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Effects of age, gender and hyperparathyroidism on lean body mass in hemodialysis patients

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Abstract. – **Hyperparathyroidism of hemodialysis patients is associated with osteo-dystrophy, impairment of cardiac function, of peripheral nerve conduction, of response to r-HuEPO and with decrease of lean body mass.**

Primary hyperparathyroidism of post-menopausal women is associated with increased fat mass (FM).

The study investigated if gender varies relationship between i-PTH, and body composition, assessed by multifrequency bio-electrical impedance analysis (BIA), cardiac function, assessed by echocardiography, and anemia, in long-term hemodialysis patients.

Seventy patients on long-term bicarbonate dialysis, 34 male and 36 post-menopausal female, were studied. i-PTH RIA, multifrequency BIA and Kt/V were assessed at three months intervals.

i-PTH (345.88 ± 199.58 vs. 224.26 ± 161.62 pg/ml, p <0.01) and FM % (39.13 ± 10.42 vs.30.95 ± 5.88, p<0.001) were both significantly higher in women vs men; BMI was not significantly different. In the total group of patients (r=0.572, p<0.001) and in women (r=0.68, p<0.001) a positive correlation was found between i-PTH and FM%, and reciprocally an inverse negative correlation with free fat mass (FFM) was observed. No significant relationship was observed in men. Decrease of blood pressure measurements and increase of left ventricular Ejection Fraction, in the comparison of beginning and end of three dialysis sessions, were significantly greater in women.

Reduced FFM of women on dialysis could have also some relationship with a more close long-term adherence to dietary protein restriction.

Hyperparathyroidism in chronic renal failure patients could share liability of bone structural abnormalities, cardiac function impairment, excitable tissue disease, and anemia. However, malnutrition, and its consequent relative decrease of lean mass, resulting from kidney disease and, possibly, from nutritional behavioral modifications, could be responsible of the multi-organ involvement of hyperparathyroidism in end-stage renal disease.

Key Words:
Hyperparathyroidism, Hemodialysis, Gender.

Introduction

Hyperparathyroidism is frequently observed in hemodialysis patients[1,2], due to complex factors, including impaired intestinal and renal regulation of calcium-phosphorus balance[3]. Its severity is associated with several clinical problems, besides osteo-dystrophy: impairment of cardiac function[4,5], peripheral nerve conduction[6], response to r-HuEPO[7]. Moreover, we reported that hyperparathyroidism of hemodialysis patients shows an association with obesity and reciprocally with lower lean body mass with possible implications for cardiovascular disease prognosis[8].

In post-menopausal women, without renal disease, primary hyperparathyroidism is associated with increased body weight, total body fat mass, and proportion of android fat[9]. All these factors may be relevant to the increased incidence of cardiovascular disease in post-menopausal women. Moreover, unadjusted bone mineral density was similar in patients with primary hyperparathyroidism and in controls (all post-menopausal women)[10], suggesting extra-skeletal effects of PTH.

Body water content is reduced in obesity[11] both in patients with and without chronic renal failure. Hemodialysis (HD) modifies both water and solutes of patients, minimally affecting fat mass[12]. While Body Mass Index (BMI) is a descriptive and established criterium for defining a generic degree of obesity, bio impedance analysis (BIA) allows a reliable, non invasive evaluation of body composition[13], i.e. of total body water content (TBW), fat mass (FM) and fat-free mass (FFM). Obesity can exert unfavourable effects on cardiovascular function and on prognosis of cardiovascular disease. While it is known that women have a reduced lean mass, and a higher percentage of fat tissue, its relationship[14], if any, with hyperparathyroidism was not previously investigated in dialysis patients.

Body compartment changes during hemodialysis can be assessed by multifrequency bio-electrical impedance analysis (BIA); echocardiography allows a non-invasive monitoring of cardiac dimensions and function changes. The two combined procedures give useful information on the relationship between body compartment changes and heart function[15].

Aim of the study was to investigate if gender (male and female) has any relevance on relationship between i-PTH RIA levels and body composition and, particularly, with lean and fat mass, in a group of long-term hemodialysis patients. Moreover, relationship, if any, between cardiac function, degree of anemia and severity of hyperparathyroidism was assessed also separately in men and women.

