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## ORIGINAL ARTICLE

Male Health

# Male patients with terminal renal failure exhibit low serum levels of antimüllerian hormone

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Male reproductive function is impaired during end-stage renal disease (ESRD). Disturbance of the hypothalamic-pituitary-gonadal axis, and therefore the regulation of sex hormones, is one of the major causes. Our focus was to include antimüllerian hormone (AMH) and inhibin B concentrations. Twenty male patients on hemodialysis, median age 40 (26–48) years, were analyzed for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, sex hormone-binding globulin (SHBG), testosterone, estradiol, AMH and inhibin B levels. We used 144 proven fertile men, median age 32 (19–44) years as a control group and analyzed differences using multiple linear regression. Males with ESRD demonstrated higher mean values for prolactin, 742 versus normal 210 mIE l<sup>-1</sup> (95% confidence interval (CI): 60.3, 729), LH, 8.87 versus normal 4.5 IE l<sup>-1</sup> (95% CI: 2.75, 6.14), and estradiol 89.7 versus normal 79.0 pmol l<sup>-1</sup> (95% CI: –1.31, –0.15). Mean value for AMH was lower, 19.5 versus normal 47.3 pmol l<sup>-1</sup> (95% CI: –37.6, –11.6). There were no differences found for FSH, SHBG, inhibin B and testosterone. The most important difference was found for AMH, a marker of Sertoli cell function in the testes, which decreased by close to 60% when compared with controls. Combined with an increase in LH, these findings may indicate a dysfunction of Sertoli cells and an effect on Leydig cells contributing to a potential mechanism of reproductive dysfunction in men with ESRD.

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**Keywords:** antimüllerian hormone; chronic kidney disease; end-stage renal disease; infertility; inhibin B; sex hormones

## INTRODUCTION

Infertility among female patients with end-stage renal disease (ESRD) has been extensively investigated. However, male reproductive function in these patients is less well-characterized.

The genesis of sexual dysfunction in patients with chronic kidney disease (CKD) is multifactorial. Disturbances in the endocrine system, testicular function, autonomic dysfunction, vascular disease, psychological factors and pharmacologic therapy are factors to be considered. Dialysis treatment has not been shown to restore hormonal changes, libido and potency in uremic men, while a successful transplantation has.<sup>1,2</sup> Disturbances in the hypothalamic-pituitary-gonadal axis, resulting in alterations in signal-feedback mechanisms and hormone production, are seen already in patients with moderate reduction in the glomerular filtration rate and often become more obvious as kidney failure progresses.<sup>3,4</sup> Earlier studies have shown elevated levels of prolactin<sup>5,6</sup> as well as the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).<sup>6,7</sup> Decreased levels of free and total testosterone have also been reported.<sup>8–10</sup> The rise in LH is thought to be the result of diminished release of testosterone from the Leydig cells because testosterone normally inhibits LH release and diminished renal clearance of LH.

Testicular function is impaired in advanced uremia.<sup>7</sup> Decreased volume of ejaculate, low or complete azoospermia and low sperm motility is common in dialysis patients.<sup>11</sup> Only successful renal transplantation can restore spermatogenesis.<sup>4,12</sup> Two important cell

types in the testes are Leydig cells that produce testosterone stimulated by LH, and Sertoli cells that are activated by FSH to nourish developing sperm cells. The Sertoli cells secrete antimüllerian hormone (AMH) and inhibin. AMH is a specific marker of Sertoli cell function and is secreted in the serum and seminal fluid. The main physiological role of AMH in the adult male seems to be the autocrine and paracrine control of testicular function.<sup>13,14</sup> Serum AMH is correlated with spermatogenesis and is lower in men with nonobstructive azoospermia (NOA) than men with OA and normal fertile men.<sup>15</sup> The role of AMH and its importance for patients with kidney failure has, to the best of our knowledge, not been studied before. There are only two reports on inhibin in patients with ESRD showing elevated levels of inhibin during renal failure, however both studies used less specific assays.<sup>16,17</sup> No results have been demonstrated for inhibin B, a selective FSH inhibitor.

Here, we examined plasma levels of hormones involved in male reproductive function in patients with terminal renal failure. As renal dysfunction has tremendous influence on many physiological functions, we wanted to investigate not only traditional sex hormones but also AMH and inhibin B to find factors that may cause oligospermia, azoospermia and infertility.

