Inappropriately high plasma leptin levels in obese haemodialysis patients can be reduced by high flux haemodialysis and haemodiafiltration

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INTRODUCTION

Recent studies have shown that nutrition is a relevant factor for the survival of patients on maintenance haemodialysis treatment [1]. Malnutrition can be found in up to 60% of the patients and leads to a substantial decrease in the patient survival rate [1]. Reduced appetite and high energy expenditure along with acidosis, blood contact with dialysis membranes and increased interleukin-1 levels after dialysis seem to be the principle pathophysiological causes [1-5].

Leptin, which is a product of the ob gene and is released from adipocytes as a hormone, seems to be a major factor in the regulation of appetite and energy expenditure in obese healthy subjects [6]. We wondered whether leptin could also have a relevant impact on nutrition in the dialysis population. In this study we measured plasma leptin levels in a cohort of patients undergoing chronic haemodialysis, and assessed the correlation of leptin levels with the individual body mass index (BMI) and food intake reflected in the calculated individual protein catabolic rate. Furthermore the behaviour of plasma leptin during different modes of haemodialysis treatment was studied.

METHODS

Patients and study design

In 46 patients (27 male, 19 female) on maintenance haemodialysis treatment fasting plasma leptin levels were measured. The mean age was 61.60 (S.D. 14.40) years and mean period since commencement of dialysis treatment was 28.9 (S.D. 29.2) months. Dialyses were performed three times a week for 4 h each. Low flux dialysers with cellulosic membranes were used in 28 patients, high flux dialysers were used in 8, and haemodiafiltrations with high flux dialysers were performed in 10 cases. Obesity was defined as a BMI $\geq 27.3$ for men and $\geq 27.8$ for women [6, 7]. Basic renal disease was diabetic nephropathy in 15, glomerulonephritis in 21, pyelonephritis in 2, vascular renal disease in 5, analgesic nephropathy in 2 and polycystic kidney disease in 1 patient.

Twenty-six healthy subjects served as controls. Mean age was 67.5 (15.97) years. Mean BMI was 22.38 (3.86) in non-obese normal subjects ($n = 11$) and 22.87 (2.86) in ($n = 30$) non-obese haemodialysis patients ($P = 0.67$, not significant). In the obese groups mean BMI was 33.63 (7.92) in normal subjects ($n = 15$) and 31.01 (2.49) in obese dialysis patients ($n = 16$) ($P = 0.35$, not significant). For calculation of the BMI of haemodialysis patients the individual dry weight of the patients was used. This is the weight below which a dialysis patient will become hypotensive with fluid removal and above which the same patient will either by hypertensive or show subtle signs of fluid expansion [8].
In 2 patients (BMI 18.30 and 21.42 respectively) on low-dose corticosteroid therapy, plasma leptin levels were also measured. These patients were not included in the calculations. The data of these patients are presented separately.

Ethics committee approval and informed consent of the participants were obtained for the study.

Rough food intake amount was assessed by measurement of the protein catabolic rate. The latter was calculated by a computer program (Up to date in Medicine, Wellesley, MA, U.S.A.)

In a further step pre- and post-dialysis plasma leptin levels were measured in three groups of patients dialysed with different modes of 4 h haemodialysis: in six patients with conventional low flux haemodialysis (dialysers: MCA 1.3, 1.6, 2.0 Altra Medical Inc., U.S.A.; CLC 1.5 Terumo Corp. Tokyo, Japan; GFS 16 Gambro Hechingen, Germany; cut-off point: molecular mass of approximately 8 kDa), in eight patients with high flux haemodialysis (dialysers: Polyflux 17, Polflux 21, Gambro Hechingen, Germany; Filtral 16 Hospal-Meyzieu, U.S.A.—France, cut-off point: molecular mass of approximately 50 kDa) and in 10 patients on haemodiafiltration with high flux membranes (dialysers: Polyflux 17, Polflux 21, Gambro Hechingen, Germany; Filtral 16 Hospal-Meyzieu, U.S.A.—France, cut-off point: molecular mass of approximately 50 kDa). Both high flux haemodialysis and haemodiafiltration allow the passing of molecules of higher molecular size [9,10]. The mean BMI was significantly higher in the patients on high flux membrane haemodialysis or on haemodiafiltration, both modes of dialysis which are more frequently applied by us to patients of higher body weight, than in the group on conventional low flux membrane dialysis. Mean BMI of patients on high flux haemodialysis or on haemodiafiltration was 29.94 (3.37) and 23.43 (4.75) respectively (P = 0.008).

All blood samples were drawn at the 4 h morning sessions starting at 07.30 h.

