Perspectives on Chronic Widespread Pain in Rheumatoid Arthritis

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MARIA ARONSSON
DEPARTMENT OF CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

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MARIA ARONSSON completed her medical degree at Lund University in 2012. She subsequently undertook her general internship in Ängelholm and completed her specialty training in rheumatology in Halmstad in 2024. Since 2018, she has been actively involved in the research group at Spenshult Research and Development Centre, and since 2024, she has also been part of the BARFOT study group. She currently works as Lead Consultant Rheumatologist at the Rheumatology Clinic in Ängelholm.

Her doctoral thesis explores various perspectives on the development of chronic widespread pain in rheumatoid arthritis, ranging from the role of small leptin molecules released from adipose tissue to psychological aspects of early interventions such as tight control.

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Maria Aronsson

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UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 10th of October at 09.00 in Lottasalen, Department of Rheumatology, Skåne University Hospital, Lund.

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Abstract:
Concomitant chronic widespread pain (CWP) in patients with rheumatoid arthritis (RA) continues to be a problem despite modern pharmacological treatment. The overall **aim** was to investigate factors involved in chronic widespread pain in rheumatoid arthritis.

Study I, compared patients with early RA (duration ≤12 months), in a tight control cohort, with conventionally managed patients. The patients in the tight control had significantly lower 28-joint disease activity score (DAS28), and reported less pain at 3, 6, 12 and 24 months, $p \leq 0.001$. Participation in the tight control, was associated with remission and acceptable pain (VAS pain<40) at 24 months.

In **Study II**, the prevalence of CWP, was investigated at 6-year follow-up, in both a tight control cohort and a conventional cohort of early RA. In the tight control cohort, 10% reported CWP with the 2019 criteria (CWP2019), compared to 23% in the conventional cohort, p=0.026. Participation in the conventional cohort, adjusted for disease duration, gender, age, and VAS pain at inclusion, had an association with CWP2019, OR 2.57 (95%CI 1.02-6.50). A high level of fear-avoidance about physical activity was associated with CWP2019.

Study III examined associations between the adipokine leptin, and CWP2019 in RA. Patients fulfilling CWP2019 had significantly higher leptin levels, waist circumference and BMI. There was a significant association between leptin levels and CWP2019 OR 1.014 (95% CI 1.007-1.020). The significant association remained when adjustments were made for BMI, gender and age.

In **Study IV**, the circadian rhythm of leptin release was explored in 11 patients with RA and 10 patients with osteoarthritis (OA). A circadian rhythm of leptin release was observed with a peak at night. The two thirds of patients that reported most pain, had numerically higher median leptin levels at all timepoints. The difference was significant or close to significant.

In **conclusion**, there is a possible connection between leptin and CWP in RA. However, the causes of CWP are multifactorial and factors such as tight control early in the disease course seem to have a potential to limit the development of CWP.

Keywords: Rheumatoid arthritis, chronic widespread pain, leptin, sensitisation, tight control, fear-avoidance, body mass index, circadian rhythm of leptin release

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Maria Aronsson

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Faculty of Medicine
Department of Clinical Sciences
Lund, Sweden

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“I am not afraid of storms, for I am learning how to sail my ship.” – Louisa May Alcott

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II. ***Aronsson M****, Bergman S, Lindqvist E, Andersson MLE. Comparison of chronic widespread pain prevalence with different criteria in two cohorts of rheumatoid arthritis. Clin Rheumatol. 2022 Apr;41(4):1023-1032. doi: 10.1007/s10067-021-05999-8. Epub 2021 Nov 23. PMID: 34812975; PMCID: PMC8913461.*

III. ***Aronsson M****, Bergman S, Lindqvist E, Andersson MLE. High leptin levels in blood are associated with chronic widespread pain in rheumatoid arthritis. Arthritis Res Ther. 2024 Dec 23;26(1):228. doi: 10.1186/s13075-024-03463-x. PMID: 39716315; PMCID: PMC11664876.*

IV. ***Aronsson M,*** *Bergman S, Lindqvist E, Andersson MLE. Circadian rhythm of leptin release in rheumatoid arthritis and osteoarthritis (in manuscript).*

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Abbreviations

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADL	Activities of daily living
Anti-CCP	Anti-Cyclic Citrullinated Peptide Antibodies; a type of ACPA test
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption
BARFOT	Better Anti-Rheumatic PharmacoTherapy study
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
BMI	Body mass index
CI	Confidence interval
COMP	Cartilage oligomeric matrix protein
CRP	C-reactive protein
CS	Corticosteroids
csDMARDs	Conventional synthetic disease-modifying anti-rheumatic drugs
CWP	Chronic widespread pain
CWP1990	Chronic widespread pain according to 1990 criteria
CWP2019	Chronic widespread pain according to 2019 criteria
DAS28	28-joint Disease Activity Score
DMARDs	Disease-modifying anti-rheumatic drugs
DRG	Dorsal root ganglia
Early RA	Symptom duration ≤12 months
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
HLA-DRB1	Human leukocyte antigen DRB1
FABQPA	Fear-Avoidance Beliefs Questionnaire, Physical Activity subscale
HLA	Human Leukocyte Antigen
Ig	Immunoglobulin
IL	Interleukin

IQR	Interquartile range
JAK/STAT	Janus kinase/Signal transducers and activators of transcription
KOOS	Knee injury and Osteoarthritis Outcome Score
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OR	Odds ratio
PAD	Peptidylarginine deiminase
PatGA	Patients' Global Assessment of their general health
QOL	Quality of life
RA	Rheumatoid Arthritis
RAOS	Rheumatoid and Arthritis Outcome Score
RF	Rheumatoid Factor
SD	Standard deviation
Sport/rec	Sport & recreation functions
tsDMARDs	Targeted synthetic disease-modifying anti-rheumatic drugs
VAS	Visual Analogue Scale
VCAM	Vascular Cell Adhesion Molecule

Preface

My first encounter with medical research was in the last term of my medical degree course in Lund. It turned out to be a challenging experience, sitting together with a friend alone in a remote, cold office, trying to figure out how to use statistical analysis software on our own. Fortunately, our friendship survived the experience and after the project was completed, we both vowed: never again!

I later realised that a research project was mandatory to complete residency as a medical doctor. Because of my previous experience with research, I was not thrilled to dive in again. However, I was relieved after my first meeting with Maria Andersson at the FOU Spenshult Research and Development Centre. She seemed to completely understand that I wanted to do the mandatory project in the simplest way possible and then move on with my life…

Here we are, almost 10 years after that first meeting, and I am still not done. I found a research group that made research enjoyable and enriching. So, this thesis is not the end, but a beginning of something new. A solid ground to launch from in future projects!

Background

Rheumatoid arthritis – brief history and clinical features

Rheumatoid arthritis (RA) was first described by the French medical doctor Landré-Beauvais in his dissertation in 1800, but descriptions of swollen joints and gout date back to the Egyptians and Hippocrates(1, 2). RA is classified as an autoimmune, systemic, inflammatory disease. It is characterised by symmetrically swollen and tender joints and frequently leads to skeletal erosion and loss of joint function, if the inflammation is left untreated. Severe cases can also have a more systemic disease course, with affection of other organ systems, such as pulmonary fibrosis, serositis, vasculitis, neuropathy, haematologic abnormalities and inflammatory eye involvement(3).

In the twentieth century, important steps were taken to treat the disease with the discovery of prednisolone and methotrexate, among other drugs. Methotrexate was one among the conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) that changed the disease course for many patients with RA(4, 5). It became possible for many patients to enter a state of remission, that is, having no or few remaining symptoms of the disease. Nevertheless, a large proportion of patients with RA still experienced disease activity. In the twenty-first century, the use of biologic treatment (bDMARDs), – specifically designed monoclonal antibodies, and new targeted synthetic DMARDs (tsDMARDs) became increasingly available. These offered additional paths to remission(6, 7). However, even today, there remain patients who do not reach the goal of remission and many more continue to have pain-related problems, despite the absence of swollen joints after initiation of pharmacological therapy(8).

Epidemiology and pathogenesis

The global prevalence of RA ranges between 0.25% and 1% in most countries(3). In one Swedish study, the prevalence rate was estimated to be 0.51%(9). A more recent study found a total cumulative prevalence of 0.77% in one year (2008), 1.11% for women and 0.43% for men(10). The differences in reported Swedish prevalence can be attributed to methodological variation; the studies had disparate age-

restrictions for inclusion and divergent methods for locating the patients. As seen in the later Swedish study, women in general are considered to have a two to three times increased risk of developing RA. The development of RA is thought to originate from a genetic susceptibility, in combination with triggering factors, such as smoking, an infection or a pregnancy, for example. The human leukocyte antigen DRB1 (HLA-DRB1) gene is associated with increased risk of RA but cannot explain the whole genetic susceptibility(3).

It is thought that the disease often evolves gradually over several years, initially through formation of autoantibodies and autoreactive T-cells, directed towards structures in the body(3). The autoantibodies analysed in clinical practice today are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). There are many more autoantibodies in RA and some of them are currently under investigation and might be helpful in the clinical practice in the future(11).

When the disease develops, tender joints appear, and over time joints become swollen. The swollen joints are often accompanied with rising levels of systemic inflammation, Figure 1. At this point, patients in general receive their diagnosis(3). For some patients, there are already signs, at this early stage, of skeletal erosions on x-ray examination of the hands and feet. These early signs of skeletal damage, along with autoantibodies and systemic inflammation with many swollen joints are negative prognostic factors for further joint damage(12).

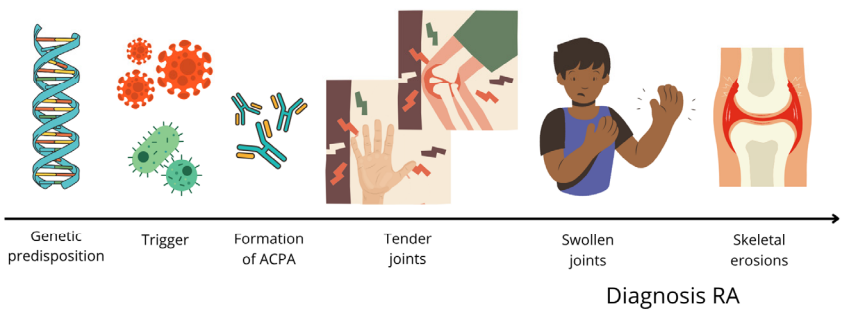

Figure 1 Development of Rheumatoid arthritis. Author's own design. Includes graphic elements from Canva.

Diagnosis of RA

Classification criteria

There are no diagnostic criteria for RA, however, there are classification criteria developed for research purposes, which are often used to support the diagnosis in clinical practice. The first classification criteria were developed in 1956(13). The criteria divided patients in terms of having definite, probable and possible RA. In short, the classification method consisted of 11 criteria and had 19 exclusion criteria. Several criteria were based on histological changes. In 1958, the criteria went through minor revision and the concept of classic RA was introduced(14). A weakness with the 1956 and 1958 criteria was that diseases like spondylarthritis, polymyalgia rheumatica, and Lyme disease could be misclassified as RA(15). As knowledge in the field of rheumatology evolved, especially with the discovery of human leucocyte antigen B27 (HLA B27) and the increasing use of rheumatoid factor (RF), new criteria were developed(15-17). The 1987 criteria were easier to use in the everyday clinic, with fewer points to consider, and the criteria related to histological changes, and all the exclusion criteria, were removed.

In recent years, when knowledge of the importance of early pharmacological treatment increased, it became clear that the 1987 criteria risked missing early RA. Therefore, new research criteria were developed in 2010(18). The 2010 criteria make an earlier diagnosis possible through the shorter symptom duration of six weeks and the greater weight given to tender joints – as opposed to counting only swollen joints. They also consider ACPA, discovered after the development of the 1987 criteria(19). In this dissertation, the RA patients in the Better Anti-Rheumatic PharmacoTherapy cohort (BARFOT)(20) and in the diurnal variation study were classified using the 1987 criteria, while the patients in the Tight control study were diagnosed by way of expert opinion that considered both the 1987 and the 2010 criteria.

Laboratory tests

ESR, CRP

To evaluate the degree of systemic inflammation, the erythrocyte sedimental rate (ESR) and the C-reactive protein (CRP) are used(21, 22). Signs of systemic inflammation can be useful, both in diagnosing RA and in the follow-up and evaluation of pharmacological treatment(18, 23, 24).

RF

The first, more specific, lab test for RA was the RF. RF was first discovered in the 1930s and consists of antibodies against the Fc-fragment of immunoglobulin G (IgG)(25, 26). The use of RF for diagnostic purposes has some limitations; above all, there is the issue of specificity. RF can be positive in other patient categories, such as in Sjögrens syndrome, and is also gradually more positive with increasing age in healthy subjects(26).

ACPA

It became possible to test for citrullinated proteins (ACPA) in the late 1990s(19). The process of citrullination is a post-translational modification (changing the protein after its production), where a conversion from arginine to citrulline takes place under the influence of the enzyme peptidylarginine deiminase (PAD)(27). ACPA tests in general have a higher specificity than RF, but there is a lack of harmonization between the various commercial ACPA tests(11). The PAD, needed to citrullinate peptides, can originate from bacteria or be released by various cell types, such as neutrophils(27).

Treatment

Pharmacological treatment and a "window of opportunity"

Modern pharmacological treatment of RA aims for early remission. The concept of a "window of opportunity" early in the disease course has been widely accepted in rheumatology. Over time, the concept has evolved – from initially referring to the first two years of disease, to in current publications often being limited to the very early or even pre-clinical phases of RA(28). It is believed that early, intense treatment can reduce the severity of the disease course and achieve drug-free remission for long periods of time(28). Some even believe that the right pharmacological treatment early in the course might prevent the disease from breaking out. Many drugs have been tried on patients with ACPA and arthralgia, some of which seem to delay the outbreak and lead to an easier to treat disease(29-32).

The corner stone of RA treatment, in both European and American guidelines, is early initiation of methotrexate, a drug in the csDMARD-group, that has immunomodulatory properties that are not yet fully understood(7, 33). Structurally, it is a folic acid analogue and thereby affects nucleotide synthesis and purine metabolism. However, several other mechanisms by which methotrexate is thought to suppress inflammation have been suggested(34). There is a reasonable amount of

research and extensive clinical experience on methotrexate use in achieving remission and slowing down skeletal erosions(7, 33, 35).

Methotrexate is, however, not sufficient for all patients. The guidelines commend the addition of biologic treatment (bDMARDs) or Janus kinase (JAK) inhibitors (tsDMARDs), if substantial improvement is not met at 3-month follow-up, in the presence of negative prognostic factors, or if the remission/low disease activity goal is not met at 6 months(7, 33). Another treatment option is a combination of older csDMARDs. Extensive studies have shown that combination therapy can be successful when tolerated(36). Often used is the combination methotrexate, sulfasalazine and hydroxychloroquine. Biologic options have shown superiority in most settings, albeit at a higher financial cost(7, 37).