Patients and Methods

70 patients, 34 male (age 62.09 ± 11.17) and 36 post-menopausal females (age 61.17 ± 12.82), on long-term maintenance dialysis (months 47.28 ± 7.37) were studied. i-PTH RIA, multifrequency BIA and kt/V were assessed at three months intervals. All patients were assessed at a monthly interval by ecg, and at six month's interval by echocardiography and abdominal echography. Additional cardiolological examinations were performed if clinically requested.

Patients were sex and age matched (45-69 years), without Heart failure (NYHA>2), severe anemia (Hb<8 g/dl), acute and/or chronic active liver disease, acute or chronic infectious disease and malignancy. Diabetes type 2 was present in 10/34 male patients, and in 12/36 female patients.

All patients were on four hours bycarbonate-dialysis, three times/week using Cellulose Acetate filters (filter surface area 1.19 ± 15 m^2), Heparin (4567 ± 1242 UI/dialysis session) and filter clearance (181 ± 43 ml/min) without differences between the two groups. Other clinical and laboratory data are summarized in Table I. K^+ concentration in dialysate was 2 mEq/l, while Na^+ ranged between 138 and 142 mEq/l. Serum calcium level between 8-10 mg /dl, phosphorus between 4.5-6.5 mg/dl were maintained in all patients by the use of calcium salts and phosphate binders taken during meals, and pulse doses of calcitriol p.o. 1-2 mg on alternate days. All patients were on r-HuEPO treatment since one year or more, with a quite satisfactory response. Basal serum aluminium level was not exceeding 30 mg/l in two consecutive controls, monitored with 4 months interval. All

Table I. Comparison of several measurements in 70 long-term dialysis patients divided by gender (Unpaired Student's *t* test).

	Men (n=34)	Women (n=36)	p
iPTH (pg/ml)	224.26 ± 161.62	345.88 ± 199.58	<0.01
BMI	27.09 ± 3.55	25.46 ± 6.10	ns
TBW%	50.85 ± 5.60	46.31 ± 5.19	<0.001
FAT%	30.95 ± 5.88	39.13 ± 10.42	<0.001
ALP (U/L)	211.83 ± 58.32	558.11 ± 253.19	<0.001
Ca (mg/dl)	9.60 ± 0.84	9.66 ± 0.76	ns
P (mg/dl)	6.22 ± 1	5.91 ± 1.30	ns
Weight (Kg)	74.87 ± 12.46	60.01 ± 12.71	<0.001
BUN (mg/dl)	71.54 ± 11.08	72.70 ± 8.29	ns
Serum Creatinine (mg/dl)	10.44 ± 1.50	8.27 ± 1.33	<0.001
Hct%	34.08 ± 6.83	31.53 ± 3.57	<0.001
kt/V	1.12 ± 0.35	1.21 ± 0.20	ns
Filter Clearance (ml/min)	167.94 ± 46.92	176.78 ± 61.83	ns
PCR (g/Kg/day)	0.94 ± 0.16	1.08 ± 0.28	<0.02
URR%	65.31 ± 8.82	70.79 ± 7.23	<0.01

patients received parenteral B_{12}, Folic Acid, l-Carnitine supplementation (7 g/week) and iron, adjusted to serum levels. Patients treated with vasodilators and/or β-antagonist drugs were excluded.

BIA study was performed with a tetra-polar multi-frequency set (Human-Im Scan®, Dietosystem, Milano, Italy) on patients sitting, thighs apart and arms abduced, according to the International Consensus Conference on body composition[13]. Disposable electrodes were placed on hand and foot contralateral to vascular access to minimize fluctuations related to graft flow and were left in place during dialysis to avoid errors due to different electrode placement[16].

Total body water (TBW), intracellular (ICW) and extracellular (ECW) water, fat mass (FM), fat-free mass (FFM), derived by Segal prediction formulas[17], body mass index (BMI), body cell mass (BCM), extracellular mass (ECM) were provided by a specific software (Dietosystem Human-Im Scan®, Master version). Kt/V and PCR were calculated according to NCDS[18].