## MATERIALS AND METHODS

### Clinical trials

The study has been registered at [ClinicalTrials.gov](http://ClinicalTrials.gov). Registration date January 21, 2011. Registration number NCT01294904.

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### Study patients

From June 2009 to May 2012 male patients with ESRD on hemodialysis (HD) were consecutively enrolled at the Department of Nephrology and Transplantation, Skåne University Hospital, Malmö, Sweden. Twenty males with a median age of 40 (26–48) years, with an average time on dialysis of 41 (2–74) months, were included. Only two patients during this period rejected participation. The patients underwent HD treatment 3–5 times weekly for 12–15 h per week. Fifteen out of 20 patients were on high-flux HD filter, Polyflu × 21 (Gambro®, Lund, Sweden). Five patients were on low-flux HD filter, Polyflu × 17 L (Gambro®). They were all free of any severe complications except hypertension that was well controlled with antihypertensive drugs. Four of the patients had diabetes. None of the patients were taking any immunosuppressive drugs. Plasma samples were obtained midweek before the dialysis treatment. All predialysis samples were drawn in the morning between 8 am and 10 am. We analyzed plasma levels of cystatin C, FSH, LH, prolactin, sex hormone-binding globulin (SHBG), testosterone, estradiol, AMH and inhibin B. All samples were analyzed at the routine clinical chemistry laboratory at Skåne University Hospital, Malmö, Sweden. Predialysis mean value for cystatin C was 6.1 (standard deviation (s.d.): 1.15) mg l<sup>-1</sup> in the dialysis patients (Table 1).

### Controls

For the control group we used 144 proven fertile men, median age of 32 (19–44) years. All subjects in the control cohort presented normal cystatin C values, mean 0.66 (s.d.: 0.13) mg l<sup>-1</sup>, and thus considered to have a normal renal function (Table 1). This control material from the Department of Reproductive Medicine, Skåne University Hospital, Malmö, Sweden, has been described previously.<sup>18</sup> The participants in the control group were required to have achieved at least one pregnancy with a female partner, stopped practicing birth control to achieve the present pregnancy and to have achieved the present pregnancy in <12 months of unprotected intercourse, without the use of assisted reproduction.

### Cystatin C

Plasma cystatin C was measured by a fully automated particle-enhanced immunoturbidimetric assay. The reagents were obtained from DAKO (Dako A/S, Glostrup, Denmark) and determination was performed on the Hitachi Modular P system. The total analytical imprecision was 2.1% for a control sample at a concentration of 1.0 mg l<sup>-1</sup> and 1.7% for a control sample at 4.0 mg l<sup>-1</sup>. Reference range: 0.55–1.15 mg l<sup>-1</sup> for age 1–50 years and 0.63–1.44 mg l<sup>-1</sup> for age >50 years.<sup>19</sup>

**Table 1: Characteristics of male patients with ESRD on HD. Control persons had normal renal function**

	ESRD patients	Controls
<i>n</i>	20	144
Age (year)	40 (26–48)	32 (19–44)
Cystatin C (mg l <sup>-1</sup> )	6.1 (1.15)	0.66 (0.13)
High-flux HD	15	0
Low-flux HD	5	0
Diabetes mellitus (%)	4 (20)	0
Renal diagnosis	Diabetes nephropathy 4 Glomerulopathy 4 Interstitial nephropathy 1 Hereditary nephropathy 3 Polycystic kidney disease 3 Urinary malformation 3 Unknown 2	

Values are given as median (range) for age and mean (s.d.) for cystatin C. s.d.: standard deviation; ESRD: end-stage renal disease; HD: hemodialysis

### Sex hormones

#### Antimüllerian hormone

Serum AMH was analyzed using a two-step immunometric ELISA, Beckman Coulter ACTIVE AMH Gen II Elisa A79758A 2009. The sensitivity of the assay was 1.0 pmol l<sup>-1</sup>. The total coefficient of variation (CV%) obtained was 2.9% at 6.7 pmol l<sup>-1</sup> and 3.8% at 68 pmol l<sup>-1</sup>.

#### Estradiol

Estradiol concentration in the serum was analyzed using an immunofluorometric method (Autodelfia; Wallac Oy, Turku, Finland). The sensitivity of the assay was 8 pmol l<sup>-1</sup>. Imprecision (CV%) was 15% at a level of 45 pmol l<sup>-1</sup> and 10% at a level of 300 pmol l<sup>-1</sup>.

#### Follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin and testosterone

Follicle-stimulating hormone, LH, SHBG and total testosterone concentrations were measured using an electrochemiluminescence immunoassay (ECLI) (Cobas-Roche, Mannheim, Germany). The sensitivities of the assays were 0.10 IU l<sup>-1</sup> (FSH), 0.10 IU l<sup>-1</sup> (LH), 0.35 nmol l<sup>-1</sup> (SHBG) and 0.087 nmol l<sup>-1</sup> (total testosterone). The CV% for FSH was 3.3% at a level of 4.9 IE l<sup>-1</sup> and 2.2% at a level of 68.7 IE l<sup>-1</sup>. The CV% for LH was 2.0% at a level of 5.0 IE l<sup>-1</sup> and 2.2% at a level of 55.2 IE l<sup>-1</sup>. The CV% for SHBG was 1.0% at a level of 22.0 nmol l<sup>-1</sup> and 1.1% at a level of 49.5 nmol l<sup>-1</sup>. The CV% for total testosterone was 2.4% at a level of 1.9 nmol l<sup>-1</sup> and 4.0% at a level of 25.5 nmol l<sup>-1</sup>.

#### Inhibin B

Serum values of inhibin B were assessed using a solid-phase enzymatically amplified three-step sandwich-type immunometric ELISA technique (Inhibin B ELISA, Beckman Coulter). The sensitivity of the assay was 10 ng l<sup>-1</sup>. Imprecision CV was not available because the method of analysis was new. The laboratory's normal range for inhibin B in adult males is 25–325 ng l<sup>-1</sup>.

#### Prolactin

Serum prolactin was measured using an ECLI; Roche. The sensitivity of the assay was 1.00 mIE l<sup>-1</sup>. The total analytical imprecision was 3% for a control sample at a concentration of 128 mIE l<sup>-1</sup> and 3% for a control sample at 460 mIE l<sup>-1</sup>.

### Statistics

Our primary goal was to find differences in plasma levels of different sex hormones between study patients and controls. We used all 144 control persons and performed multiple linear regression with age as an independent factor instead of age-matching the controls. This approach was used to avoid an effect of different median ages between study patients and controls without excluding any controls. The statistical analyses were performed with SPSS program version 21.0 (IBM Corp., Armonk, NY, USA). *P* < 0.05 was considered to be statistically significant. *P* values corresponding to age and interaction terms involving age were adjusted for multiple testing using Bonferroni correction.

### Ethical considerations

The study was approved by the regional ethics committee at Lund University, Sweden, LU 541/2008, and all subjects provided written consent to participate in the study. The study adheres to the Declaration of Helsinki.

## RESULTS

### Plasma levels

Patient characteristics are shown in **Table 1**. The renal diagnoses show a representative distribution at age of the patients. Among the hormonal analytes, predialysis plasma levels of prolactin ( $P = 0.021$ ), LH ( $P = 0.000$ ), and estradiol ( $P = 0.003$ ) turned out to be elevated compared with the control group (**Table 2, Figure 1**). Testosterone was only slightly decreased in the dialysis patients and not statistically different compared with the controls ( $P = 0.183$ ) (**Figure 2**). The most striking difference was seen for AMH that was 59% lower in the study group before dialysis compared with the control group ( $19.5$  vs  $47.3$  pmol $^{-1}$ ) (**Figure 3**). This difference was statistically lower ( $P < 0.0001$ , 95% confidence interval (CI):  $-37.6, -11.6$ ). We found no statistically significant differences in the study group concerning FSH, SHBG or inhibin B. When correcting for multiple analyses by Bonferroni, the significance for prolactin disappeared ( $P = 0.168$ ), while the other significances remained (not shown). There were no differences in AMH levels between those treated with low-flux versus high-flux membranes. The same observation was demonstrated for the other hormones (not shown).

## DISCUSSION

New insights into the possible causes of reproductive dysfunction in males with ESRD are provided here. We have shown that male patients with ESRD have close to 60% lower serum levels of AMH versus controls. Previous studies have shown oligospermia or azoospermia in males with ESRD can be a result of low testosterone levels due to disturbances in the hypothalamus-pituitary-testicular axis. Our

findings of lower serum levels of AMH may indicate a dysfunction of Sertoli cells in men with ESRD. These changes in AMH together with previous findings may provide clues as to the mechanism of reproductive dysfunction in these patients.

