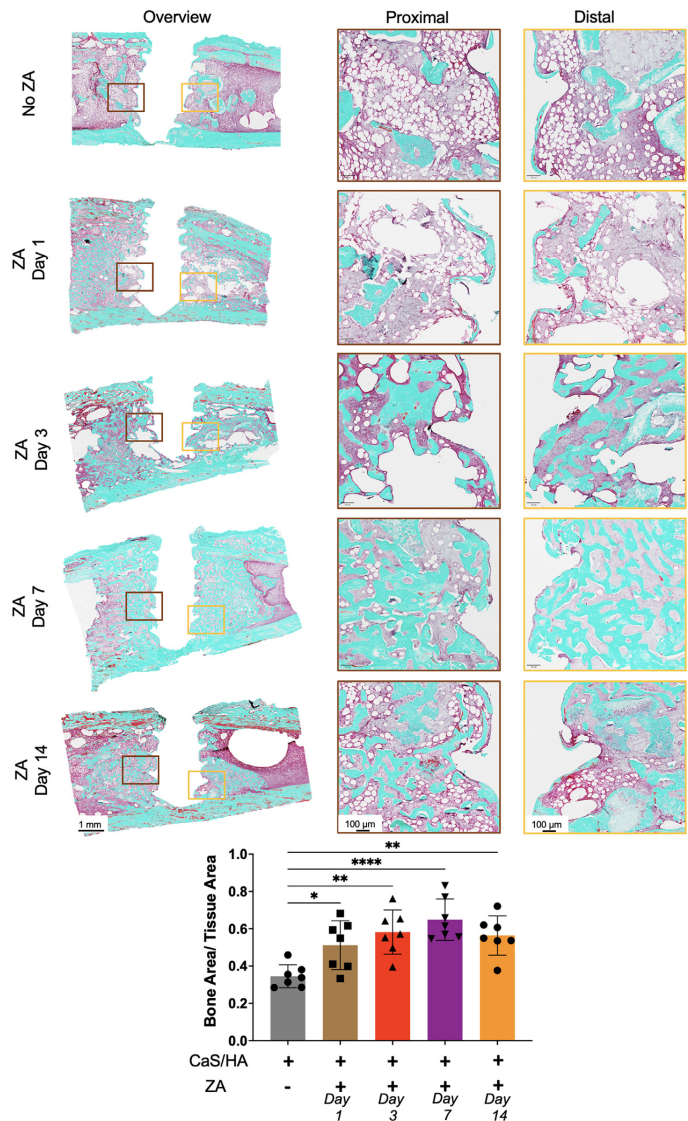


**Fig. 4.** Optimal CaS/HA implantation time is critical to achieve robust peri-implant bone formation when ZA is used to biologically activate the CaS/HA material. (A) Shows the representative 2D micro-CT slices from the experimental groups while the scatter plots in B provide a quantification of the peri-implant bone volume (BV) assessed using micro-CT, both proximally (left) and distally (right) to the implant, respectively. Black bars in the statistical comparisons indicate a comparison of the treatment group with the control group (Dunnett's post-hoc) while the brown bars indicate a comparison between the experimental groups (Tukey's post-hoc). \* indicates  $p < 0.05$ , \*\* indicates  $p < 0.01$  and \*\*\*/\* indicate  $p < 0.001$  and  $p < 0.0001$ , respectively.