Urea Reduction Ratio (URR), assessed as the percent reduction in the blood urea nitrogen concentration after dialysis[19], did not show any significant difference in the two groups. Echocardiographic examination was carried out with Toshiba Sonolayer a SSA-270A®, equipped with sectorial electronic probes; all measurements were taken according to the criteria of American Society of Echocardiography[20]. Systolic and diastolic left ventricular size and relative volumes, indexed for body surface area, were measured in M and B mode. Ejection fraction (EF), mean Circumferential FibersVelocity (mVCF), stroke volume (SV) and cardiac output (CO) were assessed as well.

Echocardiographic and BIA measurements were taken in three consecutive dialyses for each patient during the first 15 minutes and the last 15 minutes of each session. Echocardiograms were carried out by a single operator; the intra-observer variation in the assessment of linear measurements was < 3%, variability in the evaluation of ejection fraction was 3.1 ± 1.2%.

Data from heart rate and blood pressure monitoring, were recorded from 15' before beginning of dialysis till 30' after its end. Anthropometric findings and some clinical and laboratory data are shown in Table I.

Statistical analysis

Base and end-dialysis values, and differences (Δ) between beginning and end of dialysis, i-PTH and other measurements were compared in the two groups of patients by unpaired Student's *t* test. A best-fit regression analysis was performed between i-PTH vs body compartment measurements, vs weekly dose of r-HuEPO, vs echocardiographic measurements and vs haematocrit, considering all patients, and separately, men and women.

Results

i-PTH is significantly higher in women in comparison with men (Table I).

Body fat mass% was significantly higher in women: 39.13 ± 10.42 vs. 30.95 ± 5.88, $p<0.001$; BMI was not significantly different in the two groups of patients. A reciprocal lower water content, assessed as total body water, was observed in women (Table I).

Also ALP wase found significantly higher in women in comparison with men, while Ca^{++} and phosphorus were not significantly different (Table I).

In the total group of patients ($r=0.572$, $p<0.001$) and in women ($r=0.68$, $p<0.001$) positive correlations were found between i-PTH and FM% (Figure 1). No significant relationship was observed in men (Figure 2). Haematocrit was significantly lower in women without any correlation with i-PTH and FM.

PCR and URR were significantly higher in women (Table I).

The other measurements, were not significantly different between the two groups, with the particular exception of the increase of left ventricular ejection fraction (Table II). Decrease of blood pressure measurements, assessed at the beginning and at the end of dialysis sessions, were significantly greater in women in comparison with men (Table III).

Discussion

Hyperparathyroidism, assessed as i-PTH RIA, is observed at higher degree in post-