There are many factors that may explain reproductive dysfunction in men with ESRD. Chronic renal failure has a strong influence on the hypothalamic-pituitary-testicular axis resulting in hormonal disturbances and deterioration in testicular function. Our results on changes in prolactin and LH levels are consistent with previous reports. However, the plasma levels of testosterone in our study were only slightly decreased compared with other studies. The increase in prolactin on the other hand was high (+253%), but with great variability.

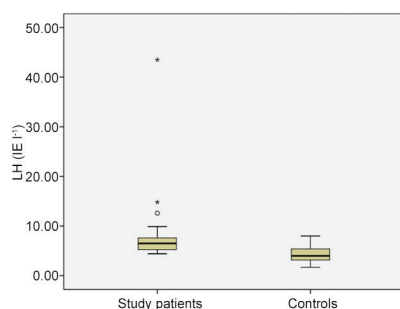
Previous reports on estradiol, most of which are several decades old, show low or normal levels among patients on HD.<sup>20,21</sup> In contrast, we found an elevated level of estradiol, which has also been shown by Bao *et al.*<sup>22</sup> These differences may be a result of different assays with our method for estradiol measurement able to detect sensitive estradiol E2, the most biologically active isotype. Several previous studies have recognized an increased level of FSH, in contrast to ours, but the results are not consistent.<sup>4</sup> Estradiol and inhibin B do not decrease and this may explain the normal levels of FSH.

This is the first study to analyze serum AMH in patients with ESRD. AMH production by the Sertoli cells of the testes remains high throughout childhood but declines to low levels during puberty and adult life. AMH levels decrease after puberty to a level that is similar to that observed in females.<sup>23</sup> AMH has also been shown to inhibit androgen synthesis in Leydig cells of rats,<sup>24,25</sup> resulting in

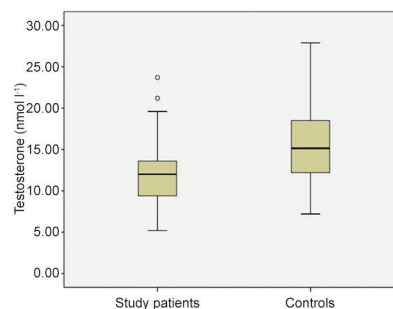
**Table 2: Plasma levels of analytes measured midweek before dialysis treatment in 20 ESRD patients. All analytes were also measured in 144 controls, except prolactin that was measured in 42 persons**

	Controls (mean±s.d.) n=144	ESRD patients predialysis (mean±s.d.) n=20	P (95% CI)	Percentage change in mean values between controls and study patients (%)
Cystatin C (mg l <sup>-1</sup> )	0.66±0.13	6.09±1.15	0.000 (5.28, 5.70)	+822
FSH (IE l <sup>-1</sup> )	4.22±1.76	4.52±2.46	0.877 (-1.02, 0.87)	+7
LH (IE l <sup>-1</sup> )	4.51±1.54	8.87±8.57	0.000 (2.755, 6.143)	+97
Testosterone (nmol l <sup>-1</sup> )	15.2±4.94	12.5±5.17	0.183 (-4.263, 0.819)	-18
SHBG (nmol l <sup>-1</sup> )	30.5±12.5	29.9±23.2	0.619 (-9.186, 5.488)	-2
Estradiol (pmol l <sup>-1</sup> )	79.0±20.7	89.7±22.9	0.003 (-1.31, -0.152)	+13
Prolactin (mIE l <sup>-1</sup> )	210.0±99.3	742±1019	0.021 (60.294, 728.95)	+253
Inhibin-B (ng l <sup>-1</sup> )	196.8±57.5	227±135	0.112 (-7.019, 66.97)	+15
AMH (pmol l <sup>-1</sup> )	47.3±25.9	19.5±13.3	0.000 (-37.6, -11.6)	-59

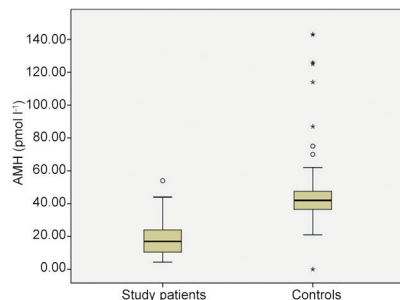
The difference between study patients and controls is given as a percentage. Statistical analysis was performed using multiple linear regression. ESRD: end-stage renal disease; s.d.: standard deviation; CI: confidence interval; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; AMH: antimüllerian hormone



**Figure 1:** Serum levels of luteinizing hormone (LH) in study patients and controls ( $P = 0.000$ ). Box plot indicates median and interquartile range. Outliers between 1.5 and 3 box lengths are depicted by "o" and extreme values more than 3 box lengths are shown by "\*".