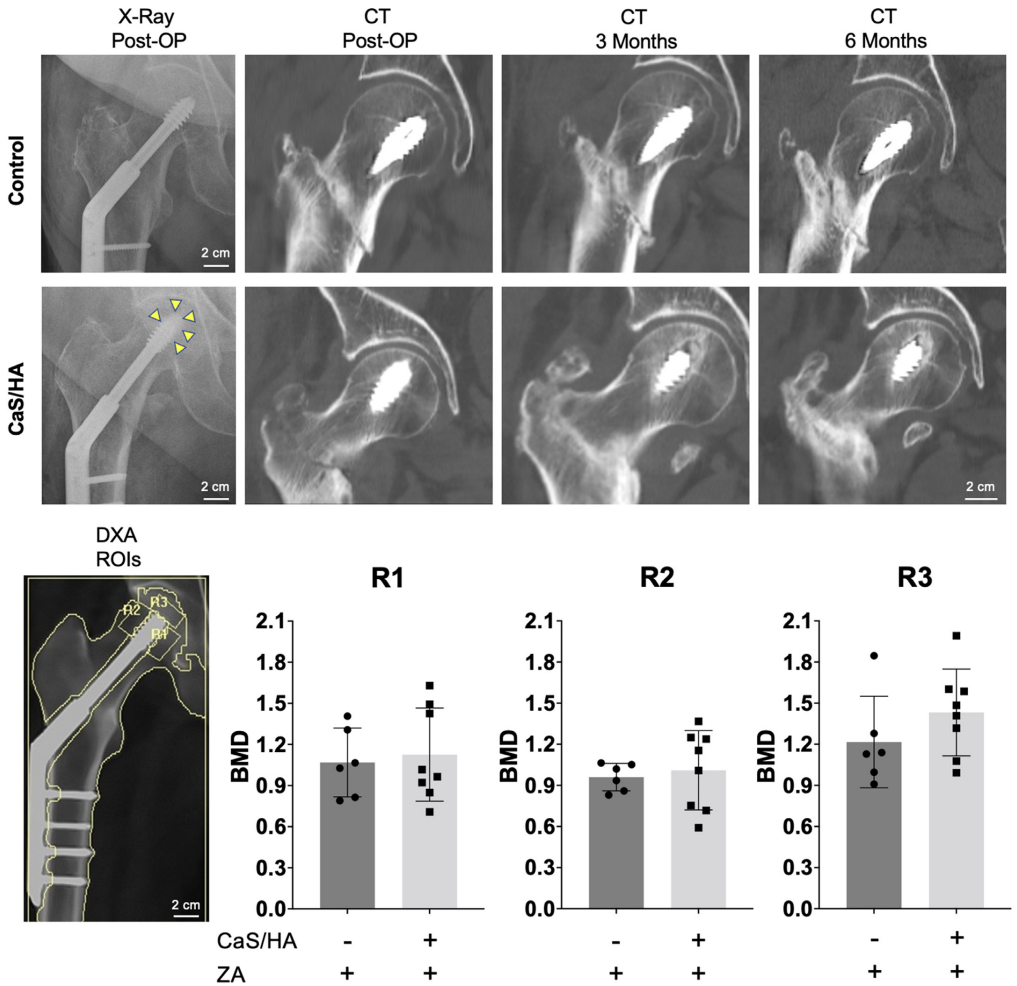
terial and consequently for bone formation at a later time point. In a small set of ITF patients, we showed that the developed method can be translated from the laboratory to a clinical setting with a positive outcome on the peri-implant BMD. The results need to be verified in a larger cohort of patients in order to determine the clinical efficacy. Finally, biologically activating a ceramic material is not only limited to the combination of CaS/HA but can also be applied to other injectable calcium phosphate-based materials.

Bone resorption in osteoporotic patients is increased and the most frequently prescribed medication to counteract the resorption are bisphosphonates from the 2nd and the 3rd generation. ZA

is a 3rd generation bisphosphonate inducing osteoclastic apoptosis via the mevalonate pathway and typically given as once-a-year infusion. In a landmark study by Black and co-workers, a yearly infusion of zoledronic acid dramatically decreased the incidence of vertebral, hip, and other fractures by 25%, 33% and 77%, respectively in post-menopausal women [34]. Bisphosphonates including ZA preferentially bind the HA crystals in the bone and this preferential binding is even more prominent in the growth plates where there is an increased bone turnover and hypothetically, more exposed HA particles that are accessible to the circulating ZA [35]. By applying the CaS/HA biomaterial at the screw-bone interface, the number of recipient HA for the systemically circulating ZA is significantly in-