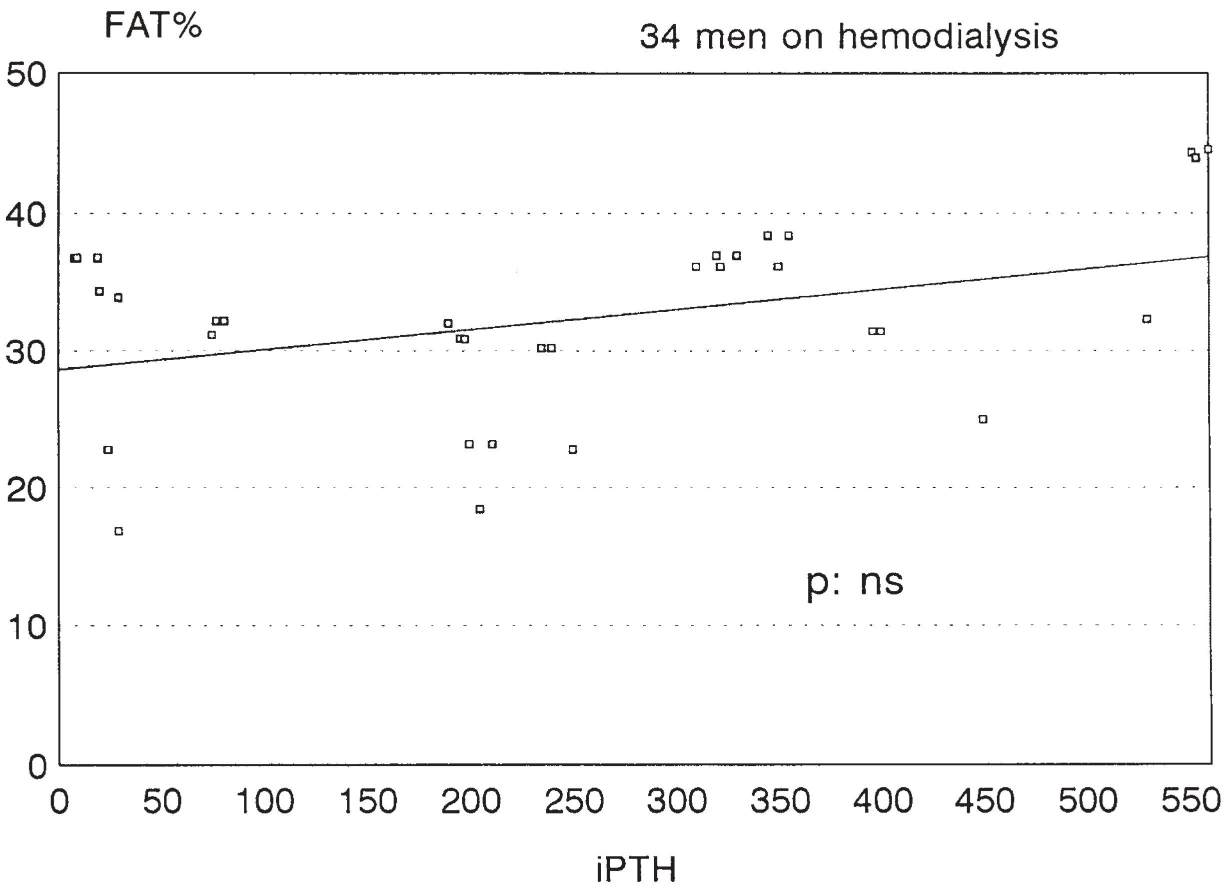

Figure 1. Regression line of fat body mass (FAT%) vs intact parathormone (I-PTH) in 36 women on long-term hemodialysis. A significant correlation was observed.

menopausal women in hemodialysis, in comparison with men, and is correlated with an increase of body fat content[14]. Obesity was reported as a feature of primary hyperparathyroidism[10], but, in our study, obesity, assessed only as BMI is not more represented among women in hemodialysis. It is not surprising that women have a higher FM in comparison with men, but the close relationship with the serum level of i-PTH in women (Figure 1) remains of difficult interpretation. It is unlikely that our finding is a chance event, given the highly significant differences between women and men respect to the higher levels of parathormone and of MS (Table I).

The close relationship between i-PTH and FM, present in the total group of patients, but, when assessed separately by gender, present only in women and not in men, suggests the intervention of a pathophysiologic mechanism. The lower TBW content, observed in women in comparison with men, seems due to the higher fat content. It can be supposed that both a lower bone mineral content and higher body fat determines lower TBW%[21]. In this setting the effect of higher levels of parathormone on bone can explain at least the skeletal component of FM. The homogenous features of treatment of these dialysis patients, also with calcitriol, make quite difficult to imagine a specific selection prejudice. A kind of insulin resistance occurs in persons with primary hyperthyroidism[22-25]. By this way it might promote increased FM, diverting carbohydrate to adipocytes. Moreover, adipocytes and osteoblasts share a common progenitor cell , and parathyroid hormone, which directly activates osteoblasts, might also influence adipocyte differentiation and function. The lower levels of hematocrit in women, in comparison with men, both treated with r-HuEPO, are also associated with higher i-PTH in women; however, also in general healthy population hematocrit and haemoglobin levels are significantly lower in