"Tight control" and "treat to target"

In the early twenty-first century, studies investigating the importance of the follow-up schemes of early RA began to appear in scientific publications. The often cited, single-blinded, randomized control trial TICORA showed in 2004 that patients with a "tight-control" follow-up (visits to the rheumatologist every month) and a clear target for remission had better outcome than patients in conventional care(38). In the TICORA trial, the pharmacological treatment consisted of older csDMARDs used in monotherapy or in combinations, in accordance with a step-up scheme. The authors saw effects on both remission and skeletal erosions in the tight control group and reported calculations on total health costs, showing that tight control could be implemented without additional costs, compared to conventional care(38).

Since then, many studies with various versions of tight control and step-up schemes have been published, including versions that utilise bDMARDs and tsDMARDs(39-42). It is now generally accepted that tight control is advantageous and that step up of treatment is important(7). The term "treat to target" has been implemented to describe the desirable mindset of augmenting treatment until either remission or low disease activity is reached(7, 33). In Sweden, a standardised clinical pathway for early diagnosis and treatment of RA has been established(43).

Persistent pain in RA

Despite massive progress in both pharmacological treatment of RA and recent guidelines that emphasises the importance of a treat to target approach, as many as around 30% of RA patients continue to battle with chronic widespread pain (CWP)(44). In the general population roughly 10% suffers from CWP and 2% has fibromyalgia, a condition distinguished by CWP in combination with fatigue, affected sleep and psychological wellbeing(45-47). Within RA and many other rheumatological conditions, the percentage of patients with concomitant fibromyalgia is around 20%, depending on the classification criteria used in the respective studies(48-50). The process by which localised pain in swollen joints evolves into widespread pain in joints and muscles is not fully understood, and the process seems to progress despite good control of inflammation in many patients(44, 51, 52). Theories on the underlying cause of widespread pain development include peripheral sensitisation, central sensitisation and various psychological explanatory models such as the biopsychosocial model of health and illness(53).

Biopsychosocial model

The biopsychosocial model, first described by Engel in 1977, highlights the close relationships between physical symptoms, psychological processes and social factors, in relation to various medical conditions(54, 55). The model is still actively used in specialised pain management centres and in treatment of stress-related mental illness, for example. The concept is that various parts of the model can cause a downward (or upward) spiral. For example, if a person experiences pain (bio-) this can lead to thoughts and emotions of concern/unease, and in some individuals, catastrophic thinking (psycho-). This in turn can lead to altered behaviour in different forms, for instance withdrawal from social interactions and relational problems (social-). The altered thoughts and emotions can also lead to difficulties sleeping (bio-), leading to more pain, anxiety and isolation, in a downward spiral fashion(53), Figure 2.

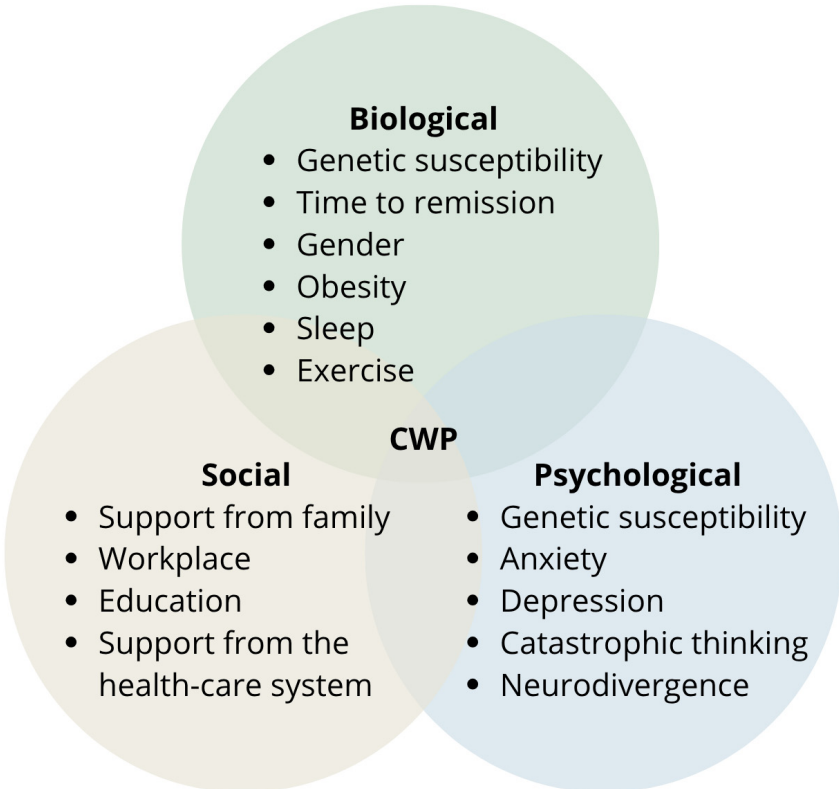

Figure 2 The biopsychosocial model, inspired by Engel(54, 55), here with focus on development of CWP, author's own design.

Peripheral and Central sensitisation

The concept that changes in the central nervous system could alter pain signals from the periphery was first proposed in the 1980s, when the term central sensitisation was coined. Initially, the term referred to spinal mechanisms, but subsequent studies have revealed numerous spinal, supraspinal and peripheral mechanisms of pain alteration(56-60), Table 1. The magnified pain caused by the sensitisation process gives rise to a so-called nociplastic pain, which is further described under "nociplastic pain" in the pain classification section of this thesis.

Some sensitisation mechanisms worth special mentioning are the wind-up and the temporal summation that describes the process, where repeated stimulation elicits stronger and stronger neural signals and enhances pain perception(58). Another sensitisation mechanism is the activation of "silent receptors". This was first described in arthritic joints in cats, where unactive, mechanically insensitive receptors in the periphery were activated by inflammation in the joint and then started to fire neural impulses(61). Spinal sensitisation processes include involvement of the dorsal root ganglia (DRG), a clustering of sensory nerve bodies of the spinal nerves that relay information on pain, temperature and proprioception from the periphery to the central nervous system. Microglial cells surround the neurons in the DRG and help them with homeostasis, communication, support and protection. In mouse models, where the sciatic nerve is injured, activation of microglia leads to an immune response in the DRG. This activation of microglia is thought to be important for contralateral spread of inflammation to the other side's DRG and to be responsible for contralateral pain sensations – a pain phenomenon also present in humans(62). IgG from fibromyalgia patients has been shown to label microglia in the DRG in mice and cause painful sensory hypersensitivity(63).

Table 1 Sensitisation mechanisms

Brain	Spinal	Peripheral
Increased responsiveness to pain	Clustering and convergence of pain-signals from different locations	Expansion of receptive fields
Increased connectivity between brain regions important in pain	Amplification of spinal reflex transmission	Elevated cytokine and chemokine concentrations and change in pH
Decreased activity in brain regions involved in pain inhibition	Decreased spinal inhibition of pain signals	Alterations of receptors on neurons
Elevated levels of substance P and glutamate in cerebrospinal fluid. Decreased gamma-aminobutyric acid (GABA)-mediated signalling	Wind-up and temporal summation	Activation of silent receptors
Alterations in shape and size of brain regions connected to pain processing	Alterations in spinal organisation	Effect of antibodies/immune complexes on nociceptors
Activation of glial cells	Activation of glial cells	

"Bottom-up" and "top-down" sensitisation

In recent years, the concept of "bottom-up" and "top-down" sensitisation has gained interest. Bottom-up sensitisation refers to a process where there is an ongoing nociceptive input, like a painful joint in RA or osteoarthritis (OA), driving the sensitisation. The problem can start at any age, depending on when the nociceptive stimuli appear(64). If the nociceptive input ceases, for example following a joint replacement surgery, the widespread pain can improve or dissolve completely(65). Conversely, in top-down sensitisation, the process is thought to originate in the central nervous system and requires no nociceptive input to maintain the progression. In this group, psychological co-morbidity is high, and the pain often starts early in life, typically following puberty. There is often a family history of pain and a high number of overlapping pain conditions(64).

In an individual patient, both bottom-up and top-down processes can coexist, which has been demonstrated with functional magnetic resonance imaging (MRI). In one study, patients with RA and high scores of fibromyalgianess (measured with the 2011 fibromyalgia score) exhibited a similar pattern of activity in the brain as patients who only had fibromyalgia(66). However, another study showed that, in patients with RA and concomitant fibromyalgia, sensitisation patterns on functional MRI correlated to higher levels of ESR. This could support an explanation model where bottom-up sensitisation from inflamed joints partially accounts for the process, and these patients could benefit from augmented anti-inflammatory treatment(67).

Autoantibodies and pain

Autoantibodies, such as RF and ACPA, can be present for several years before the onset of arthritis in patients that later develop RA(68). During this period, the patients often report arthralgia, which has led to the hypothesis that antibodies can affect our pain system even without signs of inflammation. A study from 2016 showed that polyclonal injection of ACPA could elicit pain-like behaviour in mice without signs of systemic or local inflammation(69, 70). Another study showed that mice injected with two monoclonal ACPA developed pain-like behaviour and bone loss as well as tenosynovitis. Knock-out mice without peptidylarginine deiminase 4 (PAD4) were significantly less affected by the ACPA injections(71). Human studies have shown, however, that ACPA positivity in early RA is not associated with unacceptable pain and that ACPA in established active RA is not associated with experimental pain sensitivity, measured with pressure pain thresholds(72, 73). Autoantibodies other than ACPA that have been explored in regard to pain are antibodies against the cartilage proteins type II collagen (CII) and cartilage oligomeric matrix protein (COMP)(60).

Adipose tissue and pain

When it comes to chronic pain, it is well known that overweight and obesity are associated with many different pain conditions, like fibromyalgia and low back pain(74, 75). In fact, a systematic review showed that people with obesity reported higher pain intensities than the general population, regardless of underlying diagnosis(76). Another recent study showed that a body mass index (BMI) > 30 appeared to disrupt the brain's descending pain inhibitory mechanisms in patients with fibromyalgia. The patients were assessed with neurophysiological tests, such as trans cranial magnetic stimulation and conditioned pain modulation(77). It has additionally been demonstrated that fibromyalgia patients with high BMI are significantly more impaired by their disease(78). An association between overweight and increased pain and inflammation has also been observed in RA(79, 80).

The molecular basis of these associations is not known and the role of the adipose tissue in the body has not yet been fully explored. Over the last twenty years, the understanding of adipose tissue has evolved from a concept of a simple storage facility for energy, to an intricate endocrine organ with connections to most parts of the body, including energy homeostasis, hormonal system, immune defence and more(81, 82). Adipose tissue manufactures a wide range of signalling molecules called adipokines, which in many ways resemble the cytokine signalling molecules used in the immune system(81, 83). One adipokine that shares many similarities with the cytokine interleukin-6 (IL-6) and has been quite extensively studied is leptin(84).

Leptin

Leptin was first described in mice in the 1990s as the "Obese (ob) gene product"(85). Leptin was soon thereafter linked to patients suffering from extreme overweight caused by genetic mutations in the ob gene and associated congenital leptin deficiency(86). Today, it is known that leptin has a central role in energy homeostasis. It acts through activation of leptin receptors in the regulation of appetite, bone mass, basal metabolism, reproductive function, insulin secretion and immune response(82).

It is known that elevated leptin levels in blood drive the immune system towards an T helper 1 (Th1)-oriented response, which in theory could be associated with an increased risk of autoimmunity, Figure 3. Low leptin levels, contrarily, drive the immune system towards a response with increased regulatory T cell (Treg) activity and a higher risk of infections. This is in accordance with the fact that children with congenital leptin deficiency are prone to serious infections and their mortality rate linked to infectious diseases is elevated. Supplementation with recombinant human leptin normalises many parts of the immune system in these children, for example absolute numbers of CD4+ T cells and lymphocyte cytokine release patterns(87, 88).

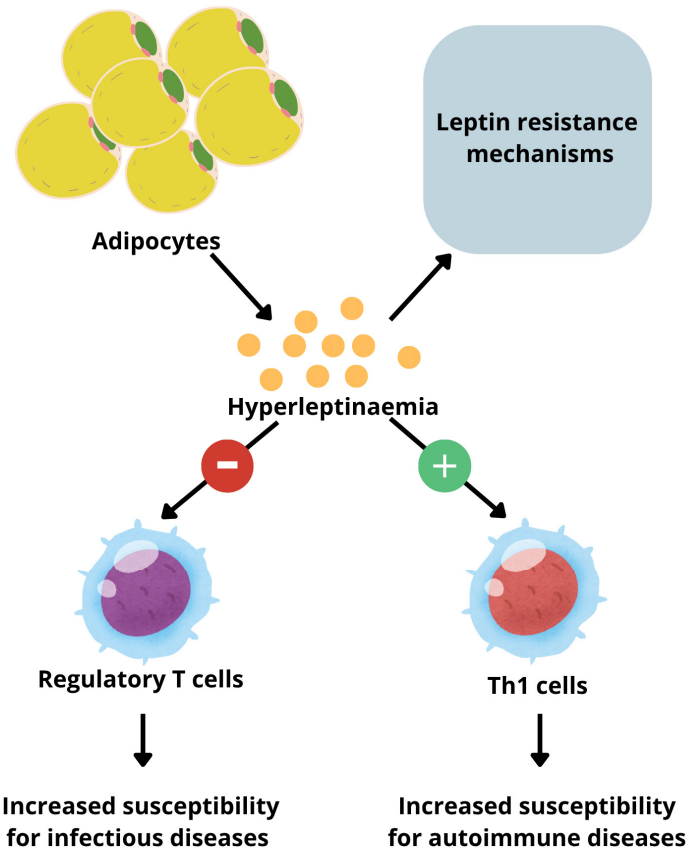

Figure 3 Simpified illustration of possible links between leptin, infections and autoimmunity. Author's own design inspired by Procaccini(88). Includes graphic elements from Canva.

Leptin resistance

In the most common form of human obesity, leptin levels are increased and hyperleptinemia causes central and peripheral leptin resistance(88). Leptin resistance is considered to arise from three distinct mechanisms – the first being saturated transport over the blood brain barrier and the second a downregulation of leptin receptors. The third mechanism involves various downstream problems in the intracellular signalling cascade, where a signal from a leptin receptor at the cell surface triggers the JAK/STAT system via the JAK 2 pathway(89).

Leptin and pain

The leptin concentration is affected by BMI and gender, where females have higher leptin levels. The difference between men and women is thought to arise from differences in sex hormones and different body compositions(90). For example, leptin receptors in the dorsal root ganglia (DRG) have been found to be upregulated by oestrogen in rats(91). As mentioned earlier, the DRG is thought to play a role in the process of pain sensitisation. One theory suggests that activation of DRG microglia surrounding the neurons could be of importance in this process(62). Studies in rats have demonstrated that leptin can affect cytokine release from microglia in vitro(92) and that spinal administration of a leptin antagonist prevented and reversed neuropathic pain behaviours in a sciatic nerve injury model(93). Another study has suggested that impaired leptin signalling in mice affects descending antinociceptive pathways(94), which could be part of the explanation to why people with impaired leptin signalling can experience altered pain thresholds, according to the authors. If these and other proposed connections between the adipokine system and the pain system could be supported by studies in humans, it could potentially inform the development of much needed new therapeutic targets for pain medication(95).