When calculating the percentage variation of plasma leptin levels by dialysis, the haemoconcentration resulting from fluid removal during the dialysis session was also taken into account. Therefore post-dialysis concentrations were corrected based on the decrease of the estimated individual extracellular fluid volume.

Laboratory measurements

Plasma leptin levels were measured using a commercially available RIA (Human Leptin RIA Kit, DRG, Marburg, Germany). The intra- and interassay coefficients of variation were 5% and 9% respectively.

Statistical analyses

For the assessment of differences in the BMI—plasma leptin level correlation between controls and haemodialysis patients a multiple regression model with stepwise variable selection was used. The dependent variable is the natural log of leptin. Residual plots confirm that the use of the logarithm of leptin is more appropriate than using the original leptin values in the regression model. For comparisons of groups, two-tailed t-tests for paired or unpaired samples were used.

For the estimation of a possible correlation between plasma leptin levels and protein catabolic rate simple regression analysis was performed. Data are expressed as means ± S.D. The level of statistical significance was defined as P < 0.05.

RESULTS

In the 46 dialysis patients and 26 controls an increase in the BMI was associated with an increment in leptin plasma levels. In both groups a sharp rise of the curve was noted when the BMIs were in the obese range. However, the increment was significantly more pronounced in the dialysis group than in the normal subjects (P = 0.001, Figure 1). When both obese groups [dialysis patients versus controls: n = 16 and n = 15 respectively, BMI = 31.01 (2.49) and 33.63 (7.92), not significant] were compared, significantly higher levels of plasma leptin were measured in the dialysis group than in the control group [50.40 (43.11) ng/ml versus 13.20 (9.72) ng/ml, P = 0.003, Figure 2].

In the non-obese groups [dialysis patients versus controls: n = 30 and n = 11 respectively, BMI = 22.87 (2.86) and 22.38 (3.86), not significant], plasma leptin levels were also higher in the dialysis patients than in the controls, but the difference did not reach statistical significance [13.30 (17.79) ng/ml and 9.63 (8.23) ng/ml respectively, P = 0.5].

The plasma leptin level was independent of the type of basic renal disease. Mean plasma leptin

![Fig. 1. Relationship between BMI and plasma leptin levels in haemodialysis patients (closed circles) and controls (open circles). The increase in plasma leptin levels is statistically significantly more pronounced in the haemodialysis group than in the control group (P = 0.001).](image-url)
levels were 30.13 (40.90) ng/ml in patients with diabetic nephropathy, 25.20 (36.55) ng/ml in patients with glomerulonephritis and 22.25 (16.3) ng/ml in cases with other renal diseases (not significant). In 2 patients on corticosteroid therapy particularly high plasma leptin levels were measured (151.76 and 35.84 ng/ml).

No statistically significant correlation between the plasma leptin levels and the protein catabolic rates could be found ($P=0.61$). In 6 patients dialysis sessions with low flux dialysers led to an increase in the mean plasma leptin level from 11.94 (16.92) to 14.74 (20.76) ng/ml. Mean percentage of the initial values after dialysis was 117.88 (9.56) ($P=0.006$) when uncorrected and 103.61 (10.78) when corrected for haemoconcentration during dialysis ($P=0.078$). In dialyses with high flux membranes ($n=8$) plasma leptin levels fell from 48.21 (51.08) to 45.26 (53.67) ng/ml ($P=0.25$), mean percentage being 86.61 (18.44) of the initial values ($P=0.085$). When the percentages were corrected for haemoconcentration mean levels were 76.95 (14.89) % of the initial values and reached statistical significance ($P=0.013$).

In 10 patients on haemodiafiltration mean plasma leptin level decreased during the procedure from 63.10 (47.33) to 39.72 (35.41) ng/ml ($P=0.017$). The mean percentages after the sessions were 71.91 (28.8) and 62.90 (24.94) of the initial values respectively (uncorrected and corrected for haemoconcentration; $P=0.013$ and $P=0.001$; Figure 3 and Figure 4).

DISCUSSION

Our data show than in haemodialysis patients as well as in control subjects higher BMIs are associated with higher plasma leptin levels. However, higher BMIs are associated with an inappropriately more pronounced increment in plasma leptin concentrations in the dialysis group than in normal controls. The relationship between BMI and plasma leptin levels shows a non-linear behaviour in both groups, which is consistent with the findings of Considine et al. [6], who described a similar relationship between plasma leptin levels and the percentage of body fat in non-renal subjects. In non-obese haemodialysis patients plasma levels were slightly higher than in non-obese controls, but the difference did not reach statistical significance. These findings are in agreement with two other recent studies, which also suggested that plasma leptin levels are higher in uraemia [11, 12]. The increase in the plasma leptin levels was independent of the type of basic renal disease.

