

Central Obesity and Hypertensive Renal Disease: Association between Higher Levels of BMI, Circulating Transforming Growth Factor β 1 and Urinary Albumin Excretion

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Objective: In this study, the relationship between circulating transforming growth factor β 1 (TGF β 1) and urinary albumin excretion (UAE) has been investigated in non-obese and central obese hypertensive patients. **Design and Patients:** Fifty-eight consecutive hypertensive outpatients both lean and with central obesity were enrolled and divided in three groups, according to their body mass index (BMI) values. Group A: 16 lean hypertensives (men with BMI <25 kg/m² and women with BMI <24.7 kg/m²); Group B: 16 overweight hypertensives (men with BMI \geq 25 kg/m² and <30 kg/m² and women with BMI \geq 24.7 kg/m² and <27.3 kg/m²); Group C: 26 obese hypertensives (men with BMI \geq 30 kg/m² and women with BMI \geq 27.3 kg/m²). **Measures:** In all patients, UAE, by immunonephelometric assay, circulating TGF β 1 by a solid-phase specific sandwich enzyme-linked immunosorbent assay (ELISA) technique, blood urea nitrogen (BUN) and creatinine, by routine laboratory methods, were determined. In addition, left ventricular telediastolic internal diameter (LVIDd), interventricular septum diastolic (IVSTd), posterior wall thickness (PWT), total and normalized to height^{2.7} left ventricular mass (LVM, LVM/h^{2.7}), relative wall thickness (RWT) and left ventricular ejection fraction (EF) by M-B Mode echocardiography were calculated. **Results:** Overweight and obese hypertensives had significantly ($p < 0.05$) higher BMI, waist-hip ratio (WHR), UAE and TGF β 1 than lean hypertensives. Obese hypertensives had significantly ($p < 0.05$) higher total and indexed LVM values than lean hypertensives. Obese hypertensives had significantly ($p < 0.05$) higher BMI, UAE and TGF β 1 than overweight hypertensives. In all subjects, TGF β 1 correlated directly with BMI ($r = 0.52$; $p < 0.0001$), WHR ($r = 0.48$; $p < 0.003$), MBP ($r = 0.31$; $p < 0.02$) and UAE ($r = 0.57$; $p < 0.0001$). Multiple regression analysis indicated that BMI, MBP and UAE were able to explain the 47.9% TGF β 1 variability ($r = 0.69$; $p < 0.0001$), and that TGF β 1 was the best predictor of UAE changes ($r = 0.60$; $p < 0.0001$). **Conclusion:** Our data suggest that TGF β 1 levels are positively associated with BMI, MBP and UAE in hypertensive subjects. This also indicates that TGF β 1 overproduction might be considered a pathophysiology mechanism of progressive renal function impairment in obese hypertensives. **Key words:** central obesity, hypertension, transforming growth factor β 1, urinary albumin excretion.

INTRODUCTION

Hypertension and obesity are disorders that are closely linked, especially when obesity is characterized by a central fat distribution. For many years, it has been well demonstrated that obese patients are more likely to be hypertensive than lean subjects and that weight gain is predictive of later onset of hypertension [1, 2]. The two most important causes of end-stage renal disease are diabetes mellitus and hypertension, both of which are closely associated with obesity [3]. Experimental data indicate that renal haemodynamic and structural change

that occur in obese dogs have some similarities to changes observed in early type II diabetes mellitus in human patients [4].

In addition, abnormalities in sodium control and in renal haemodynamics and function may be early detectable in normotensive and hypertensive obese subjects. They include a dysfunction in the renin-angiotensin system [5], a reduced renal plasma and blood flow and increased renal vascular resistance [6]. Moreover, microalbuminuria is more frequent in obese than in lean subjects and in central than in peripheral obese subjects [6].