Elevated leptin levels have been demonstrated in fibromyalgia patients, compared with BMI-matched controls, but also in patients with osteoarthritis (OA) – where higher levels were associated with CWP and with preoperative pain severity before total knee arthroplasty(96-99). Additionally, leptin levels have been found to have an association to presence and duration of chronic low back pain (100). In a small exploratory study of 3 women, where 51 cytokines were analysed for a total of 72 study days, only one of them, leptin, varied in line with pain intensity from day to day. The same authors conducted a larger cross-sectional study of 5,676 generally healthy women, where they found that BMI and leptin were independently associated with self-reported pain(101).

Leptin and inflammation

As mentioned earlier, leptin is considered to have mainly pro-inflammatory properties(102, 103). An association between leptin levels and CRP and a higher risk of all-cause mortality for those with higher leptin levels, have been described in RA(104, 105). Higher BMI and metabolic syndrome have been associated with higher disease activity in RA. After treatment, when a decrease in disease activity is seen, a simultaneous decrease in leptin levels has been described(106, 107). One study saw a connection between leptin levels and inflammation in joint sonography in overweight RA patients(108). However, other studies have not seen the same connection between disease activity and leptin in RA. There remains a lack of comprehensive understanding about the manner in which leptin and other adipokines produced in the adipose tissue and locally in and around the joints contribute to the disease process in RA and OA(109, 110).

Adipokines are produced in chondrocytes, osteoclasts, osteoblasts, synoviocytes and inflammatory cells in the joints. Theories suggest an intricate crosstalk between various adipokines, some exerting mainly pro-inflammatory and some anti-inflammatory effects, which influence effector cells in the joints(111-113). One study demonstrated lower leptin levels in synovia than in blood in patients with RA and proposed the possibility of leptin consumption in inflamed joints(114). A meta-analysis including over 900 patients has shown that RA patients with high disease activity exhibit higher leptin levels in blood. However, it is unknown if the leptin levels are the cause or the consequence of the high disease activity(115). In vitro leptin has been shown to trigger interleukin-8 (IL-8) release from synovial fibroblasts from patients with RA and OA via JAK2/STAT3(116). It has also been demonstrated that leptin in vitro augments the expression of vascular cell adhesion molecule-1 (VCAM-1), an important binding molecule for lymphocytes in sites of inflammation, in human and murine chondrocytes(117).

Leptin autoantibodies

Autoantibodies against leptin and other adipokines have been found in healthy subjects and are thought to participate in the transport of the molecules and modulation of the signal(118, 119). These antibodies have been shown to have an altered affinity in obese subjects compared to healthy controls(120, 121), and the production of antibodies appears to be affected by age and body composition(121). Naturally occurring autoantibodies acting as carriers and modulators of the adipokine ghrelin have been studied in RA patients. The study suggested an increase in autobody affinity towards ghrelin in RA patients. The formation of anti-ghrelin immune complexes was affected by both disease activity and the presence of RF(119).

Circadian rhythm of leptin release

Leptin is secreted in a pulsatile manner and has a circadian rhythm of release(122, 123). The pulses are short and require frequent sampling to be captured. A study with 6 healthy men and blood sampling every 7 minutes found 32.0 ±1.5 pulses/24 hours(122). Similar results have been demonstrated for women(124). The circadian rhythm of leptin release exhibits a peak at night and lower levels around noon(122-126). It has been demonstrated in small studies that leptin levels increase in shift workers eating at night and especially in maladapted workers that are experiencing difficulties associated with shift work(127, 128). A hypothesis about shift work inducing leptin resistance has been suggested(128). However, another small study found opposing results, where increasing misalignment between meals and the original circadian circle supressed the leptin levels(125). This demonstrates that the intricate interactions between the circadian rhythm of leptin release, meals, BMI and sleep are not yet fully understood.

Classification of pain

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". The definition was recently rewritten to better encompass the breadth of the pain experience, in light of growing knowledge on peripheral and central sensitisation and to cover all pain groups: nociceptive, neuropathic and nociplastic(129).

Pain groups

Nociceptive pain

This can be described as the healthy nervous system's response to actual or threatening tissue damage. Nociceptors (pain receptors) in the peripheral tissue transmit nervous signals through nerves to the spinal cord's dorsal horn, where they are transmitted to nerves conveying the message to the brain. At the relay station in the spinal cord, the signal can be affected by regulatory signals coming from the brain, which act as a "pain brake". Nociceptive pain is often relatively easy to treat, for example with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) (53, 59).

Neuropathic pain

This type of pain arises from tissue damage in the peripheral or central nervous system. One example is, impingement of a nerve caused by disc herniation, leading to ischiatic pain. Another example is, damage to the peripheral nerves from unsuccessfully treated diabetes mellitus, resulting in neuropathy. This sort of pain requires other treatment strategies, sometimes in the form of surgery to relieve pressure on a nerve, sometimes pharmacological treatment affecting the nervous system's transmission and signals substances. Examples of pharmacological treatments used are antiepileptics such as gabapentin and antidepressants such as duloxetine(53).

Nociplastic pain

This term refers to pain in an unhealthy nervous system, where important regulatory signals are diminished. The "pain brake" from the brain affecting upgoing signals in the spinal cord can be affected, as can the sensitivity of the peripheral nociceptors. There can also be an amplification of pain signals in the central nervous system. The phenomena are referred to as central and peripheral sensitisation and can lead to an experience of pain from stimuli that previously caused mild discomfort (hyperalgesia) or no discomfort at all, such as a hug or gentle stroke (allodynia). Treatment based on a biopsychosocial approach is generally needed and pharmacological treatment with antiepileptics, such as gabapentin, and antidepressants, such as duloxetine, can be considered(53).

ICD-11

To better describe pain and classify it in a useful way, not only for researchers and public health providers but also for patients, in 2019 the World Health Organization (WHO) approved a new way of handling pain codes(130). In the latest codebook for classification of diseases, ICD-11, CWP is classified with its own code under the subgroup chronic primary pain. The former used diagnosis of fibromyalgia is in ICD-11 included in the code for CWP(131). The diagnosis CWP according to the ICD-11, bears great resemblance to CWP2019 since it requires diffuse pain in 4 of 5 body regions for more than 3 months. However, the pain must also lead to emotional distress or functional impairment to be classified as CWP. In ICD-11, pain can also be classified as secondary to an underlying disease; chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain, and chronic secondary musculoskeletal pain(130). Promising results show that the new codes seem to better classify the patients' underlying conditions. The previous ICD-10 codes often labelled patients with the symptom pain without further specification(132). At time of writing, the ICD-11 is in the process of being

translated to Swedish and will be gradually implemented in the Swedish healthcare system in the coming years(133).

Fibromyalgia

The frequently used 1990 classification criteria for fibromyalgia requires pain with ≥3 months duration in the left and right side of the body, below and above the waist, and axially, combined with 11 tender points out of 18(134). These criteria are still commonly used, both in the clinic to help diagnose fibromyalgia and in research studies. In the twenty-first century, several adapted versions of the criteria have been published, aiming to both better encompass the psychological aspects of fibromyalgia and enable research on patient reported data without physical examination of the tender points. The original version is still in use alongside the new versions(135-138).

Chronic widespread pain 1990 and 2019

To facilitate pain research on patient-reported data, without physical examination of the tender points, the part of the 1990 fibromyalgia criteria that describes the pain distribution (below and above the waist, left and right side of the body, and axially for ≥3 months) has been used, and referred to, as chronic widespread pain (CWP). This definition of CWP has enabled the assessment of pain status across large cohorts of patients with a pain mannequin in a questionnaire(45).

The CWP1990 criteria have been criticised because a patient can be classified as having CWP with as few as three painful sites in total, see Figure 4. To better classify patients who have a severe pain problem, new criteria were suggested in 2019(139). According to these criteria, a patient should have pain ≥3 months in 4 out of 5 body regions (left upper, left lower, right upper, right lower, axial) and have at least 7 painful sites out of 15. The CWP2019 criteria is thought to better capture the widespread pain described in the ICD-11, compared to the 1990 criteria. However, neither of them captures the psychological aspects of chronic widespread pain(139). In this thesis, the CWP2019 criteria have primarily been used, to better capture patients with severe pain problems resembling the pain seen in fibromyalgia(139).

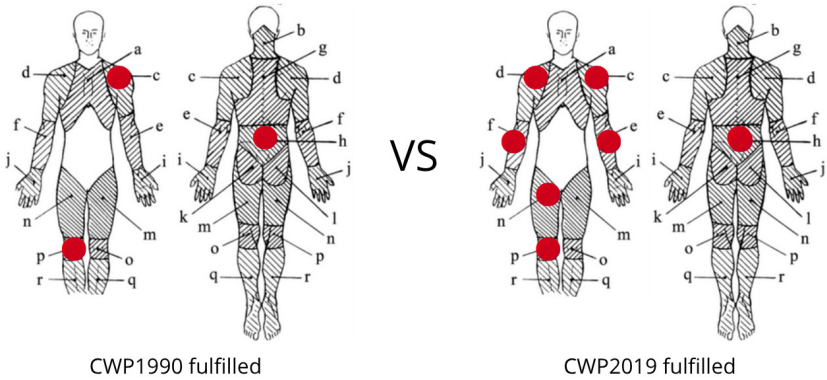

Figure 4 Comparison between the minimal number of painful sites to fulfil the 1990 and the 2019 criteria for chronic widespread pain (CWP), respectively. Pain mannequin modified by the author with permission(140).

Rationale for the thesis

Pharmacological treatment of RA has undergone a remarkable development over the last 30 years, with many novel treatment options. Additionally, a better understanding of the importance of intensive treatment early in the disease has enabled more patients to reach remission of the disease.

However, the prevalence of CWP and fibromyalgia remains high in patients with RA, despite modern treatment options. Patients with concomitant generalised pain often suffer from psychological problems, and their quality of life and ability to work and contribute to society can be reduced. It is essential to study this population of patients, both to find factors associated with development of CWP, and to determine the optimal follow-up to reduce the risk of CWP. These subjects are investigated in Study I and II of this thesis.

Another area of special interest in the development of CWP is the process of pain sensitisation, where painful joints are thought to contribute to the process of acute localised pain evolving into generalised pain, through “bottom-up sensitisation”. However, the underlying reasons for increased sensitisation in patients with RA are not yet fully understood. The previously known connection between obesity and generalised pain, also demonstrated in patients with RA, is investigated in Study III and IV. The adipokine leptin, secreted mainly from the adipose tissue and with possible connections to the process of sensitisation, is investigated in relation to CWP and pain. Additionally, Study IV explores the circadian rhythm of leptin release in patients with RA and OA, to facilitate further studies in the field.

Overall aim

The overall aim of this thesis was to investigate factors involved in chronic widespread pain development in rheumatoid arthritis, and to explore relevant prognostic factors and outcome measures.

Specific aims

Study I

To determine whether an intensive tight control regime for early RA patients, with monthly visits to the physician in the first 6 months but without specific treatment schemes, could increase the remission rate and improve patients' reported pain

Study II

To investigate the prevalence of CWP1990, CWP2019 and fibromyalgia 6 years after the onset of rheumatoid arthritis and compare two patient cohorts, one with tight control and one with conventional follow-up early in the disease course.

Study III

To investigate whether there is an association between leptin levels and chronic widespread pain in patients with RA.

Study IV

To investigate whether there is a circadian rhythm of leptin release in patients with RA and OA and to conclude whether patients in existing cohorts with pain and high leptin levels can be identified at any timepoint during the day.

Methods

Overview of studies

This thesis is based on four quantitative studies, briefly summarised in Table 2.

Table 2 Overview of studies

	Study I	Study II	Study III	Study IV
Study design	Longitudinal, comparative	Cross-sectional, comparative	Cross-sectional	Prospective descriptive
Participants/ controls	100/100	80/101	334	21
Data sources	Clinical data	Questionnaire, clinical data	Questionnaire, clinical data, laboratory data	Questionnaires, clinical data laboratory data
Statistics	Pearson Chi², Mann-Whitney, Simple and multiple logistic regression,	Pearson Chi², Fisher's exact, Mann-Whitney, Shapiro-Wilk normality test, Simple and multiple logistic regression	Pearson Chi² Fisher's exact, Mann-Whitney, Simple and multiple logistic regression	Fisher's exact, Mann-Whitney exact
Main outcome variables	DAS28-remission, VAS pain, HAQ	CWP1990, CWP2019, FABQPA	Leptin, CWP2019, BMI, waist circumference	Diurnal leptin, RAOS/KOOS-pain

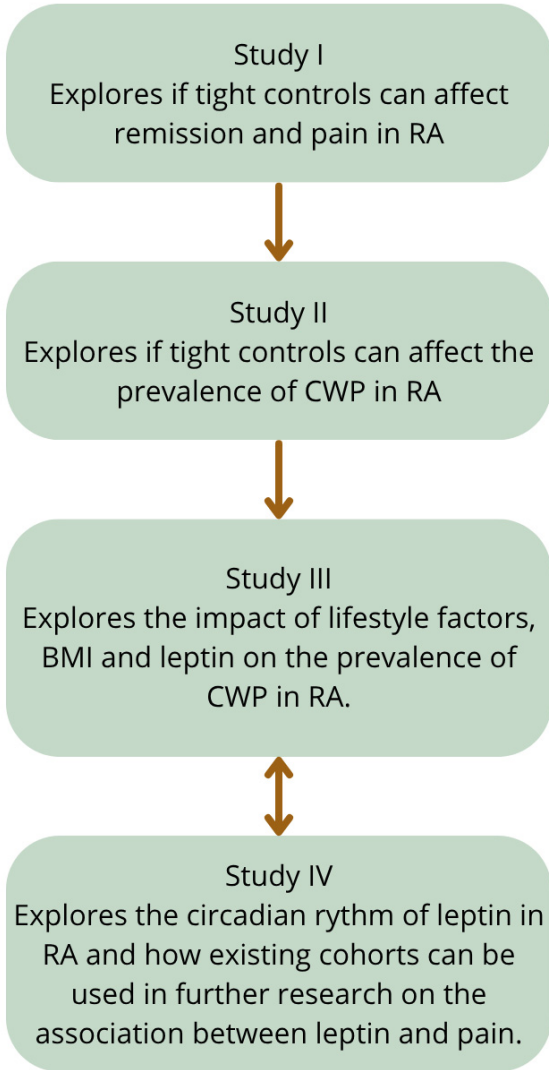

Figure 5 Overview of the included studies and their relationship in the thesis

Data collection and participants

Cohorts

Tight control cohort

Patients from this cohort were included in Study I and II. The Tight control was a single-centre study of patients with early RA (symptom duration ≤12 months), consecutively included between 2011 and 2016. The diagnosis of RA was set by a rheumatologist, and the exclusion criterion was previous rheumatological disease. The patients received monthly visits to their physician for the first 6 months, followed by visits at 9, 12 and 24 months. If the patient had not reached remission at six months, the monthly visits could continue until 12 months. The study did not include any specific treatment guidelines. The physicians were encouraged to follow clinical practice and strive for early remission. The target was remission (DAS28 <2.6). At each visit, the patients reported general health, pain and fatigue on a Visual Analogue Scale (VAS) and filled in both a Health Assessment Questionnaire (HAQ) and EuroQol-5 dimensions (EQ5-D). The physicians reported CRP and ESR, along with tender joints, swollen joints, disease activity and current medication. Disease activity measured with DAS28 was calculated at each visit. X-rays and serum samples for a biobank were taken at set intervals.