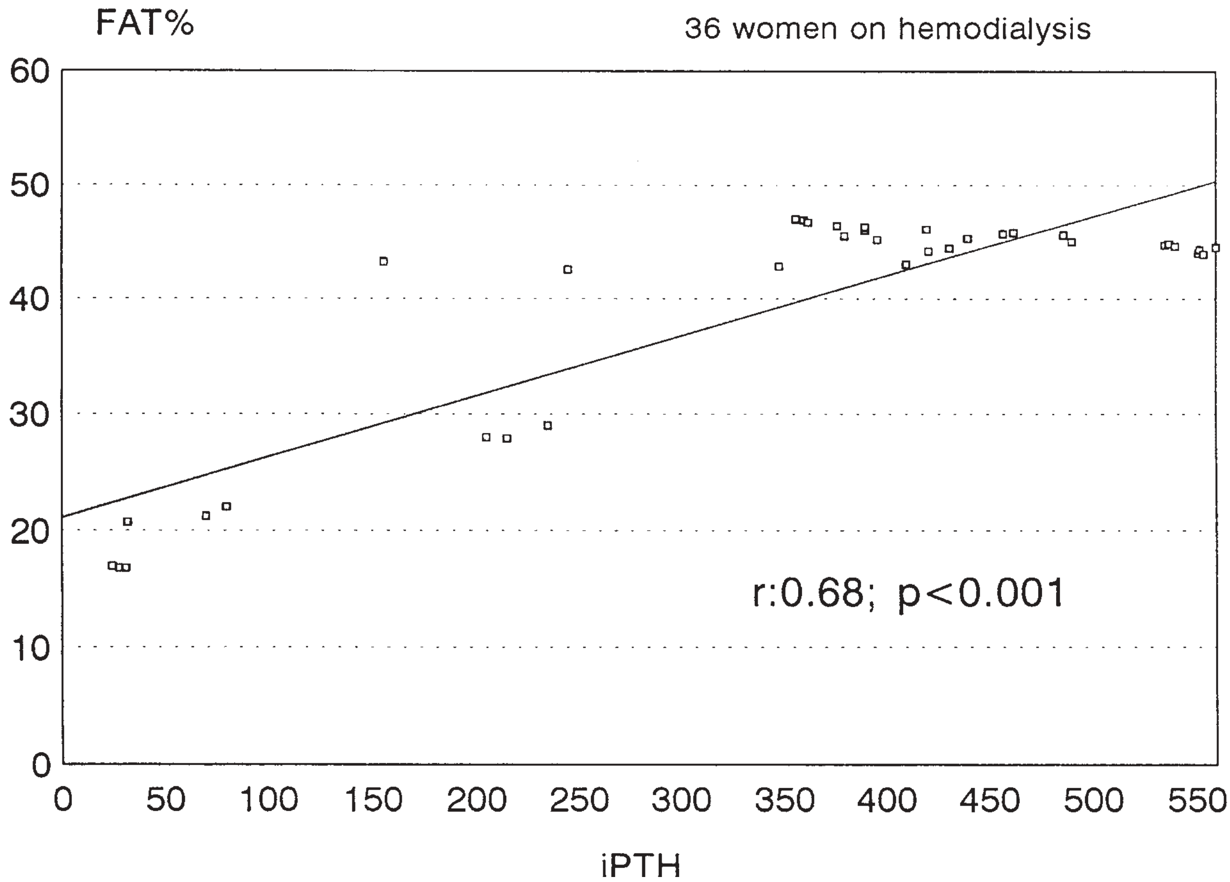

Figure 2. Regression line of fat body mass (FAT%) vs intact parathormone (I-PTH) in 34 men on long-term hemodialysis. No significant correlation was observed.

women. The higher PCR and URR in women can be due to a slight but significant higher protein intake and/or protein hypercatabolism, otherwise well balanced by dialysis, as showed also by the greater kt/V. The significant lower ejection fraction and mVCF, observed in wo-

Table II. Comparison of bood pressure, heart rate and echocardiographic measurements in 70 long-term dialysis patients divided by gender (Unpaired Student's *t* test).

