Leptinemia and its relation to sex hormones and obesity in patients with chronic renal failure.

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Abstract

Background: Chronic renal failure is a predominant reduction in glomerular filtration rate (GFR) sufficient to produce alterations in well-being and organ function. Endocrine abnormalities common in chronic renal insufficiency is the association of higher serum leptin levels in their patients. Leptin is a protein hormone produced mainly by adiposites. Serum leptin concentrations positively correlate with body mass index (BMI) and body fat content. Changes of androgens synthesis and metabolism develop early after the onset of renal insufficiency and are likely to be caused by primary hypogonadism and/or disturbances of the hypothalamic pituitary –axis.

Aim: The aim of the present work is to analyze the contribution of serum testosterone and estradiol concentrations with leptinemia in hemodialyzed patients together with waist circumference and BMI. In order to shed some light on the mechanism of biodegradation of leptin by the kidneys in both genders and how it is affected by body composition and weight.

Subjects and Methods:
A total of 45 subjects were involved in this study, 30 of them had chronic renal failure and the remaining 15 subjects were normal healthy individuals served as a control. Five mls of blood were withdrawn from each subject by vein puncture, patients and control. ELISA technique was used for the measurement of serum leptin level while RIA technique was used for the measurements of testosterone and estradiol levels. Data were expressed as mean±SD. results were evaluated using the student t-test for paired data. Conventional methods were used for the correlation and regression analyses.

Results:
Results obtained showed that the level of serum leptin and serum estradiol in patients with chronic renal failure were significantly higher than that in healthy subjects, whereas testosterone level was significantly lower in patients than in healthy subjects. The anthropometrical measurement in patients with chronic renal failure had significantly higher values of waist but significant lower values of BMI. Male with chronic renal failure showed a significant lower level of serum leptin concentration than in females. However the anthropometrical measurements (BMI & waist) of males were significantly higher than those in the females. Serum leptin level was positively correlated with serum estradiol whereas it had an inverse correlation with testosterone. Leptin had positive correlation with each of the studied anthropometrical measurements (BMI & waist). All results are thoroughly discussed in the text.
Conclusion:
Increased levels of serum leptin and estradiol in CRF patients is a reflection of the increased waist circumference and the poor ability of the kidney for biodegradation of both these hormones. On the other hand testosterone had a significant effect on serum leptin levels as can be shown through its positive effect in males rather than in females.

Introduction
Chronic renal failure is a predominant reduction in glomerular filtration rate (GFR) sufficient to produce alterations in well-being and organ function. It represents an evolutionary process that is initiated by various causes, all with the common results of persistent and usually progressive damage of varying severity to the kidneys (1)

Patients with renal insufficiency show from the onset of their disease, a pattern of hormonal changes resulting from complex disturbances at the hypothalamic, pituitary and gonadal level. This endocrine dysfunction can only partially be influenced by renal replacement therapy such as hemodialysis or kidney transplantation. Impaired function of the hypothalamic, pituitary and gonadal axis is not reversed by initiation of otherwise effective hemodialysis therapy (2).

Other endocrine abnormalities common in chronic renal insufficiency is the association of higher serum leptin levels in their patients (3).

Leptin is a protein hormone produced mainly by adipoocytes. Serum leptin concentrations positively correlate with body mass index (BMI) and body fat content. Malnourished patients or lean individuals have decreased leptin levels proportional to the less of body fat. Increased levels of leptin in patients with chronic renal failure can be explained to lower clearance of leptin by the kidney and increased insulin and pro-inflammatory cytokine stimulation of leptin synthesis (4).

Changes of androgens synthesis and metabolism develop early after the onset of renal insufficiency and are likely to be caused by primary hypogonadism and/or disturbances of the hypothalamic –pituitary –axis.

The aim of the present work is to analyze the contribution of serum testosterone and estradiol concentrations with leptinemia in hemodialyzed patients together with waist circumference and BMI, in order to shed some light on the mechanism of biodegradation of leptin by the kidneys in both genders and how it is affected by body composition and weight.