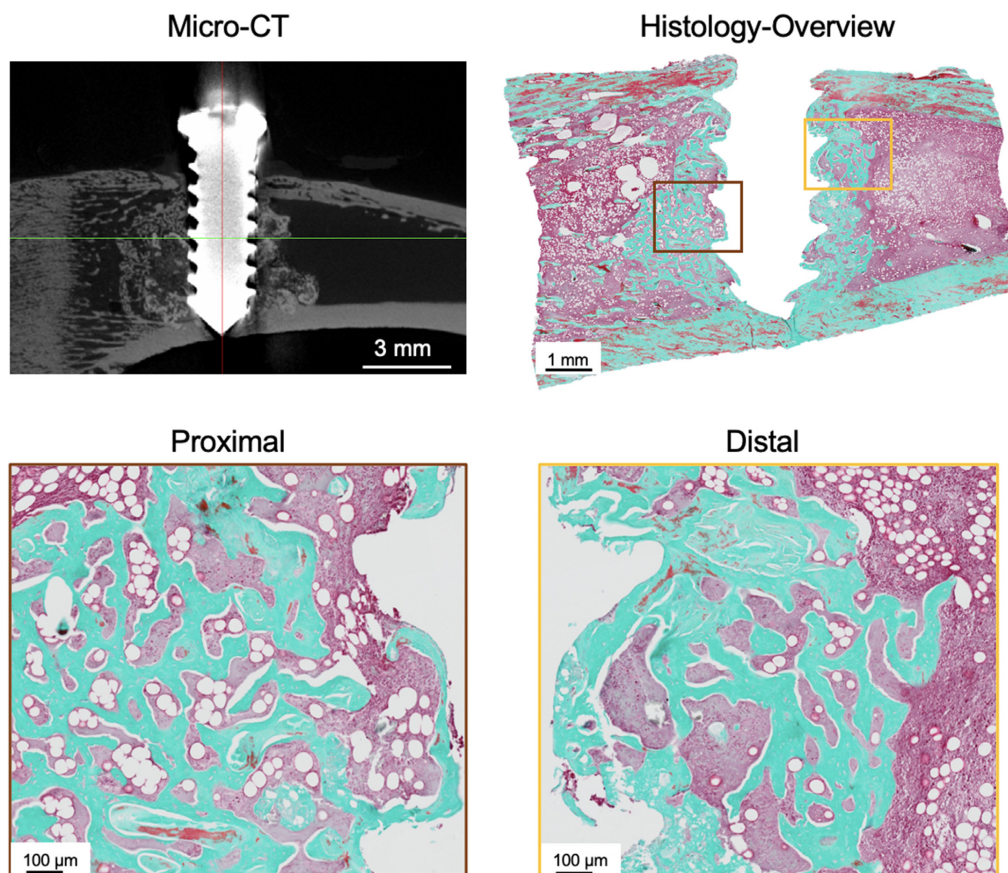
**Fig. 5.** Analysis of peri-implant bone formation using histology 6-weeks post in-vivo implantation. Images in the left panel provide an overview of the entire specimen (1X) while the images in the middle panel represent a high magnification (4X) image the tissue composition proximal (brown box in the overview image) to the implant and the images in the right panel (orange box in the overview image) represents the tissue composition distal to the implant. Decalcified paraffin-embedded sections were stained with Goldner's Trichrome staining which stains cancellous bone as green, cortical bone with mixed shades of green and red, and connective tissue as pink. Remnants of the CaS/HA material were stained light green.