It is well known that an impaired renal function may be often recognized in hypertensive patients. Additionally, a relationship between amount of urinary albumin excretion (UAE) and risk of progression in kidney disease has been reported in diabetic and hypertensive subjects [7]. In any case, the final pathway is represented by progressive sclerosis of glomeruli. Such a main role is played by transforming growth factor $\beta 1$ (TGF $\beta 1$), a multifunctional cytokine that regulates cell growth, differentiation, matrix production [8], blocks matrix degradation [9] induces fibrosis in many tissues, including kidney, blood vessels, lung and heart [10]. Data from experimental studies seem to indicate that high circulating levels of TGF $\beta 1$ can mediate renal fibrosis and loss of function [11]. In addition, overproduction of TGF $\beta 1$ has been found in salt-sensitive rats [12] and it has been involved in the long-term sequelae of hypertension, including LVH [13], vascular remodelling [14] and progressive renal disease [9, 15]. Although these results emphasize the role of TGF $\beta 1$ overproduction on hypertensive target organ disease [4, 10, 13–15], so far few data [16] are available on the relationship between TGF $\beta 1$, degree of obesity and UAE in hypertensive subjects. Accordingly, the present study has been designed to evaluate the relationship between body mass index (BMI), fat distribution, circulating TGF $\beta 1$ and one of the most important markers of early renal damage, such as UAE, in a population of hypertensive subjects. For these reasons circulating TGF $\beta 1$ and albumin excretion rate were examined in lean, overweight and obese hypertensive subjects. The principal aim of the study was to evaluate whether higher levels of circulating TGF $\beta 1$ were associated with UAE in obesity-induced hypertension.

PATIENTS AND METHODS

Patients

Fifty-eight consecutive outpatients were enrolled (27 males and 31 females, aged 43–70 years). The patients were attending antihypertensive centre of the Department of Internal Medicine at the University of Palermo, Italy. Subjects were included when blood pressure (average of three determinations) was greater than 140/90 mmHg on at least two occasions while the patients were off their medications [17]. Records of patients taking antihypertensive drugs were reviewed to ascertain the validity of the diagnosis of hypertension, and patients were included if blood pressure had been greater than 140/90 mmHg on two occasions, before treatment. Systolic (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) were taken. MAP was calculated from the equation $[DBP + 1/3 (SBP - DBP)]$.

Subjects were defined as overweight and obese based on their sex-specific 85th percentile of BMI value, as

reported in the Italian consensus conference of obesity [18].

Accordingly, the men with BMI ≥ 25 kg/m² and < 30 kg/m² and women with BMI ≥ 24.7 kg/m² and < 27.3 kg/m² were considered overweight subjects, whereas the men with BMI ≥ 30 kg/m² and women with BMI ≥ 27.3 kg/m² were considered obese. In addition, the men with BMI < 25 kg/m² and women with BMI < 24.7 were considered lean subjects. Central fat distribution was defined based on the sex-specific 85th percentile of waist-hip ratio (WHR). The cut-off value of central obesity was considered ≥ 0.81 for women and ≥ 0.92 for men [18].

Exclusion criteria included secondary hypertension, diabetes mellitus, cardiovascular diseases (defined as myocardial infarction, stroke within previous 6 months, heart failure), endocrinal diseases, renal failure, alcoholism and psychiatric problems. According to BMI values, all the hypertensive subjects were classified in the following groups:

Group A (lean hypertensives): 16 subjects (nine females and seven males; BMI 23 ± 1 kg/m²; WHR 0.8 ± 0.06 cm).

Group B (overweight hypertensives): 16 persons (six females and 10 males; BMI 28 ± 1 kg/m²; WHR 0.9 ± 0.05 cm).

Group C (obese hypertensives): 26 patients (16 females and 10 males; BMI 33 ± 5 kg/m²; WHR 0.92 ± 0.06 cm).

Methods

Each patient gave informed consent after receiving a detailed description of the study procedure. The study was approved by the Ethics Committee of our Institution. Patients underwent a general analytical laboratory parameters profile, including urine analysis, blood urea nitrogen (BUN), creatinine, glycaemia and electrolytes (serum sodium, potassium, chloride), by routine laboratory methods.