Subjects and methods
A total of 45 subjects were involved in this study, 30 of them had chronic renal failure and the remaining 15 subjects were normal healthy individuals served as a control. Age range of the patients was between 25 and 45 years with a mean of 37±8.2 years and a mean BMI of 24.3±3.3 kg/m². Sixteen of the patients were females with a mean BMI of 22.6±3.1 kg/m². The remaining 14 patients were males with a mean BMI 25.3±2.2 kg/m². The age range of the control subjects was also between 25-45 years with a mean of 30±10.3 years, with normal weights and a mean BMI of 29.0±4.7 kg/m².

Five mls of blood were withdrawn from each subject by vein puncture, patients and control. The blood was then transferred into plastic tubes, left for 2 hours before centrifugating them at 500rpm for 10 minutes to get as much serum as possible.

Enzyme linked immuno assay (ELISA) was used for the measurement of serum leptin level.

Radio immuno assay (RIA) technique was used for the measurements of testosterone and estradiol levels.
The radio immune assay kits for the measurements of the mentioned parameters were obtained from DIOsorin, still waster, Minnesota USA. Data were expressed as mean±SD. Results were evaluated using the student t-test for paired data. Conventional methods were used for the correlation and regression analyses.

**Results**
Mean (±SD) of the studied hormones (serum leptin, testosterone and estradiol) and the anthropometrical measurement (BMI and waist circumference) are shown in table (1).

Table 1: Mean (±SD) of the studied hormones (serum leptin, testosterone and estradiol) and the anthropometrical measurement (BMI and waist circumference)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy subjects</th>
<th>CRF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. investigated</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>BMI kg/ m²</td>
<td>29.0 ± 4.7</td>
<td>24.3 ± 3.3**</td>
</tr>
<tr>
<td>Waist circumference cm</td>
<td>55.2 ± 3.5</td>
<td>60.7 ± 3.4**</td>
</tr>
<tr>
<td>Leptin ng/ ml</td>
<td>10.4 ± 4.4</td>
<td>26.6 ± 8.6**</td>
</tr>
<tr>
<td>Testosterone</td>
<td>14.7 ± 13.0</td>
<td>8.9 ± 9.7**</td>
</tr>
<tr>
<td>Estradiol</td>
<td>134 ± 137</td>
<td>230 ± 19.6**</td>
</tr>
</tbody>
</table>

** p<0.01

This table shows that the level of serum leptin and serum estradiol in patients with chronic renal failure is significantly higher than that in healthy subjects, whereas testosterone level is significantly lower in patients than in healthy subjects. The anthropometrical measurement in patients with chronic renal failure had significantly higher values of waist but significant lower values of BMI. The difference in leptin level between both genders are shown in table 2.

Table 2: Mean (±SD) of serum leptin, BMI, waist circumference in female and male with chronic renal failure.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Female with CRF</th>
<th>Male with CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. investigated</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>BMI kg/ m²</td>
<td>22.6 ± 3.1</td>
<td>25.3 ± 2.2</td>
</tr>
<tr>
<td>Waist circumferences cm</td>
<td>55.8 ± 3.7</td>
<td>75.2 ± 3.0</td>
</tr>
<tr>
<td>Leptin ng/ml</td>
<td>30.1 ± 7.8</td>
<td>22.5 ± 8.0</td>
</tr>
</tbody>
</table>

** p<0.01

Males with chronic renal failure show a significant lower level of serum leptin concentration than in females. However the anthropometrical measurements (BMI & waist) of males are significantly higher than those in females. Serum leptin level is positively correlated with serum estradiol whereas it had an inverse correlation with testosterone. Leptin had positive correlation with each of the studied anthropometrical measurements (BMI & waist). (Figures 1-4).
Figure 1: Correlation between serum leptin level & BMI in chronic renal failure with $r=0.59, p<0.01$

Figure 2: Correlation between Serum leptin level & waist circumference in chronic renal failure group with $r=0.78, p<0.01$
Figure 3: Correlation between serum leptin level & testosterone level in chronic renal failure group with r = -0.55, p<0.01

Figure 4: Correlation between leptin level & estradiol level in chronic renal subjects with r = 0.62, p = 0.01
Discussion
Chronic renal failure is characterized by a predominant reduction in glomerular filtration rate (GFR) sufficient to produce alterations in well-being and organ function. The number of patients with chronic renal failure is increasing worldwide (4,5). Patients with chronic renal failure show higher leptin levels than healthy subjects which is due to decreased leptin clearance by the kidneys (Table 2).
In the meantime there is an increased stimulation of leptin synthesis in obese subjects due to elevated insulin and proinflammatory cytokine levels (6), as serum level of leptin reflects the amount of energy stored in adipose tissue (7). Also short term energy imbalance as well as serum levels of several cytokines and hormones influence circulatory leptin level (8).