BARFOT cohort

Selected patients from the BARFOT study were used as a reference cohort for the Tight Control patients in Study I and II. In Study III, selected BARFOT patients were used as study group. The BARFOT was a large multicentre study of early RA (symptom duration ≤ 12 months) that included patients consecutively between 1992 and 2006 and followed them for 15 years(20). The RA diagnosis was set with the 1987 criteria(15). The patients had visits to the physician at 3, 6, 12 and 24 months, and thereafter according to a predefined schedule until the end of the study. Extra visits were possible, if needed. The physicians were encouraged to strive for remission and early methotrexate initiation. When bDMARDS became available, they were used based on the clinical judgement of the physician responsible for the patient's care. At each visit, patient-reported variables like general health, pain and fatigue on a VAS, HAQ and EQ-5D were recorded. The physicians reported CRP and ESR, along with tender joints, swollen joints, disease activity and current medication. Disease activity measured with DAS28 was calculated at each visit. X-rays and serum samples for a biobank were taken at set intervals.

Study I

The first study in the thesis took a single-centre longitudinal approach. It investigated the effect of a tight control regime on disease activity, remission, HAQ and VAS pain in 100 patients with early RA from the Tight control cohort, with monthly visits to the physician for the first six months, as described above. The Tight control cohort was compared with 100 conventionally managed patients from the same clinic, treated by the same physicians as the Tight control patients.

The conventional reference cohort consisted of two subgroups: subgroup A and B. Subgroup A contained 30 patients from the same time period as the Tight control who fulfilled the inclusion criteria for the Tight control – but had not been included in the original study. They were approached with a letter and signed a written consent to be part of the conventional cohort. The conventional subgroup B consisted of 70 patients from the same clinic, who received their RA diagnosis between 2004 and 2006 and were included in the BARFOT cohort(20). There were no significant differences at baseline between subgroup A and B in, age, symptom duration, smoking, RF, ACPA, VAS pain, ESR, DAS28, HAQ or swollen joint count. Both groups had, on average, three visits to the physician in the first 6 months, which is in line with the standardised clinical pathway for early diagnosis and treatment of RA in Sweden(43). Therefore, they were merged into a single conventional reference cohort.

The median age in the Tight control cohort was 63, vs. 58 in the conventional cohort. There were no significant differences in gender, disease, duration, ESR, VAS pain at baseline, RF or ACPA status between groups.

Study II

In this cross-sectional, comparative, single-centre study, the prevalence of CWP was investigated in two RA cohorts, using both the 1990 and the 2019 criteria for CWP. In total, 181 patients were included. Of these, 80 came from the Tight control study described earlier, which had monthly visits to the physician for the first 6 months. The other 101 patients, used as a reference cohort, came from the BARFOT multicentre study, described above. The BARFOT patients selected for the current study were included in the BARFOT cohort between 2001 and 2006 and participated in a questionnaire in 2010, a median of 6 years after disease onset (83% response rate). Only BARFOT patients from the same clinic as the Tight control patients were included in the current study. In 2019-2020, a corresponding questionnaire was sent out to the Tight control patients, a median of 6 years after disease onset, corresponding to the BARFOT questionnaire. The 80 patients that responded were included in the current study (74% response rate).

The median age of the participants was 64 in the Tight control, vs. 58 in the BARFOT. The percentage of women was 64%, vs. 65%, respectively. RF positivity

was 61% in both groups and ACPA positivity was 68%, vs. 69%, respectively. In the Tight control, 65%, and in the BARFOT, 50% were ever smokers.

Both questionnaires contained inquiries on pain and fatigue on a VAS and comorbidities including patient-reported diagnosis of fibromyalgia and a pain mannequin(140). Data from the mannequin were used to calculate CWP with the 1990 and 2019 criteria. Furthermore, the questionnaire included HAQ to measure function in daily life and EQ-5D to measure quality of life. In the questionnaire sent to the Tight control cohort, we additionally included questions on physical activity, an Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) and a Fear-Avoidance Beliefs Questionnaire, whereas, in the current study, we used only the part concerning physical activity (FABQPA).

Study III

The third study took a cross-sectional approach and investigated lifestyle factors and metabolic factors associated with CWP2019 in RA. The study was based on 334 patients from the RA multicentre cohort BARFOT, described earlier. In 2010, a questionnaire was sent to 1,910 eligible BARFOT patients; 1,534 responded, which gave a response rate of 80%. Of these 1,534 patients, 334 submitted blood samples within one year of completing the questionnaire, as part of the original BARFOT protocol. These 334 patients were selected for the current study. The selected patients had inclusion dates in the BARFOT cohort between 1994 and 2006, median year 2002. Their median age was 64 and 71% were women. Their median BMI was 25.4. Serologically, 61% were RF-positive and 62% were ACPA-positive.

The median disease duration at the time of the questionnaire was 8 years, SD 4.1. The questionnaire included inquiries on weight, height, waist circumference, pharmacological treatment, tender joints, swollen joints, alcohol, smoking and a pain mannequin. Data from the pain mannequin was used to calculate CWP with the 2019 criteria. The serum samples collected as part of the original BARFOT protocol were stored at -80°C in the BARFOT biobank. Samples from the 334 participants in the current study were analysed to determine their leptin levels, using an enzyme-linked immunosorbent assay (ELISA) method (Alpco).

Study IV

In this prospective, descriptive single-centre study leptin levels were investigated over a 24-hour period in patients with RA and OA. The 21 participants had serum samples for leptin drawn every 4 hours (7 samples in total per patient). The data collection took place in 2001-2002 and analysis of the data has also resulted in an earlier publication on diurnal variation of COMP(141). After collection of the venous blood samples, the serum was stored at -80°C. Of the 21 participants, 11 had RA and 10 had OA. The RA patients were admitted to the hospital for individualized training and the OA patients were provided with overnight accommodation. The two patient groups had their meals at the same times and were encouraged to go to bed at 22.00. The RA patients had individualised training sessions for 1-2h in the morning and afternoon and the OA patients had a 30-minute walk together at 14:00. The RA patients completed a Rheumatoid and Arthritis Outcome Score (RAOS) questionnaire and the OA patients a Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire.

The RA group consisted of 11 consecutively recruited patients with erosive disease, of whom 10 were seropositive. They were 91% women and had a median disease duration of 20 years. Their median age was 66 and median BMI 22.5. They had ongoing medication, as follows: 73% csDMARD, 9% bDMARD, 18% no DMARD, 27% corticosteroids.

The 10 OA patients all had clinically verified OA, according to the ACR criteria(142), and seven of them also had radiographic knee OA, with a Kellgren-Lawrence score ≥2 or osteophytes(143). The OA patients were recruited from the Spenshult cohort, a prospective study of OA initiated in 1990(144). The OA patients were 50% women and had a disease duration >10 years. Their median age was 62 and their median BMI 28.4.

Outcome measures

Pain, health, function

CWP1990, CWP2019

To assess chronic widespread pain, Study II used CWP in accordance with the 1990(134) and 2019(139) criteria, while Study III used only the 2019 criteria. The history of CWP1990 and CWP2019 is described in more detail in the Background section of this thesis. The pain mannequin in the questionnaires was used to calculate CWP1990(140). It included 18 pain sites. Fulfilment of CWP1990 requires pain in the left and the right side of the body, above and below the waist, and axially. Additionally, the duration of pain needs to be ≥3 months.

The pain mannequin in the questionnaires was originally constructed to assess CWP1990. To adapt our mannequin so that it was as close as possible to the 15 sites used in the 2019 definition of CWP, we excluded the chest and knees from the calculations. This enabled us to have five main pain regions, with 3 pain sites in each, resulting in a pain site score of 0-15, as in the original 2019 criteria. Since there was a minor modification of the original score, the term CWP2019, rather than the originally proposed WP2019(139), has been used in the articles and thesis. The difference between our CWP2019 and the original WP2019 is that our mannequin incorporates the feet in the lower leg and that the arms are divided into pain sites in a slightly different manner. Our mannequin has combined shoulder/upper arm, lower arm, and hand. The original WP2019 has shoulder, upper arm and lower arm. Fulfilment of CWP2019 requires having pain ≥3 months affecting at least 4 of 5 pain regions and 7 of 15 pain sites, see illustration in Background, Figure 4.

VAS pain, fatigue, general health

A visual analogue scale is used to let the patient grade their symptoms and can be used for pain, fatigue and general health, for example. The grading is scored 0-100, best to worst. VAS pain was used in Study I-III, VAS fatigue in Study II and III, and VAS general health in Study I, where it was used to calculate DAS28.

Acceptable pain

In Study I, the term “acceptable pain” was used if VAS pain is <40. It derives from an earlier study investigating the level of pain usually perceived as unacceptable among patients. It states that a level of VAS pain ≥40 is generally perceived as unacceptable pain(145).

KOOS, RAOS

In Study IV, the Swedish version of the Knee injury and Osteoarthritis Outcome Score (KOOS) was used to assess pain and symptoms in the osteoarthritis group of patients. It includes questions on five subscales regarding symptoms from the knee: Pain, Symptoms, Activities of daily living (ADL), Sport and Recreation functions and, finally, Quality of life (QOL). All subscales are scored 0-100, worst to best, meaning that lower scores represent higher pain levels, in contrast to the VAS pain score(146, 147).

An adaptation of KOOS, modified for patients with rheumatoid arthritis, the Rheumatoid and Arthritis Outcome Score (RAOS), was used in the RA group of patients in Study VI. The questions in the five subscales are essentially the same as in the KOOS, as is the scoring 0-100, worst to best. The difference between RAOS and KOOS is that KOOS explores symptoms from the knee only, whereas, in RAOS, the questions refer to symptoms from the whole leg (hips, knees and feet)(148).

HAQ, EQ-5D

The Health Assessment Questionnaire (HAQ) was used to assess function in activities of daily living in Study I-IV, range 0-3, best to worst(149-151).

To measure health-related quality of life, EuroQol 5 dimensions (EQ-5D), with the standard British time trade-off based preference set, was used in Study II, range ≤1(152, 153).

Fibromyalgia

Patient-reported diagnosis of fibromyalgia was used in Study II and III. We have no record of how the patients received their diagnosis or which criteria were used. However, clinical practice in Sweden, which is also recommended by the National clinical decision support, is to use the 1990 criteria(134, 138).

Disease activity

Tender, Swollen 28-joint score

In this thesis, the physician's 28-joint score for tender and swollen joints were used in Study I and self-reported 28 joint score for tender and swollen joints were used in Study II and III, see Figure 6. Additionally, the physician's 28 joint scores were used in calculating DAS28 and DAS28-3.

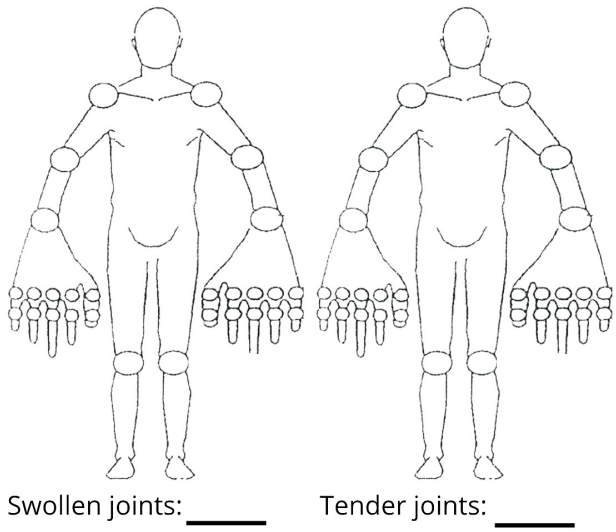

Figure 6 A mannequin for self-reported 28-joints score.

DAS28 and DAS28-3

In Study I, 28-joint Disease Activity Score (DAS28) was used to evaluate disease activity. It is calculated using a mathematical formula with constants and four clinical variables: physician's tender joints, physician's swollen joints, ESR and self-reported general health(23, 24). In DAS28-3, an alternative formula is used, which is based on the same first three clinical variables but does not include self-reported general health(154, 155). When evaluating disease activity with DAS28, range 0-9.4, patients are grouped based on their score, as follows: remission <2.6, low disease activity 2.6-3.19, intermediate disease activity 3.2-5.1, High disease activity >5.1(156).

Lifestyle and metabolic factors

BMI, Waist circumference

BMI was used in Study II, III and IV. In Study II and III, it was calculated from self-reported length and weight. In Study IV, the patients were measured and weighed at the clinic. Waist circumference, used in Study III, was self-reported in the questionnaire. Clear instructions were included in the questionnaire, on how to measure, and a picture demonstrating where to hold the measuring tape.

AUDIT-C

In Study II, the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) was used. This short form of AUDIT is focused on establishing whether or not a person has a risk consumption of alcohol. The total score range is 0-12, and a score ≥4 in women and ≥5 in men is considered a consumption associated with increased risk(157).

FABQPA

The Fear-Avoidance Beliefs Questionnaire (FABQ) was developed to assess the amount of fear and avoidance a person expresses about physical activity and work. It was originally developed for patients with back pain but has been used in many patient groups, including RA(158-161). The instrument consists of two subscales, one related to physical activity and the other to work. The subscale concerning physical activity (FABQPA) was used in Study II, albeit the participants filled in the entire FABQ.

The FABQPA includes 4 items about physical activity causing pain and injury, which are rated 0-6, together producing a total score range of 0-24. A value of ≥8 was considered a high level of FABQPA. The threshold was based on the median value in the Tight control, which was 8, and a previously published study of Swedish RA patients that used the same cut-off for high FABQPA(160).

Physical activity

Questions on physical activity included in the questionnaire for Study II were reused from the 2016 Swedish national health survey and included questions on the number of minutes spent each week on moderate and vigorous physical activity(162).

Biochemical markers

Inflammatory markers

The erythrocyte sedimentation rate (ESR)(21) and the C-reactive protein (CRP) were used to assess inflammation in Study I and II. The analyses were done at the patient's nearest hospital lab.