**Figure 2:** Serum levels of testosterone in study patients and controls ( $P = 0.183$ ). Box plot indicates median and interquartile range. Outliers between 1.5 and 3 box lengths are depicted by "o" and extreme values more than 3 box lengths are shown by "\*".



**Figure 3:** Serum levels of antimüllerian hormone (AMH) in study patients and controls ( $P = 0.000$ ). Box plot indicates median and interquartile range. Outliers between 1.5 and 3 box lengths are depicted by "o" and extreme values more than 3 box lengths are shown by "\*".

low testosterone levels. Our finding of greatly decreased levels of AMH is important since it may reflect Sertoli cell impairment in men with ESRD. There are reports of azoospermia associated with low levels of AMH in infertile men without renal disease.<sup>15,26</sup> This finding is interesting because we now show an association between low levels of AMH and ESRD. Previous knowledge of azoospermia in ESRD, in combination with our findings, suggests that there may be an association between low levels of AMH, ESRD and azoospermia. Abnormal spermatozoa and impaired spermatogenesis have been described previously in men with CKD.<sup>27,28</sup> Xu *et al.*<sup>28</sup> also demonstrated normalization of spermatozoa after transplantation. However, the causal relationship needs further exploration. The uremic milieu may interfere with testicular function in a more profound way and explain the low levels of testosterone and reproductive dysfunction in these men. Our new findings of low AMH levels and previous reports on low levels of testosterone indicate a dysfunction of both Sertoli cells and Leydig cells in men with ESRD.

There are several studies of AMH in infertile men with normal kidney function. Some studies have found a correlation of serum AMH levels with sperm count<sup>29</sup> and reduced serum AMH levels in men with oligozoospermia compared with controls.<sup>26</sup> However, this has not been confirmed by all studies.<sup>30</sup> Serum AMH levels have been found to be lower in NOA than in OA patients and normal fertile men.<sup>15,31</sup> Most patients in this study were treated with high-flux filters. The different cut-off values for low- and high-flux filters may result in different serum levels of analytes between the filters. However, AMH has a molecular weight >200 kDa, which means that this molecule is not cleared by either the low-flux or high-flux filters.

There are only two reports about inhibin in ESRD patients and both demonstrated elevated levels of inhibin versus controls.<sup>16,17</sup> However, it is well known that earlier assays demonstrated problems of specificity. The antibody employed was known to cross-react with both the alpha-subunit and the precursor molecule of inhibin. Thus, the results of these studies may not be comparable with ours. Inhibin complexes occur in two forms; A and B. This is the first study to analyze inhibin B in ESRD. We could not find any increased nor decreased levels of inhibin B. One might expect that both AMH and inhibin B would be affected. However, our finding is in agreement with current knowledge regarding the different regulation of AMH and inhibin B synthesis in Sertoli cells. Thus, inhibin B production is dependent on FSH regulation and in adult males, is derived from both Sertoli cells and primary spermatocytes. AMH is purely a Sertoli cell product and is also regulated by intratesticular testosterone.<sup>32</sup>

### Strengths

The men were relatively young compared with those in other studies. All samples, both controls and study patients, were analyzed at the same time at the same laboratory. We used standardized biochemical analyses at one laboratory in close cooperation with the Department of Reproductive Medicine at Skåne University Hospital, Malmö, Sweden.

### Weakness

The major limitation is the small number of study patients. This is explained by the relatively few patients in this age group on dialysis. Many of these patients are transplanted preemptively before starting dialysis. The immunoassays for inhibin B and AMH have not been evaluated in uremia and the quantitative validity of the immunoassays is not established.

### CONCLUSIONS

Low serum levels of AMH in combination with altered plasma levels of several sex hormones in males with ESRD may indicate a dysfunction of Sertoli cells and Leydig cells. The low levels of AMH may be part of the explanation of azoospermia and infertility in males with ESRD. Further studies are needed to confirm our findings and evaluate the significance of the association we found for AMH and also the potential pathophysiological relevance for these changes.

### AUTHOR CONTRIBUTIONS

DE, AG and AC designed the study. DE collected the samples. DE, AG and AC analyzed the data and wrote the paper. All authors critically reviewed and approved the final manuscript.

### COMPETING INTERESTS

All authors declare that there are no competing interests.

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