The pathophysiological consequences of increased free circulating leptin levels in CRF patients as well as the possibility of contribution of chronic hyperleptinemia to anorexia and malnutrition of CRF patients require further investigation (9). Hyperlipidemia is one of the commonest changes in serum lipid during chronic renal failure (10). This has been attributed to either a reduction in the clearance or excessive hepatic synthesis which is induced by high level of insulin.

There is an accumulating body of clinical and experimental data implicating obesity as an important factor in renal disease (11), but epidemiologic data linking obesity to CRF have been scarce so far. Some studies have investigated the association between obesity and proteinuria in the general population (12); however, few epidemiologic studies have quantified the possible link between obesity and established renal failure in population-based settings. Relative risk estimate that were consistent with our study were reported in a cohort study with a small number of incident CRF cases (13). In the meantime it is widely known that obesity markedly increases risk for diabetes and hypertension and that both diabetes and hypertension are important contributors to ESRD (14).

The BMI-CRF risk relationship seems to be somewhat stronger and evident in a lower BMI range in men than in women, Table 2). However, no BMI gender interactions attend statistical significance.

In adult individuals, variations in body weight mainly result from changes in the adipose tissue mass. An increase in adipose tissue mass results either from an enhanced deposition of triglycerides (TG) into adipocytes or from a rate of lipolysis in adipocytes lower than the rate of free fatty acid esterification. The resulting positive fat balance lead to expansion of adipose tissue mass and volume (15,16) this was initially suggested that hemodialysis patient had significant higher waist proportion in comprise to healthy controls.

Patients with renal insufficiency show, from the onset of their disease, a pattern of hormonal changes resulting from complex disturbances at the hypothalamic, pituitary and gonadal level. The causes appear to be multifactorial, with clear contribution of co-morbidities and therapy. This endocrine dysfunction can only partially be influenced by renal replacement therapy, such as hemodialysis or kidney transplantation. The beneficial effects of androgens on erythropoiesis and nutrition are well documented in dialysis patients (17,18).

There are gender–related differences in the morphology and function of kidneys, resulting in a bigger size, higher numbers of nephrons, greater intrarenal blood flow, and higher intrarenal resistance in male rats. These are supposed to be mediated partially by intrarenal hormone receptors, which are localized in most parts of the nephron. Androgens, but also to some extent oestrogens, stimulate the proliferation of mesangial...
cell and matrix accumulation as well as the synthesis of cytokines, vasoactive
substances (rennin –angiotensin system, endothelins) and growth factors (IGF-1, growth hormone), which may contribute to the progression of kidney diseases. On the other side, oestrogens may also have some protective effects in kidney diseases, by lowering plasma lipids and by antioxidative effects on cell membranes (19, 20, 21).

Leptin is secreted by adipocytes into the blood stream (22), and could thus be the signaling factor in a feedback system to the brain, informing the brain about the amount of fat mass in the body (23).

In humans, leptin mRNA expression and serum levels are much higher in obese individuals compared with lean subjects and correlate strongly with body fat (24). From the present study data of highly positive correlation between leptin and waist of both genders, which document the previous points.

Also, exogenous follicle-stimulating hormones (FSH) administration, increase leptin levels together with oestrogens (25).

In children oestrogen could explain up to 5% of the variance in leptin concentration (26).

Androgens, on the other hand, have inhibitory effect on leptin secretion (27). Leptin and testosterone levels are inversely correlated. Testosterone could account for about 10% of the variation of leptin in a multiple regression model in young boys (28). Thus, the suppressive effect of androgens can partly explain the gender differences in body composition and fat distribution (29).

In Conclusion: Increased levels of serum leptin and estradiol in CRF patients is a reflection of the increased waist circumference and the poor ability of the kidney for biodegradation of both these hormones. On the other hand testosterone had a significant effect on serum leptin levels as can be shown through its positive effect in males rather than in females.

References
Available at http://www.socialstyrelsen.se/Amnesord/halso_sjuk/