Leptin

Leptin analyses in Study III and IV were done using an enzyme-linked immunosorbent assay (ELISA, Alpco). The analyses were performed in duplicates in accordance with the manufacturer's instructions. Standard curves and two controls per plate were included. The laboratory staff member performing the analyses was blinded for patients' characteristics.

The blood samples were taken from the BARFOT biobank and stored samples from a previous diurnal variation study(20, 141). All blood samples were stored at -80°C.

Clinical data

To describe the participants in Study I-III, baseline data on ACPA/RF status, age, smoking and disease duration were retrieved from the BARFOT and Tight cohort databases. In Study IV, the information was retrieved from the medical records and the Spenshult cohort database(144).

Pharmacological treatment

In Study I and II, pharmacological treatment was reported by the physicians in the cohort databases. In Study III, self-reported data on medication was used. In Study IV, a combination of self-reported data and information from the medical record were used.

Statistical analyses

Statistical analyses were carried out using SPSS statistics software, IBM USA (Study I-II version 26 and Study III-IV version 29). The level of significance was set to 0.05. All studies used complete case analysis without multiple imputation of data. Non-parametric methods were used for comparisons, given that all the studies contained variables that were not normally distributed. The normality of the data was tested with the Shapiro-Wilk normality test. Categorical variables were presented as numbers and percentages, and statistical comparisons were made using Pearson's chi-square test and, if $n<5$, Fisher's exact test. Continuous variables were reported as medians with quartile 1-quartile 3 (q1-q3) used as dispersion measure,

except in Study IV, where median and interquartile range (IQR) were used. Statistical comparisons between continuous variables in Study I-III were made with Mann-Whitney U test and in Study IV with exact Mann-Whitney U test, because of the small number of participants.

Some exceptions from using non-parametric methods were made, as follows: in Study III, mean and standard deviation (SD) were used to describe the participants' disease duration at the time of the questionnaire. Additionally, in Study IV, mean and SD were used in the Discussion section, where results from KOOS and RAOS were compared and discussed in relation to previous studies.

In Study I-III associations were investigated with simple and multiple regression analysis. In Study I and III, adjustments were made for relevant variables based on discussions among authors and in Study III, a Direct acyclic graph (DAG) analysis was done. In Study II, the selection of variables used in the multiple regression analysis were made based on their p value in the simple logistic regressions, where variables with $p>0.3$ were included in the multiple logistic regression model.

In the planning of Study I, power calculations were made for the main outcome DAS28. With 5% significance level and an effect size of at least 0.5, and a power of at least 80%, 64 patients were needed in each group. In Study II, no separate power calculation was made. In Study III, we hypothesised that the association between leptin and CWP2019 would resemble the association recently demonstrated in OA in fewer than 300 participants(98). Therefore 334 participants were considered sufficient for Study III. For Study IV, the number of participants was chosen based on earlier studies of diurnal variation and circadian rhythms(123, 126, 141).

Statement on the use of Artificial intelligence

No generative artificial intelligence tools were used to produce or enhance the content of this thesis. ChatGPT (developed by OpenAI) was utilized solely as a reference tool, like a dictionary or thesaurus, to look up individual words, synonyms, and general grammatical concepts.

Ethics

All studies included in this thesis were carried out in accordance with the Declaration of Helsinki(163). Written consent to participate was obtained from all patients included in Study I-IV. The databases were managed in accordance with ISO 9001(164).

Study I

Ethical approval was obtained from the Regional Ethical Review Board in Lund, Sweden for the Tight control (LU 2012/604) and the conventional cohort, subgroup A and B (LU2018/824, LU 398-01).

Study II

Ethical approval was obtained from the Regional Ethical Review Board in Lund, Sweden for the Tight control (LU 2012/604, LU2018/824) and the conventional cohort (LU 398-01).

Study III

Ethical approval was obtained from the Swedish Ethical Review Authority (2022-03178-01). Ethical approval for the BARFOT biobank was obtained from the Regional Ethical Review Boards in Lund, Gotenburg, Stockholm and Linköping (398-01, 282-01, 02-345, 01-263), Sweden.

Study IV

Ethical approval was obtained from the Regional Ethical Review Board in Lund (LU 684-00, LU 421-02) and the Swedish Ethical Review Authority (2025-00375-02, 2025-00549-02).

Results

Study I: Tight control, remission and pain

Tight control

This study examined the effect of a tight control regime, with monthly visits to the physician for the first 6 months for early RA. The 100 patients in the Tight control cohort were compared with 100 patients from the same clinic that had conventional follow-up, receiving approximately 3 visits in the first 6 months. The study did not include any specific treatment scheme for any of the groups.

Disease activity and pain

The Tight control group had significantly lower disease activity, measured with DAS28, at 3, 6, 12 and 24 months, compared with the conventionally managed group, $p<0.001$. The DAS28 remission at 12 months was 71% in the Tight control vs. 46% in the conventional group, and at 24 months it was 68% vs. 49%, respectively, $p<0.05$. The Tight control group reported significantly less pain at 3, 6, 12 and 24 months, $p<0.001$, Figure 7. No significant difference in CRP between the groups was observed at inclusion or follow-up.

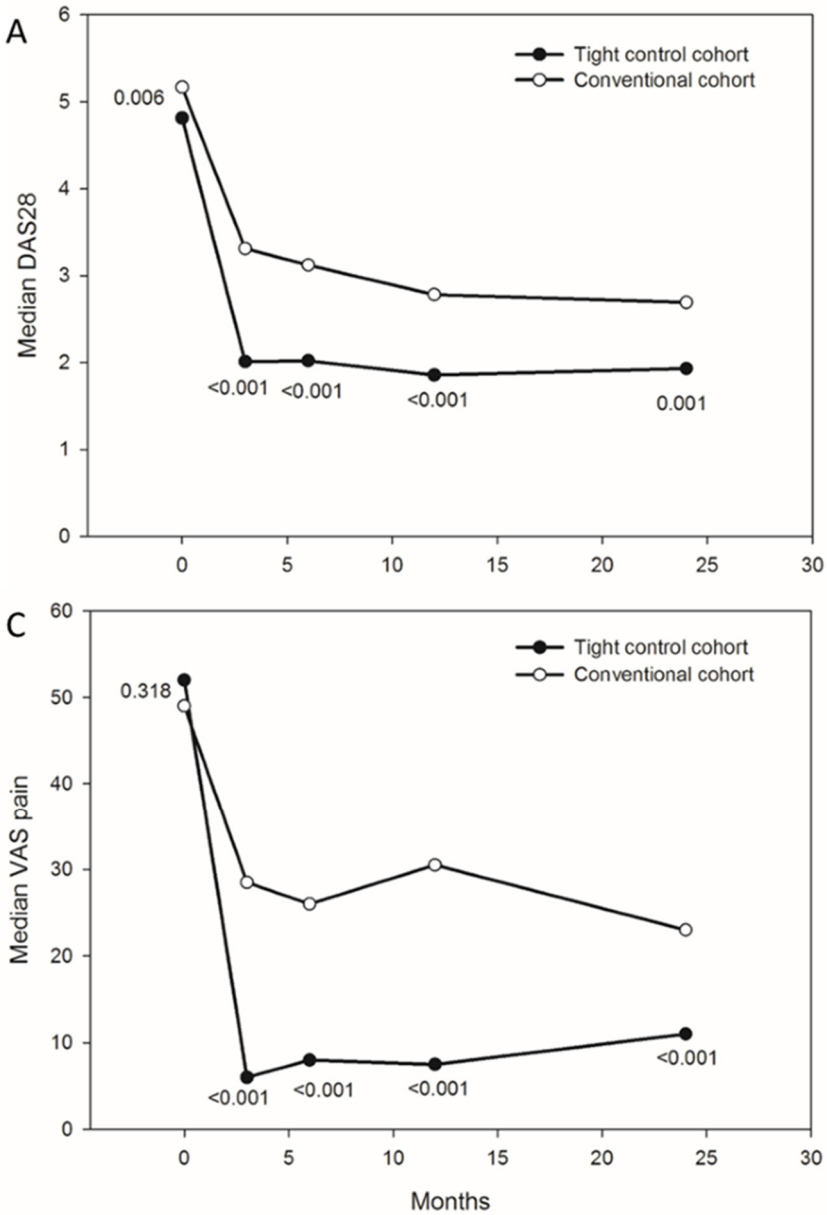

Figure 7 Outcome in the two cohorts over 24 months. Panel A shows median disease activity score (DAS28). Panel C shows median Visual Analogue Scale (VAS) pain. Part of Figure published in Paper I.

Pharmacological treatment

The patients in the Tight control group received more combination treatment with more than one csDMARD and more corticosteroids, whereas the patients in the conventional group received more bDMARDs, at 12 and 24 months, $p<0.05$. However, on analysing the number of patients receiving methotrexate in some form: as monotherapy, as part of combination therapy or in addition to biologic therapy, there was no significant difference in methotrexate usage between the cohorts. Additionally, there was no significant difference in the number of patients that had ever tried a bDMARD during the 2-year study period, between the two cohorts.

Factors associated with remission

To examine whether differences in treatment or baseline factors could explain the better outcome in the Tight control group, multiple logistic regressions were performed with the dependent variable being remission, at 12 and 24 months, respectively, Table 3. The calculations revealed that the chance of remission at 12 and 24 months was around four times higher in the Tight control group. This effect could not be explained by differences in medication, age, disease duration at inclusion or disease activity at inclusion.

Table 3. Factors associated with remission at 12 and 24 months: results from multiple logistic regression analyses.

		Remission at 12 months	**Remission at 24 months**
		OR (95% CI)	**OR (95% CI)**
Cohorts	Conventional	1	1
	Tight control	**3.78 (1.61-8.84)**	**4.55 (1.77-11.69)**
Age, years		1.01 (0.98-1.03)	1.0 (0.97-1.02)
Duration, months		1.13 (1.0-1.29)	1.04 (0.91-1.20)
Incl. DAS28, 0-9.4		**0.71 (0.51-0.97)**	0.79 (0.55-1.14)
Corticosteroids	No	1	1
	Yes	0.91 (0.39-2.12)	**0.29 (0.12-0.74)**
DMARDs	No DMARD	1	1
	csDMARD	1.52 (0.31-7.53)	5.35 (0.91-31.33)
	Comb. csDMARDs	0.76 (0.12-4.68)	4.54 (0.64-32.30)
	bDMARD	1.05 (0.15-7.43)	**11.66 (1.53-89.16)**
N		157	131

Remission, DAS28<2.6; OR, odds ratio; CI, confidence interval; Age, age at inclusion; Duration, disease duration at inclusion; Incl. DAS28, 28-joint Disease Activity Score at inclusion; DMARDs, Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional Synthetic Disease Modifying Anti-Rheumatic Drug; Combination of csDMARDs, >1 csDMARD; bDMARDs, biologic Disease Modifying Anti-Rheumatic Drug with or without combination therapy with csDMARD. Note: significant OR in bold writing.

Factors associated with acceptable pain

To better characterise the patients' pain experience, factors associated with having acceptable pain (VAS<40) at 24 months were analysed in a multiple logistic regression model. Participation in the Tight control had an independent positive association with having acceptable pain at 24 months, OR 9.67 (95% CI 2.90-32.24). Treatment with csDMARDs or bDMARDs also had significant positive associations for acceptable pain at 24 months, and treatment with corticosteroids had a negative association, Table 4.

Table 4 Factors associated with acceptable pain (VAS<40mm) at 24 months: results from multiple logistic regression analysis.

		VAS pain <40 at 24 months
		OR (95% CI)
Cohort	Conventional	1
	Tight control	**9.67 (2.90-32.24)**
Age, years		1.01 (0.98-1.04)
Duration, months		1.03 (0.88-1.21)
Incl. VAS pain, 0-100mm		0.99 (0.97-1.01)
Corticosteroids	No	1
	Yes	**0.22 (0.066-0.73)**
DMARDs	No DMARD	1
	csDMARD	**7.14 (1.13-45.22)**
	Combination of csDMARDs	9.51 (0.97-93.46)
	bDMARD	**10.06 (1.10-92.06)**
N		134

OR, odds ratio; CI, confidence interval; Incl. VAS pain, Visual Analogue Scale of pain at inclusion; Age, age at inclusion; Duration, disease duration at inclusion; DMARDs, Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional synthetic DMARD; Combination of csDMARDs, >1 csDMARD; bDMARD, biologic Disease Modifying Anti-Rheumatic Drug with or without combination therapy with csDMARD. Note: significant OR in bold writing.

Study II: Tight control and chronic widespread pain

This longitudinal study examined the prevalence of CWP (measured with the CWP1990 and CWP2019 criteria) after 6 years in 80 RA patients from the Tight control cohort and 101 RA patients from a conventional cohort. Additionally, factors associated with CWP2019 were investigated.

Prevalence of CWP and fibromyalgia

After 6 years, the Tight control cohort had significantly lower prevalence of CWP2019 with 10% compared to 23% in the conventional cohort, p=0.026. For CWP1990, the prevalence was 27% in the Tight control and 31% in the conventional cohort. The self-reported fibromyalgia prevalence was 0% in the Tight control cohort and 5% in the conventional cohort, p=0.058, Figure 8, Table 5.

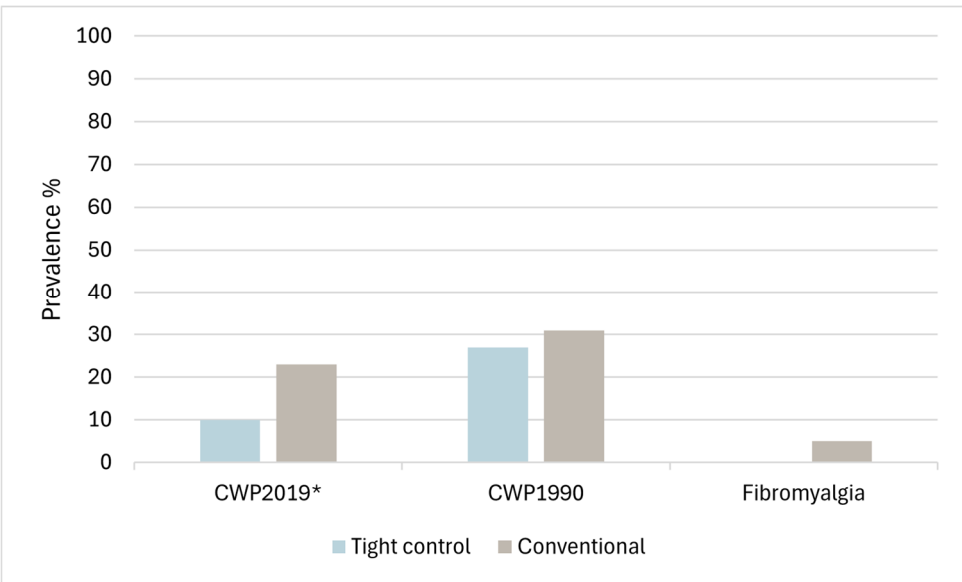

Figure 8 Prevalence of CWP2019, CWP1990 and fibromyalgia in the Tight control cohort and conventional cohort, respectively. *Significant difference, p=0.026.