	Men (n=34)	*Women (n=36)*	*p*
pre-dial syst BP (mmHg)	146.94 ± 24.56	157.22 ± 22.15	ns
pre-dial diast BP (mmHg)	78.33 ± 5.42	80 ± 15.81	ns
HR (b/min)	75.11 ± 6.94	77.33 ± 7.44	ns
LVEDD (cm/m²)	2.91 ± 0.39	3.30 ± 0.64	<0.003
LVESD (cm/m²)	1.94 ± 0.48	2.44 ± 0.56	<0.001
LVEDV (ml/m²)	76.13 ± 17.48	84.32 ± 26.71	ns
LVESV (ml/m²)	31.31 ± 17.20	42.69 ± 18.29	<0.001
SV (ml/m²)	44.82 ± 11.93	41.63 ± 14.64	ns
CO (l/m²)	3.35 ± 0.85	3.15 ± 0.92	ns
LA (cm/m²)	2.03 ± 0.45	2.45 ± 0.48	<0.001
EF%	60.22 ± 15.13	50.13 ± 12.84	<0.005
A/E	1.36 ± 0.25	1.50 ± 0.41	ns
mVCF	1.11 ± 0.37	0.87 ± 0.26	<0.002

Table III. Comparison of changes of bood pressure, heart rate and echocardiographic measurements in 70 long-term dialysis patients divided by gender (Unpaired Student's *t* test).

	Men (n=34)	Women (n=36)	p
Δ pre-dial syst BP	-7.17 ± 20.19	-35.56 ± 39.80	<0.001
Δ pre-dial diast BP	3.89 ± 9	- 5.56 ± 17.22	<0.005
ΔHR	-1.67 ± 6.59	3.78 ± 11.02	<0.01
ΔLVEDD	-8.79 ± 22.02	-17.61 ± 33.58	ns
ΔLVESV	-2.27 ± 17.70	-10.25 ± 21.39	ns
ΔSV	-6.59 ± 17.01	- 7.36 ± 13.87	ns
ΔCO	-0.49 ± 1.37	- 0.44 ± 1.06	ns
ΔLA	0.11 ± 0.68	- 0.5 ± 0.6	ns
ΔEF	-2.39 ± 17.51	5 ± 7.5	<0.02
Δkg	-3.28 ± 0.69	- 2.74 ± 0.94	<0.01
ΔA/E	-0.21 ± 0.11	- 0.19 ± 0.18	ns

men, indicate a kind of reduced systolic function. However, no close correlation was found between echocardiographic measurements and i-PTH. So it is not possible inferring a direct relationship between hyperparathyroidism and cardiac morphology and function. The more prominent decrease of blood pressure with hemodialysis in women, without difference in body weight changes, suggests a more pronounced circulatory instability during body water depletion with hemodialysis.

The increase of EF only in women can be temptatively explained. Women, in comparison with men, have lower pre-dialysis EF, very close to abnormal measurements, associated with higher i-PTH levels. So, women seem to get a significant advantage by the decrease of body water, that probably parallels a decrease of blood volume, with a resulting more efficent systolic function.

The increased cardiovascular mortality[26,27] in post-menopausal women with higher prevalence of obesity could have a kind of cross-relationship with the otherwise reported higher incidence of cardiac disease in dialysis patients with hyperparathyroidism[28,29]. It is possible that we are facing with two aspects of the same problem: hyperparathyroidism, affecting both FM content and muscle and myocardial metabolism and function, can worsen the cardiovascular prognosis of these patients. Reduced female sexual hormone production could exert a critical role both on parathyroid function and on body fat mass percentage and distribution. However, in our view, long-term effects of different nutritional behaviours, and specially of altered protein-caloric intake in women with kidney disease, can be operating. It was reported that in women with nutritional protein restriction a very significant increase of i-PTH can be induced[30].

In our patients the reduced FFM of women on maintenance dialysis could have some relationship with a more close long-term adherence to dietary protein restriction.

The widespread hypothesis that hyperparathyroidism in end-stage renal disease and dialysis patients could share liability of bone structural abnormalities, cardiac function impairment, excitable tissue disease, and anemia is still convincing. However, malnutrition, and its consequent relative decrease of lean mass, resulting from kidney disease and nutritional behavioral modifications, could be responsible in the multi-organ involvement of hyperparathyroidism in end-stage renal disease.

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