**Fig. 6.** Peri-implant bone formation and bone mineral density in ITF patients treated with the developed approach. The top panel shows a post-operative X-ray image (left) from a patient from the control group who was treated with a standard-of-care approach followed by ZA administration 1–2 weeks post-surgery. A time-lapse CT imaging from the same patient is provided immediately post-op, 3-months later and 6-months later. The middle panel shows the X-ray and CT images from a patient treated with CaS/HA augmentation followed by systemic ZA, 1–2 weeks post-surgery. Yellow arrows in the X-ray image show the presence of radiopaque CaS/HA material. Notice a shell of cancellous bone formed around the implant 6-months post-surgery.

creased and our experiments with fluorescent ZA therefore show a preferential accretion of ZA to the synthetic HA particles from the CaS/HA material when compared with the natural HA in the bone. This phenomenon is novel, to the best of our knowledge, and could change the way systemic ZA is administered to achieve targeted uptake in the area of interest and subsequently improve bone formation in the cancellous environment, which is of particular importance for anchorage of orthopedic hardware in fragile bone. Furthermore, our binding kinetics experiments using fluorescently marked ZA shed light on another important property of the

fast-resorbing CaS/HA material, which could be of importance to the overall uptake of ZA in the material as well as the eventual bone formation [17]. We could demonstrate a direct relationship between the CaS/HA implantation time and the ZA uptake locally in the material for up to a period of one-week following which the uptake of ZA declined at the two-week time point. CaS/HA biomaterial has a fast-resorbing CaS phase comprising 60 wt% of the material. This would imply that the total amount of accessible particulate HA in the CaS/HA material increases with time post-implantation and therefore based on the results from this study,



**Fig. 7.** Systemically administered ZA biologically activates other calcium phosphate materials including  $\beta$ -TCP. The image in the top, left panel shows a representative 2D micro-CT slice of a proximal tibia with a stainless-steel implant augmented with a  $\beta$ -TCP material followed by systemic administration of ZA at 1-week. Top, right is a Goldner's Trichrome stained overview image of the specimen while the panels at the bottom show the tissue composition both proximal (left) and distal (right) to the implant. Cancellous bone can be seen in green, cortical bone as mixed shades of green and red and connective tissue as pink.

an optimal window of ZA administration ranges between day 3 and day 7 of CaS/HA application. This also coincides well with the micro-CT findings with gradual resorption of the CaS material at days 3 and 7. One could argue that if the resorption of the CaS phase were to determine the uptake of ZA in the CaS/HA material, why was the ZA uptake in the material not the highest at day 14? Our in-vivo findings from the micro-CT investigation show that the CaS/HA material starts to resorb (as seen by reduced density and increasing porosity) on day 3 and day 7 without noticeable bone formation around the material at these time points. On the contrary, the material was surrounded by a shell of cancellous bone already at the day 14 time point, which could potentially reduce the accessibility and therefore the overall uptake of ZA in the HA material at later time points.

ZA has with some promising results been used in patients undergoing surgical treatment of osteoporotic fractures with a goal

to prevent future fractures as well as for improving anchorage of implants in patients undergoing joint arthroplasty. An important point to note, however, is that the literature is divided when it comes to reaching a consensus on the optimal timing of ZA administration in the clinical scenario. It has long been debated that the introduction of ZA in the acute fracture healing phase might lead to a delayed fracture healing response. A majority of experimental studies have used ZA as a single infusion at 1–2 weeks post-fracture based on data from Amanat and co-workers, who showed using  $^{14}\text{C}$  labelled ZA that the optimal time window to administer ZA in a closed fracture model in rats was between one to two weeks post-operation [27]. This finding was later clinically verified in one of the earliest clinical trials investigating the effect of zoledronic acid on hip fracture healing. They reported that ZA infusion < 2-weeks post fracture was inferior to giving the infusion at later time points ranging between 4-weeks and 12-weeks [36].