Table 5. Comparison of self-reported survey data for the two cohorts, in average 6 years from inclusion.

	Tight control n=80	Conventional n=101	p-value
CWP1990, n (%)	21 (27)	31 (31)	0.546
CWP2019, n (%)	8 (10)	23 (23)	**0.026**
Fibromyalgia, n (%)	0 (0)	5 (5)	0.058
VAS pain (0-100), median (q1-q3)	20 (0-40)	30 (20-50)	**0.012**
HAQ (0-3), median (q1-q3)	0.0625 (0.0-0.625)	0.375 (0.0-0.813)	**0.018**

CWP, chronic widespread pain; CWP1990, dichotomized CWP according to 1990 definition; CWP2019, dichotomized CWP according to 2019 definition; VAS, Visual Analogue Scale; HAQ, Health Assessment Questionnaire. Note: significant p-value in bold writing.

Association between being in the conventional cohort and having CWP2019

A multiple logistic regression adjusted for gender, age, disease duration and VAS pain at inclusion showed a significant association between being in the conventional cohort and having CWP2019 at 6-year follow-up, odds ratio (OR) of 2.57 (95% confidence interval (CI) 1.02-6.50), compared to being in the Tight control cohort. No significant associations were found for having CWP1990, Table 6.

Table 6 Factors associated with having CWP1990 and CWP2019 at 6-year follow-up in the two cohorts: results from multiple logistic regression analyses

	CWP1990 OR (95% CI)	CWP2019 OR (95% CI)
Tight control cohort	1	1
Conventional cohort	1.24 (0.60-2.56)	**2.57 (1.02-6.50)**
Male gender	0.48 (0.22-1.03)	0.56 (0.22-1.44)
Age, years	1.0 (0.98-1.03)	1.0 (0.97-1.03)
Duration, months	0.99 (0.88-1.11)	0.94 (0.81-1.08)
Inclusion VAS pain,(0-100)	1.01(1.0-1.02)	1.01 (0.99-1.02)
N	171	171

CWP1990, chronic widespread pain according to 1990 definition; CWP2019, chronic widespread pain according to 2019 definition; OR, odds ratio; CI, confidence interval; Age, age at inclusion; Duration, disease duration at inclusion; VAS, Visual Analogue Scale. Note: significant OR in bold writing.

Additional factors associated with CWP2019 in the Tight control cohort

In the Tight control cohort, additional variables including lifestyle questions and a tool to measure fear-avoidance about physical activity, were included in the questionnaire at the 6-year follow up. There was a significant association between high fear avoidance about physical activity (FABQPA ≥ the median 8) and CWP2019, OR 10.68 (95% CI 1.01-112.14) but no associations between risk consumption of alcohol or physical activity and CWP2019, Table 7.

Table 7 Factors associated with having CWP2019 at 6-year follow-up in the Tight control cohort

	CWP2019 Simple logistic regression OR (95% CI)	**CWP2019 Multiple logistic regression OR (95% CI)**
Gender	0.54 (0.10-2.89)	
Age, years	1.0 (0.94-1.06)	
Duration, months	0.75 (0.54-1.03)	0.82 (0.60-1.14)
Incl. VAS pain, (0-100)	1.02 (0.99-1.05)	1.02 (0.97-1.06)
High FABQPA, (0-24)	8.13 (0.95-69.76)	**10.66 (1.01-112.14)**
High AUDIT-C, (0-12)	3.06 (0.62-15.18)	4.67 (0.70-31.14)
Moderate physical activity	0.66 (0.13-3.28)	
N	52-79	59

CWP2019, chronic widespread pain according to 2019 definition; OR, odds ratio; CI, confidence interval; Age, age at inclusion; Duration, disease duration at inclusion; Incl. VAS pain, Visual Analogue Scale for pain at inclusion; High FABQPA, ≥8 on the Fear Avoidance Beliefs Questionnaire on Physical Activity; High AUDIT-C, Alcohol Use Disorders Identification Test Consumption ≥4 for women and ≥5 for men indicating risk consumption; Moderate physical activity,≥ 150 minutes/week. Note: significant OR in bold writing.

Study III: Leptin and chronic widespread pain

In this cross-sectional study of 334 patients with RA, the prevalence of chronic widespread pain according to the 2019 criteria (CWP2019) was investigated and associations between CWP2019 and the adiponectin leptin, BMI and waist circumference were explored.

CWP2019, prevalence and clinical data

The findings revealed that 21% of the participating RA patients had CWP2019. The patients with CWP2019 had higher leptin levels, waist circumference and BMI. Additionally, they had more fatigue, tender joints and swollen joints together with worse function, measured with HAQ. They were to a greater extent female and had less RF and ACPA positivity, Table 8.

Table 8 Characteristics for RA patients with and without chronic widespread pain, CWP2019

	CWP2019 n=69	**No CWP2019 n=264**	**p-value**
Age, years, median (q1-q3)	64 (56-74)	65 (55-73)	0,841
Gender, female, n (%)	57 (83)	178 (67)	**0.014**
RF positive, n (%)	34 (49)	171 (65)	**0.018**
ACPA positive, n (%)	29 (45)	159 (67)	**0.001**
Swollen joints, median (q1-q3)	5 (2-10)	1 (0-3)	**<0.001**
Tender joints, median (q1-q3)	12 (5-18)	2 (0-5)	**<0.001**
HAQ (0-3), median (q1-q3)	1.13 (0.56-1.50)	0.25 (0-0.75)	**<0.001**
VAS pain (0-100), median (q1-q3)	60 (40-70)	30 (10-50)	**<0.001**
VAS fatigue (0-100), median (q1-q3)	70 (50-80)	30 (10-60)	**<0.001**
BMI, median (q1-q3)	27.23 (23.73-30.81)	24.75 (22.60-27.68)	**0.002**
Waist circ., cm, median (q1-q3)	96 (85-106)	90 (83-99)	0.051
Leptin ng/ml, median (q1-q3)	29.84 (10.84-60.84)	13.91 (6.41-33.47)	**<0.001**

CWP, chronic widespread pain according to 2019 criteria; OR, odds ratio; CI, confidence interval; RF, Rheumatoid Factor; ACPA, Anti-Citrullinated Protein Antibodies; Swollen joints, self-reported 28 swollen joint count; Tender joints, self-reported 28 tender joint count; HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale; BMI, Body Mass Index; Waist circ., waist circumference; *One patient did not fill in the pain mannequin, so no CWP2019 could be calculated. Note: significant p-value in bold writing.

Association between leptin and CWP2019

There was an association between leptin levels and CWP2019, OR 1.014 (95% CI 1.007-1.020), that remained significant after adjusting for age, gender and BMI/waist circumference, Table 9.

Table 9 Association between leptin and having CWP2019 (Model 1), adjusted for age, gender and BMI (Model 2) and waist circumference (Model 3)

	Simple and multiple logistic regression analyses for having CWP2019		
	Model 1	**Model 2**	**Model 3**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Leptin, ng/ml	**1.014 (1.007-1.120)**	**1.008 (1.000-1.017)**	**1.010 (1.001-1.019)**
Age		1.003 (0.982-1.024)	0.989 (0.964-1.014)
Gender, female		1.805 (0.861-3.782)	2.366 (0.898-6.234)
BMI		1.053 (0.979-1.132)	
Waist circ., cm			1.021 (0.992-1.051)
N	333	321	256

CWP2019, chronic widespread pain according to 2019 definition; OR, odds ratio; CI, confidence interval; Age, age at time of questionnaire; BMI, Body Mass Index; Waist circ., waist circumference; Note: significant OR in bold writing.

The association between leptin and CWP2019 also remained significant when adjustments were made for various pharmacological treatments. Smoking or alcohol use did not affect the association between leptin and CWP2019. Swollen joint count, used as a proxy for inflammation, had an association with CWP2019 OR 1.147(CI 1.090-1.207), but could not explain the association between leptin and CWP.

Higher leptin levels – higher OR for CWP2019

To additionally investigate the association between leptin and CWP2019, the patients' leptin values were divided into quartile groups. The patients with the highest leptin levels were placed in group q4 and the ones with the lowest levels in q1. A simple logistic regression with the q1 group as a reference then revealed a trend, where higher leptin levels gave higher OR for CWP2019, Figure 9.

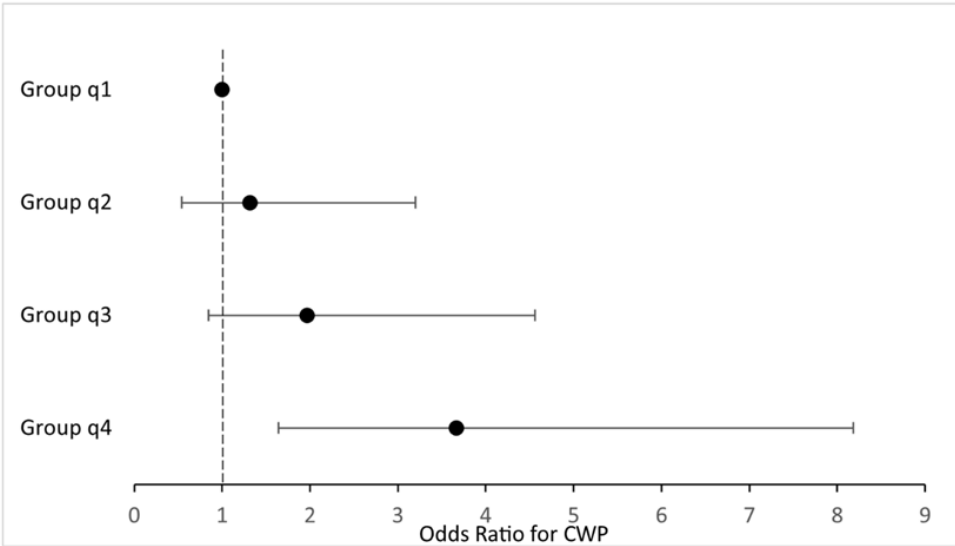

Figure 9 Associations between leptin levels and CWP2019 analysed with a logistic regression model. Odds ratio with confidence intervals. The leptin levels are divided into quartiles were the lowest quartile (Group q1) is the reference. Figure published in Paper III.

Study IV: Circadian rhythm of leptin and pain

This diurnal variation study of leptin investigated leptin levels using a 24-hour blood sampling protocol, with samples drawn every 4 hours in 21 patients with RA (n=11) and OA (n=10). Additionally, pain and symptoms were examined with questionnaires (RAOS and KOOS).

Circadian rhythm of leptin release

The study demonstrated a circadian rhythm of leptin in both the RA and OA patients with a peak around midnight and lower levels during daytime, Figure 10. Leptin medians in the RA patients were numerically 1.4 to 2.1 times higher, but the difference did not reach statistical significance and could possibly be explained by a greater number of women in the RA group, Table 10.

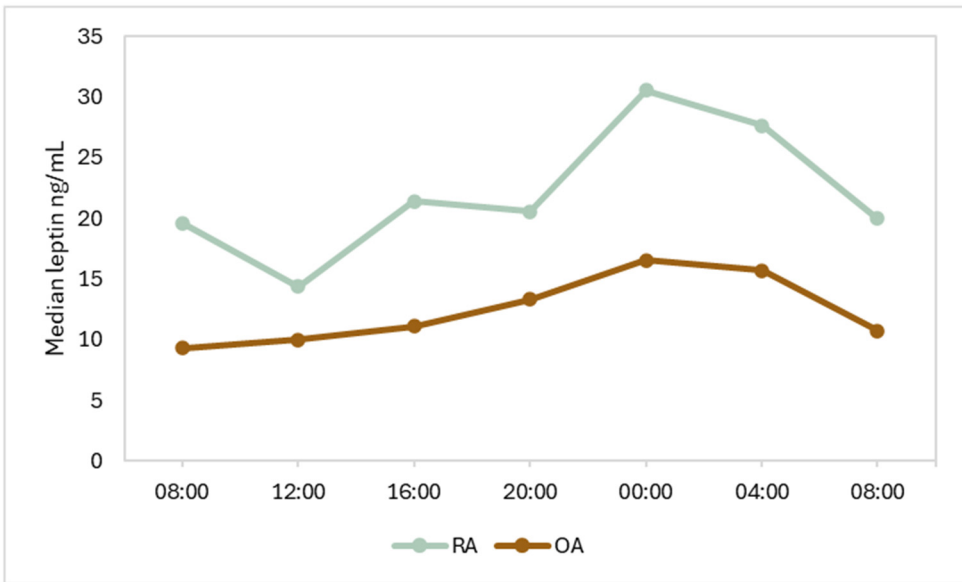

Figure 10 Median leptin levels at each measure point for patients with RA and OA, respectively.

Table 10 Descriptives of the participants, divided by diagnosis

	RA **n=11** **median (IQR)**	**OA** **n=10** **median (IQR)**	**p-value**
Age, median (IQR)	66 (16)	62 (2)	0.223
Sex, women, n (%)	10 (91)	5 (50)	0.063
Seropositive, n (%)	10 (91)	NA	NA
BMI, kg/m^2	22.5 (5.4)	28.4 (5.1)	**0.043**
Pain (0-100; worst to best)	58 (33)	63 (53)	0.512
Symptoms (0-100; worst to best)	50 (39)	68 (38)	0.197
ADL (0-100; worst to best)	53 (32)	70 (43)	0.223
Sport/Rec (0-100; worst to best)	8 (35)	18 (21)	0.696
QOL (0-100; worst to best)	25 (44)	44 (28)	0.173
cDMARD, n (%)	8 (73)	NA	NA
bDMARD, n (%)	1 (9)	NA	NA
No DMARD, n (%)	2 (18)	NA	NA
CS, n (%)	3 (27)	NA	NA
NSAID, n (%)	9 (82)	1 (10)	**0.002**

RA, Rheumatoid Arthritis; OA, Osteoarthritis; IQR, Interquartile Range; No, number included; BMI, Body Mass Index; ADL, Activities of Daily Living; Sport/rec, Sport & Recreation functions; QOL, Quality Of Life; cDMARD, conventional Disease-Modifying Antirheumatic Drug; bDMARD, biologic Disease-Modifying Antirheumatic Drugs; CS, Corticosteroids; NSAID, Non-Steroidal Anti-Inflammatory Drugs. Note: significant p-value in bold writing.

Individual measurements of leptin

Examination of individual measurements of leptin revealed that patients with high leptin levels at the first measure point, tended to have continuously high levels throughout the rest of the measurements, Figure 11.