The mechanism which causes inappropriately high plasma leptin levels in uraemia is not clear. We believe that several factors could be responsible: first, a disturbed elimination of leptin in chronic failure and, second, an increased release of leptin due to uraemia per se or to increased cortisol levels encountered in renal failure [13]. Interestingly, particularly high levels were measured in two patients,
who were on glucocorticoid therapy. This is in agreement with two previous studies which described an increase in circulating leptin levels in non-uraemic patients after administration of glucocorticoids [14, 15]. Moreover, in one study, a relationship between the plasma cortisol level and the degree of malnutrition could be found [16].

One could speculate that, due to the muscle wasting encountered frequently in haemodialysis patients, similar BMIs of normal subjects and haemodialysis patients might reflect a different percentage of body fat, and that in the absence of muscle wasting higher BMIs would have been found in the dialysis patients [1]. Unfortunately there is no accurate method for the assessment of body fat in patients with renal insufficiency, since most methods distinguish poorly between fat and water, which is frequently increased in uraemia [17–19]. Several considerations, however, let us assume that the BMI in both groups is comparable and that such a possible influence can be neglected: (i) in normal subjects muscle mass is also relatively low in comparison to the amount of fat mass and total body water [20], (ii) according to various studies using different methods both body fat and lean body mass may decrease [21], (iii) the fluid retention occurring in uraemic conditions would even compensate arithmetically any muscle wasting in this context [22], and (iv) in the normal population reduced muscularity can occur in the older age groups, which includes both our control subjects and patients [23].

We believe that our study suggests an impact of leptin on nutrition in the dialysis population. Both predominant effects of leptin, decreased appetite and increased energy expenditure, are important mechanisms in the pathogenesis of malnutrition in the dialysis population [6]. Numerous studies have shown that the capability of leptin to decrease appetite and to increase energy expenditure is mediated through a depressing effect on neuropeptide Y concentrations in the hypothalamus [6, 24]. It is possible that leptin might behave differently in uraemic settings particularly regarding the percentage of the free plasma leptin and the cerebrospinal fluid barrier for leptin. Unfortunately there are no data available to support this to date. One could speculate, however, that similar to the behaviour of several hormones and drugs a higher percentage of free leptin — which ranges from approximately 50 to 80% of total plasma leptin in normal subjects — and a lower cerebrospinal fluid barrier for leptin could lead to an even more pronounced effect of leptin in uraemia than in normal conditions [25–29].

In our opinion leptin could have an impact, particularly in the long-term course of haemodialysis treatment, leading to reduced appetite and consequently to less body fat and a new steady state at a lower leptin blood level. On the other hand, in our study, no statistically significant correlation between plasma leptin levels and the protein catabolic rate as a marker of food intake could be found. Two factors could be responsible for this discrepancy. First, high plasma leptin levels do not necessarily result in low appetite, since an individual variation of sensitivity to leptin exists, which seems to be at least in part responsible for obesity in normal subjects, and second, measurements of the protein catabolic rate reflect the momentary food intake and not a long-term phenomenon [1, 6].

Leptin could not be removed by conventional dialysis with low flux membranes. This is consistent with the high molecular mass of leptin of about 16 kDa, a size at which molecules cannot pass low flux membranes. However, dialyses with high flux membranes and particularly haemodiafiltration, which both allow passing of high-molecular-mass substances, led to a substantial decrease in plasma leptin levels [9, 10]. Theoretically these results could have been influenced by a physiological diurnal fluctuation in leptin plasma levels. However, since no decrease of plasma leptin levels could be noted in the patients with conventional membrane dialysis, from whom plasma samples were drawn simultaneously, a relevant influence by such a mechanism seems to be negligible. Although filtration seems to be the principle mechanism for leptin removal, adsorption by the dialyser membrane may also be an additional factor as could be demonstrated for various other proteins [30].

The higher initial values of plasma leptin measured in the patients on high flux membranes or haemodiafiltration compared with those in the conventional dialysis group can be explained by the higher BMIs in the former. In general we prefer both modes to conventional dialysis in patients with higher body weight.

It has been claimed that patients on high flux membrane haemodialysis fare better and have more of an appetite than patients on low flux haemodialysis treatment [31]. Our study, which shows that leptin plasma levels can be reduced by high flux haemodialysis and haemodiafiltration, suggests that leptin levels could play a role in this context.

REFERENCES