Subsequent studies from the HORIZON trial however did not find any increased risk of delayed fracture healing in patients that were infused with ZA as early as the first 2-week period after fracture healing [37]. As a matter of fact, at present, hip fracture patients in Norway receive ZA infusion immediately during the acute fracture management phase and in the majority of cases within 5 days of surgery. Although previous studies investigating the timing of ZA administration have been performed with a focus on time to fracture healing, these findings could also be extrapolated to scenarios where a fracture fixation device is augmented with a ceramic biomaterial that could be biomodulated using a systemic bisphosphonate. Results from the ZA binding kinetics experiment and the eventual effect on bone formation strongly suggest that there is an optimal time window during which an optimal effect of ZA binding to the CaS/HA material can occur. In the case of the CaS/HA augmented fracture fixation devices, if the drug administration after CaS/HA augmentation is done too early (day 0–1), limited HA particles are exposed to recruit the systemically circulating ZA and if the administration of ZA is done too late (day 14), there is a risk that a bone shell around the material will prevent ZA binding to the HA particles in the CaS/HA material. These results are encouraging and support the hypothesis that an optimal response on bone formation can be achieved using our approach when ZA is administered during the time the patient is still in the hospital (typically between 3 and 7 days).

Although ZA is known to be a potent osteoclast inhibitor, our group has earlier reported that local or systemic delivery of ZA in the cancellous compartment of bone leads to increased bone formation when HA-based recipient biomaterials are present but similar results could not be observed in the cortical compartment [19,20,23]. There are other studies in the literature that have reported similar findings and that ZA plays a bifunctional role in bone depending on the concentration of ZA. Mesenchymal stromal cells treated with low dose ZA have been shown to have an increased osteogenic potential [24] while others have shown that circulating MSCs harvested from ZA-treated patients have an increased expression of osteogenic markers including elevated expression of RUNX2 and osteonectin [38]. On the other hand, some reports contradict the anabolic effects of ZA and suggest that exposure to  $\mu\text{M}$  doses of ZA impairs the osteogenic differentiation of MSCs [39]. In our study, we show that ZA seeks the HA particles in the CaS/HA material and these “biomodulated” HA particles in turn exert a positive effect on bone formation both in the animal studies and the clinical study on ITF patients.

As mentioned earlier, ZA positively affects peri-implant bone mineral density and helps in preserving it compared with no treatment. But this effect of ZA is predominantly due to its ability to limit the osteoclastic activity in this patient group with high bone remodelling. What happens with the interface i.e., the surface of the implant and bone immediately surrounding the implant and does ZA promote peri-implant bone formation? The biological evidence of this phenomenon from a clinical perspective is sparse due to obvious reasons of not being able to perform a destructive test to evaluate peri-implant bone such as high-resolution CT, biomechanical testing, and histology. The only reliable evidence from clinical studies is the fact that ZA administration reduces implant micromotion and consequent failure rates in ZA vs. placebo groups [40]. Finally, when it comes to ITFs there are no large-scale RCTs evaluating the role of ZA in promoting the fixation of trochanteric fracture fixation devices. Cengiz and co-workers evaluated the effect of ZA in the surgical management of ITFs in a cohort of 114 patients with unstable ITFs and reported that the functional outcome post-surgery was better in the ZA-treated groups vs. the placebo group and the ZA-treated group also showed reduced mortality [41]. ITFs are surgically treated with internal fixation either using the DHS and a femoral plate or an intramedullary