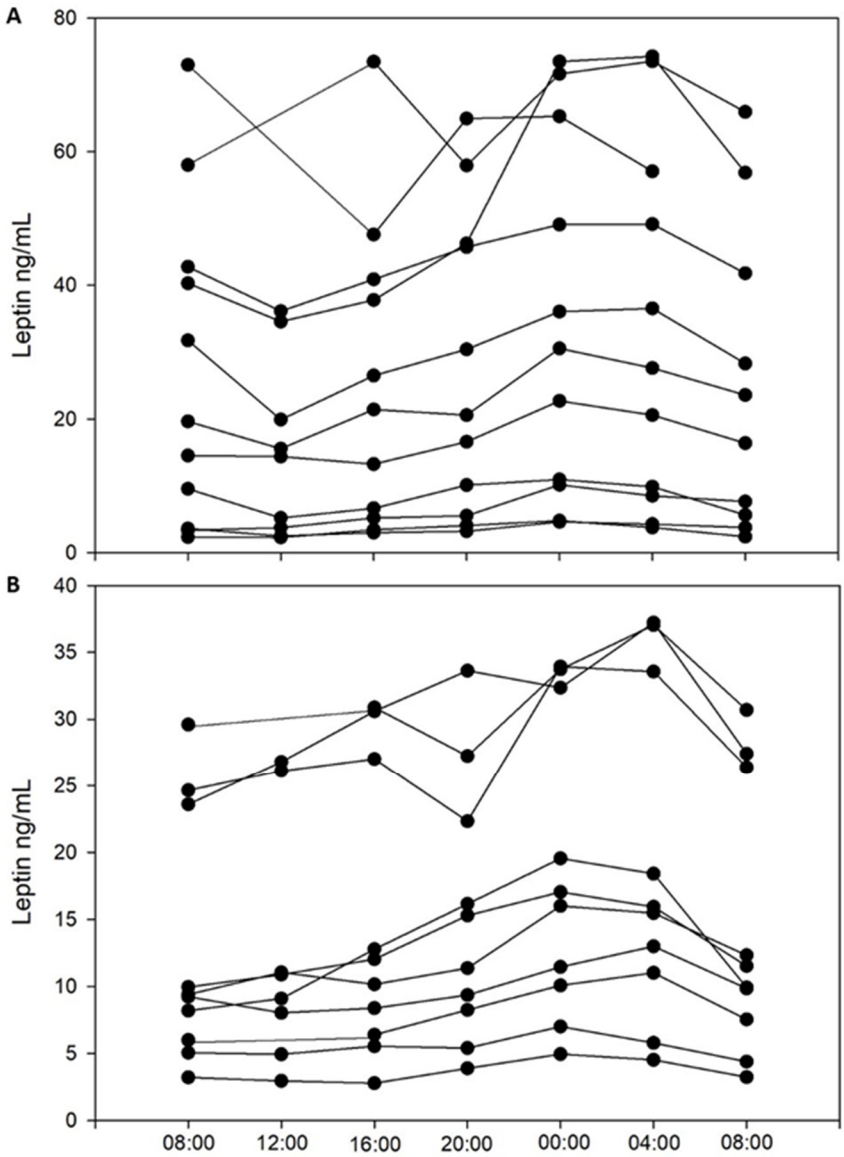

Figure 11 Panel A, shows individual leptin levels in individuals with RA. Panel B, shows individual leptin levels in patients with OA. From manuscript IV.

Pain and leptin

Comparison between the one third of patients reporting the least pain and the two thirds reporting the most pain in the RAOS and KOOS questionnaires revealed a numeric difference in their median leptin levels at all time points. The difference was statistically significant or close to significant. The measure point with the lowest leptin median in the high-pain group was at noon, the leptin median being 17.14. That value was higher than all measure point medians in the low-pain group, Table 11.

Table 11 Comparison of leptin levels at all timepoints between patients (RA and OA) with self-reported low and high pain, respectively. Pain from the RAOS and KOOS questionnaires

	1/3 with least pain **n=7** **median (IQR)**	**2/3 with most pain** **n=14** **median (IQR)**	**p-value**
08:00, Leptin, ng/mL	8.20 (6.74)	24.11 (32.37)	**0.016**
12:00, Leptin, ng/mL	8.04 (7.93)	17.14 (23.63)	0.070
16:00, Leptin, ng/mL	8.38 (9.36)	26.76 (32.01)	**0.046**
20:00, Leptin, ng/mL	9.35 (12.09)	24.79 (36.24)	0.056
00:00, Leptin, ng/mL	11.45 (14.60)	33.05 (42.42)	0.079
04:00, Leptin, ng/mL	12.99 (13.88)	35.06 (40.42)	0.056
08:00, Leptin, ng/mL	9.85 (8.28)	26.41 (29.67)	0.067

RA, Rheumatoid Arthritis; OA, Osteoarthritis; RAOS, The Rheumatoid and Arthritis Outcome Score (0-100; worst to best); KOOS, The Knee injury and Osteoarthritis Outcome score (0-100; worst to best); IQR, Interquartile Range; 1/3 with least pain had RAOS/KOOS pain score >69.43; 2/3 with most pain had RAOS/KOOS pain score < 69.44. Note: significant p-value in bold writing.

The patients with the highest leptin levels reported significantly more pain and symptoms in the questionnaires. They also experienced worse function regarding activities of daily living, sport activities and had reduced quality of life, Table 12.

Table 12 Symptoms from the RAOS and KOOS questionnaires for the third of patients with the highest leptin levels at first measure point, compared to the rest

	1/3 with highest leptin **n=7** **median (IQR)**	**2/3 with lowest leptin** **n=14** **median (IQR)**	**p-value**
Pain (0-100; worst to best)	38.89 (30.56)	68.06 (34.03)	**0.004**
Symptoms (0-100; worst to best)	39.29 (32.14)	75.0 (36.61)	**0.001**
ADL (0-100; worst to best)	39.71 (32.35)	72.79 (34.56)	**0.016**
Sport/Rec (0-100; worst to best)	2.5 (12.50)	17.5 (38.75)	**0.053**
QOL (0-100; worst to best)	18.75 (31.25)	50.0 (34.38)	**0.016**

RAOS, The Rheumatoid and Arthritis Outcome Score; KOOS, The Knee injury and Osteoarthritis Outcome score; IQR, Interquartile Range; ADL, Activities of Daily Living; Sport/rec, Sport & Recreation functions; QOL, Quality Of Life. Note: significant p-value in bold writing.

Discussion

The subject of chronic widespread pain development in RA is complex and multifactorial. This is reflected in the broad span of this thesis: from the small leptin molecule and its circadian rhythm of release, to abstract concepts like security and hope in a time of despair for those newly diagnosed with RA. This thesis sheds light on some parts of the puzzle, but the bigger picture, and how all the pieces fit together, remains relatively obscure, even though great progress has been made in the field since the biopsychosocial model was first proposed(54, 55).

The first two studies in this thesis explore the effect of a tight control management of early RA, with focus on pain development. The findings are compared to another cohort with conventionally managed patients. In Study I, the studied outcomes are remission and patient-reported variables, like VAS pain. In Study II, chronic widespread pain prevalence (CWP1990 and CWP2019 criteria), and factors associated with CWP2019 are investigated. A previously known factor associated with CWP is obesity(165), and in Study III the adipokine leptin, produced mainly in the adipose tissue, is studied in relation to CWP2019 in RA. Previous research in the field has demonstrated a circadian rhythm of leptin release in other types of participants. Study IV in this thesis, assesses the diurnal variations of leptin in RA and OA patients, to identify if there is an optimal time point for leptin sampling in pain research.

Tight control

It is known from previous research that intensive therapy with various combinations of pharmacological treatment, paired with tight controls, is advantageous in early RA(39-42). In this thesis, it is also proposed that tight control – without specific treatment schemes for the physician to follow – is beneficial. In fact, it seems to be helpful for remission, pain and chronic widespread pain. So why is that?

Pharmacological treatment

Because there was no treatment scheme to follow in the tight control studies in this thesis, differences in medication between groups were thoroughly examined to look for confounding factors affecting the results. Surprisingly, the findings clarified that the patients in the conventional cohorts received more bDMARDs than those in the tight controls, who, on the other hand, to a higher extent received combination treatment with more than one csDMARD. Therefore, the higher rate of remission in the tight control could not be explained by more bDMARDs. However, it is possible that the success of tight control, in general, is linked in part to pharmacological treatment. Previous research has demonstrated that fewer patients discontinue their csDMARD in a tight control setting(38). Advantages of a tight control regime include being able to react quickly to perceived adverse effects, adjust the dosing, add adjunctive therapy and educate and reassure the patient repeatedly.

There was a higher use of corticosteroids in the Tight control patients of this thesis, compared with the conventional patients, but it was not positively associated with remission or absence of pain. Instead, there was a negative association, both between corticosteroids and remission and between corticosteroids and acceptable pain levels. Possibly, the physicians in the Tight control, working in a "treat to target" environment, were more inclined to use corticosteroids in an attempt to approach remission in the patients where remission was hard to reach. The higher use of corticosteroids, however, could not explain the difference in remission or pain between groups. It is possible that the patients in the Tight control received more intra-articular injections and that this affected the outcome. The studies in this thesis did not gather information on intraarticular injections, but a reasonable assumption could be that physicians in a tight control setting would have more time to give intraarticular injections when deemed necessary.

Chronic widespread pain

Another aspect of tight control relates to the biopsychosocial aspect of pain. In this thesis, the prevalence of CWP2019 in the Tight control cohort was lower than in the conventional cohort. When proposing the new CWP criteria in 2019, Wolfe et al. conclude that CWP2019 captures a group of patients that bear great resemblance to those fulfilling fibromyalgia 2016 criteria(139). This is a group of patients that often has concomitant psychological problems, like anxiety, depression and sleep disturbances. The question is: What can be achieved by seeing patients often, early in their RA disease, in terms of giving them a sense of hope, security and empowerment? If our modern pharmacological treatment works to limit the bottom-up sensitisation from painful joints, could a tight control setting limit the top-down sensitisation enhanced by anxiety? Nervousness about a new diagnosis, uncertainty regarding the prognosis and the future in terms of family planning, work and how the pain situation will develop can cause anyone to feel anxiety. Some of our patients are more prone to experiencing exacerbated anxiety and depression and

could benefit from extra support from the rheumatology clinic. Close contact, with regular monthly visits early in the disease could probably facilitate support, reduce anxiety, and help physicians establish a good relationship with the patient. A strong therapeutic alliance is essential, and it is not only to maximize placebo and minimize nocebo effects of pharmacological treatment(166). In a wider sense, a strong therapeutic alliance could, hypothetically, be beneficial to maximise the brain's descending inhibitory pain modulation. To improve the numbers, where a high proportion of patients with RA develop CWP2019, rheumatology clinics need to be aware of, and work both with, the bottom-up and the top-down sensitisation processes in parallel.

Fear-avoidance about physical activity

It is possible that a tight control setting can better assist patients on their journey towards acceptance of the diagnosis, management of symptoms and empower them to continue to be physically active. This raises the question: What then characterized the patients that had CWP2019 at 6-year follow-up, despite being in the Tight control cohort? Even though the prevalence of CWP2019 was lower than in the conventional cohort, some patients still fulfilled CWP2019 in the Tight control. The most important lifestyle factor associated with CWP2019 in this group was a high level of fear-avoidance behaviour about physical activity. This highlights the need for a rehabilitation team approach in RA patients. It is possible that early detection and intervention by a rehabilitation team could have prevented CWP development in these individuals with a high level of fear-avoidance about physical activity. However, in this study, fear-avoidance was not measured at baseline. So, an alternative explanation could be that these patients developed fear-avoidance about physical activity as a result of their CWP, or that they had both fear-avoidance and CWP2019 before they received their RA diagnosis. However, the latter is probably less likely, given that the analyses that established the association between fear-avoidance and CWP2019 were adjusted for VAS pain at baseline.

Metabolic factors and leptin

Risk of CWP

Early detection of patients at risk for development of CWP has been a goal in previous studies. Factors like female sex, elevated BMI, and tender and swollen joints have been demonstrated as risk factors for developing CWP in RA(44, 165). In the third study of this thesis, a previously undescribed association between the adipokine leptin and CWP2019 in RA is reported. The association remained significant after adjustment for BMI or waist circumference, suggesting that mechanisms other than solely the number of adipocytes may influence leptin levels in these patients. Apart from the adjustments for BMI, the analysis models also included adjustments for age and female gender. Previous studies have revealed that leptin levels vary through life and that they are higher in women, probably in part explained by various oestrogen effects(90, 91, 124).

Leptin

Leptin resistance has been described in the field of obesity research and is additionally thought to affect cognitive abilities and depression. The resistance is believed to arise through three different mechanisms: saturated leptin transport over the blood brain barrier, downregulation of leptin receptors, and problems in the downstream signalling cascade in the JAK2 pathway(89). The fact that leptin signalling involves the JAK2 pathway is of particular interest, as previous studies have suggested that JAK inhibitors may offer advantages over TNF inhibitors in the treatment of pain in rheumatoid arthritis(167-169). This thesis demonstrates that patients with CWP2019 had significantly higher leptin levels. Since, the association between leptin levels and CWP2019 remained after adjustment for BMI, it is possible that one or more of these leptin resistance pathways are operational in the patients with CWP2019, possibly affecting sensitisation. This field requires more research.

Another question relates to whether the adipokine system constitutes a missing link between obesity and CWP. The myriad of adipokines affecting various target organs and each other have only recently been mapped out, in terms of their links to the immune system and various parts of the brain, such as the hypothalamus(89, 90, 112). In this thesis, leptin was analysed, but in further studies it would be advantageous to include other adipokines as well. Leptin was selected as the first adipokine to be tested for an association with CWP2019 because there are previous reports that link leptin with other types of pain, and results from another study by our research group on OA and CWP, that observed a similar association(93-95, 98-100).

A connection between leptin and pain could also be seen in the fourth study of this thesis, on diurnal variation of leptin. It demonstrated that there is a circadian rhythm

of leptin release in RA and OA with a nightly peak, a finding that is similar to that found in previous reports in other categories of participants(122, 123, 126, 127). It was striking that the median leptin levels in the participants reporting most pain was higher at all timepoints. This aligns with the results from Study III, where we saw a higher OR for CWP2019 for higher leptin levels.

The studies in this thesis were not designed to measure pulsatility in leptin release; however, an earlier pilot study that measured leptin every seventh minute in one obese and one lean woman demonstrated that the pulsative pattern of leptin release appeared to be the same in these individuals, but the amplitude of the spikes were higher in the obese woman(122). Although it was a small study, this implies that both higher production and, as discussed earlier, possible leptin resistance can affect leptin levels in obese patients. Hypothesizing that leptin is involved in pain sensitisation, this could offer an understanding of previous findings, reporting more CWP in obese. However, it is also possible that, rather than being part of the cause of sensitisation, leptin levels could be a consequence of it. Some researchers suggest that inflammation can cause higher leptin levels and that this, in turn, contributes to obesity and more inflammation. This downward spiral could potentially contribute to the link between autoimmune diseases and, not only, cardiovascular diseases, but also, cancer(170). Many earlier studies of leptin and inflammation in RA have used DAS28 as a disease activity measure, a score known to be affected by CWP, since the tender joint greatly affects the result(156). This can make it difficult to know if leptin in these studies is connected to inflammation, pain, or both(115).