nail with a blade/screw going into the femoral head [42]. We recently established a surgical method that standardizes the augmentation procedure of fracture fixation device in ITFs without the use of additional pressure or risk of leakage into the surrounding vasculature [26]. In the same study, we could show that the application of CaS/HA material enhances the immediate mechanical anchorage of a lag screw in an osteoporotic saw bone model with a 4-fold increase in the pull-out strength compared to un-augmented controls and results similar to PMMA. Kok et al., also recently demonstrated the ability of the CaS/HA material to interdigitate into trabecular bone using trabecular bone plugs from human femoral heads [16]. Based on the combined findings from the previous studies and the present study, augmenting an existing ITF fixation device using CaS/HA or other settable calcium phosphate materials would: 1) increase the immediate mechanical strength of fracture fixation by a) filling the screw bone-interface to enhance screw purchase and b) interdigitating and thereby reinforcing the nearby trabecular structures to withstand increased stress, and 2) the calcium phosphate phase of the material could also act as a recruiting moiety for ZA thereby enhance the peri-implant bone formation. This chemical binding of ZA to HA or calcium phosphate materials and the increased bone formation as we have demonstrated in this study has the potential to reduce the re-operation rate in patients undergoing surgical treatment for ITFs. Furthermore, the described approach is not limited to osteoporotic ITFs but can likely be extended for the clinical management of other osteoporotic fractures. A common complication observed in vertebral compression fractures as well as instrumented spinal fusion procedures in osteoporotic patients is the loosening of fracture fixation hardware, with higher failure rates than in ITFs. We have recently shown that application of a CaS/HA material at the interface of a pedicle screw and osteoporotic bone enhances the initial mechanical anchorage of the implants by 39 % when compared with un-augmented controls [43]. If combined with the current developed approach, the HA material could additionally be biologically activated by systemically administered ZA, potentially leading to fewer re-operations than current standard of care.

Our study has several limitations. First and foremost, although we demonstrate using fluorescent imaging that ZA seeks the CaS/HA material and this affinity of ZA is dependent on the time interval the CaS/HA material has been in the defect, we could not measure the total amount of ZA bound to the material and neither do we know the local concentrations of ZA near the implant. More studies would be needed to answer these important questions. Furthermore, in our animal studies, we have used only one specific dose of ZA that has commonly been reported in pre-clinical studies and therefore further dose-finding studies are necessary to evaluate the minimum required dose of ZA to achieve a satisfactory peri-implant bone regeneration response. This study does not investigate whether other types of bisphosphonates including the orally consumed drug alendronate, one of the most commonly prescribed bisphosphonates would also be efficient in enhancing peri-implant bone formation similar to ZA. Another important limitation of this study is that despite large increases in peri-implant bone formation using the developed approach, we did not test the implant anchorage biomechanically as that could have elucidated the functional integration of the implant with the host bone. Finally, although the data from our RCT study on ITF patients shows increased peri-implant BMD without fixation failure, the aim was not to demonstrate a clinically relevant efficacy of the developed method for the reduction of reoperations due to the limited size of the study. A larger RCT would be required and is planned as a nested study in an existing ongoing national hip fracture registry for achieving efficient power in recruitment and outcome follow-up [44].

## 5. Conclusions

Local application of an injectable CaS/HA material followed by systemic administration of the bisphosphonate ZA enhances peri-implant bone formation in an osteoporotic rat model of implant integration. Peri-implant presence of a CaS/HA material as a recipient for systemically circulating bisphosphonate is necessary to achieve a robust peri-implant bone formation. Timing of ZA administration is critical to the outcomes pertaining to the increased peri-implant bone formation. ZA should be administered within 3–7 days post CaS/HA implantation in order to achieve an optimal bone regeneration response at a later time point. In a small set of ITF patients, we showed that a CaS/HA material can be applied at the interface of osteoporotic bone and a DHS during a surgical procedure. Furthermore, our results from this initial feasibility study indicate an increase in peri-implant bone formation in the treatment group, however the data needs to be validated in a large patient cohort before treatment efficacy can be established. Finally, it is not only HA that can act as a recipient for the systemically circulating ZA and other calcium phosphate materials such as tricalcium phosphate elucidate a similar effect. Large animal studies as well as large RCTs are necessary to validate our findings before the developed approach is considered clinically effective.

## Declaration of competing interest

D.B.R., L.L., M.T. and Y.L. are shareholders in Moroxite AB and Moroxite F AB, Lund, Sweden. All other authors have nothing to disclose.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.actbio.2024.03.005](https://doi.org/10.1016/j.actbio.2024.03.005).

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