Methodological considerations

This thesis contains studies with rather diverse methods. Study I is a retrospective comparative study of two longitudinal cohorts of patients with early RA. Study II is a cross-sectional comparative study. Study III is a descriptive cross-sectional study, and Study IV is a smaller prospective descriptive study.

Cohort studies

Study I and, in part, Study II-III, are based on data from the Tight control cohort and the BARFOT cohort. Working with cohort data has both advantages and limitations. Compared with registry data from national registries, advantages with cohort data are that the data often is more complete, with less missing data, and that patients are followed using the same interval. Usually, the cohort is monitored, with reminders sent to patients to come for scheduled check-ups and to physicians, to take x-rays at certain time-points, etc. If the clinic fails to register data from visits, it can be retrieved from the medical record, to improve the cohort. This work is usually done by someone responsible for the cohort, so it can save time to use an existing cohort.

A limitation of cohort studies is that, when you have additional research questions that were not considered when the cohort was initiated, the existing data can be insufficient to elicit a conclusive answer. Usually, compromises have to be made. For example, in Study II, it would have been advantageous to have a record of CWP2019 at baseline, to examine development of CWP2019 over time. However, since this was not considered at the beginning of the cohort studies, the first record of CWP2019 was made after an average disease duration of 6 years. Therefore, Study II was constructed as a cross-sectional study. Other limitations of cohort data are the risk of selection bias at inclusion and bias caused by patients lost to follow-up. Not all patients have the time and ability to participate in a cohort. There are risks of missing younger patients busy with work and family, patients affected by concomitant disease, and the oldest patients, who can have trouble with transportation to visits, or cognitive impairment that makes it difficult to complete questionnaires, etc.

Internal and external validity

The Tight control cohort and the BARFOT cohort both had the goal of including all eligible patients with early RA referred to the clinic. This limits the risk of confounding through selection bias and strengthens the internal validity of the studies. However, not all patients suitable for the Tight control study were included – as described in more detail in the section "Selection of controls". In Study I and II, the participants came from the Spenshult clinic that was the sole clinic that offered rheumatologic care in the county of Halland at the time. In Study III, the whole multicentre BARFOT cohort was used. Since the study population came from a whole county with representation of both wealthy and less prosperous areas, or from multiple centres, the external validity of Study I-III is presumed to be good.

When it comes to Study IV, the internal validity is weaker, since the participants with RA were included consecutively from patients with RA admitted for rehabilitation, while the OA patients were invited to participate from the larger Spenshult cohort(144). When it comes to the study design at large, the daily schedule for the participants, the blood sampling, the storage of samples and the analyses of samples, the internal validity was good. The number of patients in both RA and OA was small and this limits the external validity. However, the number of participants is well in line with other similar studies on circadian rhythm of leptin release. These studies, which involve admitted patients and repeated blood sampling for a 24-hour period, require significant resources and are usually conducted with fewer numbers of participants. The fact that our results aligned with findings in other studies of the circadian rhythm of leptin release in other populations is a strong indicator of an accurate result in this type of small study(123, 126).

Selection of controls

With more and more data supporting the advantages of tight control, it is beginning to be ethically questionable to have a control group in a tight control study. This raises problems in terms of assessing the impact of the intervention. Common approaches to this problem are: to compare the results with another centre, with historical controls, or with another cohort. When comparing with another centre, there is a substantial risk of bias, in that variation in local traditions and physicians carrying out assessments can affect the results. When comparing with historical controls, it is important to bear in mind that there has been a remarkable development in pharmacological treatment of RA. This can affect the results, if the historical controls are taken from a time period that is not comparable, because of differences in pharmacological options. When using another cohort as a control group, difficulties can include finding a matching cohort with similar inclusion and exclusion criteria that includes patients within the appropriate time frame.

In Study I, a part of the conventional cohort used for comparison, subgroup A, was created by inviting patients with certain diagnoses (RA, polyarthritis) from the same time period and clinic as the Tight control cohort to participate in a control group for the Tight control. Ethical approval was established before invitation. After the patients' written approval, the medical records were reviewed to see if they had fulfilled the inclusion criteria for the Tight control cohort. It turned out that 30 of them could be included (fulfilled RA diagnosis and had ≤12 months' duration of symptoms and no previous rheumatic disease). In most cases, there was no explanation in the medical record as to why they were not asked to participate in the Tight control cohort, and in some cases the medical record stated that the patients had declined, because they lived far away or preferred not to come as often to the clinic. Because 30 patients was an insufficient number to achieve sufficient statistical power in the study, subgroup A was combined with the last included patients in the BARFOT study from the same clinic, subgroup B – up to 100 patients in total in the conventional cohort.

This way of combining two subgroups of patients to form a conventional cohort is not ideal and must be taken into account when interpreting the results. Originally, the intention was to fill the conventional cohort with only subgroup A patients, on the basis that we had found many patients in the medical records with a registered RA-diagnosis. However, it turned out many of them had received various rheumatological diagnoses at different visits and were judged to match better with, for example psoriatic arthritis when the medical records were reviewed. An alternative approach would have been to use more BARFOT patients in the conventional cohort and exclude the patients in subgroup A. A decision was made that having 30 patients from exactly the same time period as the Tight control was the better option for that study. In Study II, on the other hand, the alternative method was used, and the conventional cohort consisted of BARFOT patients only, on the basis that they had already filled in an appropriate questionnaire.

This aspect of the discussion highlights the problems involved in studies that are not designed as randomized control trials (RCTs). However, all study questions cannot be addressed by RCTs and a study with some kind of reference cohort often provides greater insights than a purely descriptive study. The strengths of both Study I and II are that they are both relatable studies from a "real-life" setting that demonstrates that small adjustments, like how often you see the patient early in the disease, can make a difference. Additionally, an advantage was that all patients came from the same clinic and were treated by the same physicians.

Leptin levels

In Study III, a cross-sectional study of multicentre BARFOT patients, blood samples taken from within one year of the completion of a questionnaire were used to analyse leptin levels. This approach could be questioned, and the optimal study design would certainly be to request the patients to fill in the questionnaire and collect the blood samples on the same occasion and at a fixed time of day. However, in practice, this optimal approach is demanding to orchestrate, so we decided to use already collected data. There is a risk that day-to-day variation in leptin levels, and changes in weight among the participants during the year from the questionnaire, could have influenced the results of the study. The risk is reduced by the fact that the study was reasonably large, with 334 participants, and the fact that a previous longitudinal study in the BARFOT cohort demonstrated relatively stable BMI values over time(79).

The next methodological issue is timing of the blood samples in the day. No specific time of day, only the date, was recorded for the blood samples in the BARFOT biobank. Given that previous studies in other populations of patients and healthy individuals had demonstrated a circadian rhythm of leptin release, it is possible that this could affect the result of Study III. For example, if patients with fibromyalgia tended to book their appointments at the lab later in the day, that could affect their reported leptin values and be a confounding factor that would affect the results. Additionally, there were no previous studies of diurnal variation of leptin in patients with RA, so it was difficult to assess the possible effect of the timing of blood sampling. To investigate these two methodological difficulties, Study IV was conducted. Study IV explores the diurnal variation of leptin in RA and OA. Additionally, it connects the leptin values to the patient-reported pain and establishes that the patients with the most pain have higher median leptin levels at all timepoints. This strengthens the results from Study III and, additionally, in part reproduces – in another group of patients – the finding that patients with higher leptin levels experience more pain. Nonetheless, when interpreting the results, it is important to consider the fact that different methods were used to measure pain in the two studies.

Conclusions

- Tight control management was beneficial for remission and pain in early RA. The effect did not seem to be dependent on physicians following a specific treatment scheme, but the tight control in itself appeared to exert an independent effect.
- RA patients who received tight controls early in the disease had less chronic widespread pain, CWP2019, after 6 years.
- Fear-avoidance about physical activity was associated with CWP2019 in the patients who fulfilled CWP2019 despite taking part of a tight control program.
- High leptin levels were associated with CWP2019, adjusted for BMI, age, and female gender. The higher the leptin value, the higher OR for CWP2019.
- Leptin had a circadian rhythm of release in RA and OA patients, with a peak at night and lower levels during the day.
- The patients who reported most pain had higher median leptin levels throughout the day.

Clinical implications

A tight control program for early RA has been shown to be beneficial in many studies(38) and this thesis implies that there are positive effects, even on a long-term outcome like CWP2019. It would probably be beneficial to implement tight control for patients with early RA. The problem seen in many rheumatology clinics today is that there are also other patient groups that require care, and that the number of rheumatologists is limited. It is recommended to make the most of the resources available, and collaborate with rehabilitation teams in rheumatology clinics, so that patients with early RA can be offered as many visits as possible.

The subject of the costs of tight control in early RA, has not been covered in this thesis. However, Grigor et al., showed in the TIGORA study that tight control with csDMARDs could be achieved without increased costs(38). In the era of biosimilars, the cost of the most commonly used bDMARDs has decreased, so it is to be hoped that this is true also for tight control involving bDMARDs. The cost of each person developing CWP2019 should not be underestimated. If a tight control setting can decrease the number of patients with chronic widespread pain, as is suggested in this thesis, a lot can be achieved, both in terms of financial savings and better quality of life for our patients.

Regarding leptin, the research on connections to the pain system is still in a preclinical phase. Recombinant leptin was initially explored for weight loss purposes, given that patients with leptin deficiency were overweight. However, the use for this indication had little effect because most obese patients in fact have high, rather than low leptin levels. Leptin replacement is used today in patients with either leptin deficiency or lipodystrophy with good results(170, 171). Researchers have proposed a link between the gut microbiota and high leptin levels and leptin resistance. Some researchers believe that, in the future, a reset of the gut microbiota can be used to reset the leptin system(170). While awaiting further leptin studies, the current evidence about leptin further strengthens the need to collaborate with the patient's rehabilitation team, to support them in their efforts to achieve a healthy lifestyle and to avoid obesity, despite the patient having a rheumatological condition.

Future research perspectives

To better assess the sensitisation process when patients develop CWP2019, a prospective study following CWP2019 from baseline and at long-term follow-up in a tight control setting of early RA would be beneficial. This could be combined with blood sampling for adipokines and testing for fear-avoidance over time. The best design, from a research perspective, would be an RCT with a control group. However, it is becoming increasingly ethically questionable to conduct such a study, given the amount of evidence we now have that supports a positive effect of tight control in early RA. It would probably have to be a descriptive study, perhaps comparing results with another clinic or an existing cohort.

With regard to leptin, studies in patients with other rheumatic diseases and CWP2019 would be valuable, to see if the same association can be found between leptin and CWP2019, as observed in OA and RA. Additionally, studies of leptin before and after disease debut of CWP2019 could investigate the question of whether the higher leptin levels arise first, followed by a sensitisation process with CWP2019, or conversely, that patients with chronic widespread pain develop high leptin levels over time.

Last, but not least, it would be incredibly interesting to investigate regulatory leptin antibodies in patients with CWP2019 and rheumatic disease.

Populärvetenskaplig sammanfattning

Ledgångsreumatism, även kallad reumatoid artrit (RA), drabbar 0.5-1% av befolkningen. Sjukdomen ger ledinflammation, med ömma och svullna leder, och på längre sikt kan den även orsaka skador på skelett och leder samt påverka andra organ i kroppen, speciellt om den är otillräckligt behandlad. De senaste 30-åren har behandlingen av RA genomgått en revolutionerande utveckling och många nya läkemedel för att behandla inflammationen vid RA har tillkommit. Det visar sig dock i studier, att många reumatiker trots modern behandling lider av långvarig spridd smärta i kroppen (CWP). Tillstånd som fibromyalgi och CWP är mycket vanligare bland reumatiker än i den allmänna populationen. Man tror att det kan bero på att långvarig smärta i leder kan aktivera smärtsystemet och göra detta mer känsligt för smärtsignaler, en process som brukar kallas sensitisering.

Studierna i denna avhandling syftar till att öka kunskapen om långvarig spridd smärta hos RA-patienter och vilka faktorer som påverkar utvecklingen av denna. Vilken betydelse har uppföljningen tidigt i förloppet? Livsstilsfaktorer? Metabola faktorer som övervikt och ämnen som produceras av fettväven?

Den första studien i avhandlingen jämför en grupp RA-patienter som träffat sin läkare varje månad tidigt i sjukdomsförloppet med en grupp RA-patienter som i stället besökt sin läkare var tredje månad. Patienterna som hade täta kontroller initialt, med besök varje månad, hade lägre sjukdomsaktivitet och mindre smärta under uppföljningen, som pågick fram tills 2 år efter insjuknandet.

Studie nummer två undersökte förekomst av långvarig spridd smärta hos RA-patienter 6 år efter sjukdomsdebut. En grupp med RA-patienter som haft täta kontroller varje månad tidigt i förloppet jämfördes med en grupp patienter som träffat läkare var tredje månad. Förekomsten av långvarig spridd smärta var signifikant lägre i gruppen som haft täta kontroller. Man såg även att de patienter som uttryckte rädsla och undvikande beteende gentemot fysisk aktivitet i högre grad rapporterade långvarig spridd smärta, även om man justerade för faktorer som smärta vid insjuknandet.

Den tredje studien undersökte huruvida livsstilsfaktorer och ämnet leptin som produceras av fettväven, har en koppling till långvarig spridd smärta hos RA patienter. Den visade att höga leptinvärden var associerade med långvarig spridd smärta, även om man justerade för faktorer som ålder, kön och BMI. Kopplingen var starkast för de med högst leptinvärden.

Den sista studien i avhandlingen analyserade hur leptinnivåer varierar över dygnet hos patienter med RA och artros. Den tittade även på hur mycket smärta och andra symtom patienterna rapporterade. Studien visade på en dygnsrytm för leptin, där mest leptin utsöndras under natten. De patienter som hade mest smärta, hade även högre medianvärden på leptin vid alla mätpunkter under dygnet.

Sammanfattningsvis kan man säga att avhandlingen ger stöd för ett brett synsätt gällande långvarig spridd smärta hos RA patienter. Mekanismerna bakom utvecklingen av ett överaktivt smärtsystem är otillräckligt kartlagda, möjligen spelar ämnen som utsöndras från fettväven, såsom leptin, en roll i processen. Vi känner även sedan tidigare till, att psykologiska och sociala faktorer som ett gott stöd från omgivningen och avsaknad av depression och ångest kan verka positivt på processen och minska överaktivering av smärtsystemet. Här kan täta kontroller tidigt i sjukdomen bidra både genom att ge en snabb minskning av sjukdomsaktivitet och inflammation, men även genom att förmedla hopp och trygghet till patienten och på detta vis bromsa utvecklingen av ett överaktivt smärtsystem.

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