UAE

To eliminate the intra-individual day-to-day variability of UAE, three consecutive 24-h urine collections were used. In addition, to assess the completeness of a 24-h urine collection, clearance of creatinine was evaluated. UAE was measured by immunonephelometric assay (Boehring Institute; limit of detection, 0.1 mg/dl; inter-assay coefficient 3.5%). Microalbuminuria was defined as a level of UAE ≥ 30 and < 300 mg/24 h.

TGF $\beta 1$

Peripheral venous blood was obtained from each patient and the sera were isolated and stored at -70°C . TGF $\beta 1$ levels were determined by using a solid-phase specific

Table I. Clinical characteristics, renal function, urinary albumin excretion and TGFβ1 values in lean (Group A), overweight (Group B) and obese (Group C) hypertensive patients

	Group A: Lean, no. 16	Group B: Overweight, no. 16	Group C: Obese, no. 26
Sex (F/M)	9/7	6/10	16/10
Age (years)	46 ± 9	51 ± 3	53 ± 7
BMI (kg/m ²)	23 ± 1	28 ± 1 ^a	33 ± 5 ^a
WHR (cm)	0.8 ± 0.06	0.9 ± 0.05	0.92 ± 0.06
SBP (mmHg)	161 ± 16	159 ± 10	168 ± 15
DBP (mmHg)	98 ± 18	91 ± 11	101 ± 15
MBP (mmHg)	119 ± 16	113 ± 10	123 ± 13
UAE (mg/24 h)	150 ± 20	248 ± 21 ^a	450 ± 26 ^{ab}
BUN (mg/dl)	35 ± 6	37 ± 12	39 ± 10
Creatinine (mg/dl)	0.9 ± 0.2	1 ± 0.2	1 ± 0.2
TGFβ1 (ng/ml)	2.8 ± 2.1	5 ± 3.2 ^a	7.3 ± 4 ^{ab}
Minimum	0.87	2.4	3.3
Maximum	7	14.3	19.3
Median	2.1	3.8	5.5

^a*p* < 0.05 vs A; ^b*p* < 0.05 vs B.

Differences of TGFβ1 among the groups were analysed by Mann–Whitney *U* test.

TGFβ1, transforming growth factor (1; BMI: body mass index; WHR, waist–hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BUN, blood urea nitrogen; UAE, urinary albumin excretion.

sandwich (R&D Systems, Inc. Minneapolis, Minnesota) enzyme-linked immunosorbent assay (ELISA) technique [19]. The interassay and intra-assay variations for determining TGFβ1 were 8% and 6%, respectively. The sensitivity, and hence minimum level of detection of TGFβ1 by sandwich ELISA, was 5 pg/ml.

Echocardiography parameters

All patients underwent an echocardiography examination M and B Mode, by a computerized echocardiography (ESAOTE, Italy) for the determination of following parameters: left ventricular telediastolic internal diameter (LVIDd), interventricular septum diastolic (IVSTd), posterior wall thickness (PWTd), total left ventricular mass (LVM) normalized to height^{2.7} (LVM/h^{2.7}) [20–24].

The relative wall thickness (RWT) by formula [(PWTd/LVIDd)×2] was also calculated. Ejection fraction (EF) from left ventricular end-diastolic and end-systolic volumes was measured from the apical four-chamber view, using the ellipsoidal single-plane algorithm [25]. Mean EF was automatically calculated by the echocardiographic processing system. In our laboratory, the EF calculated over five consecutive beats permitted optimal reproducibility and accuracy also in obese subjects [25]. The presence of left ventricular hypertrophy (LVH) was established when LVM/h^{2.7} was >51 g/m^{2.7} for men and females [20, 26].

Statistical analysis

Differences among three groups were analysed by one-

Table II. Left ventricular geometry and function in lean (Group A), overweight (Group B) and obese (Group C)

	Group A	Group B	Group C
LVIDd (mm)	4.7 ± 0.3	4.7 ± 0.3	4.8 ± 0.3
IVSTd (mm)	10.5 ± 1	10.6 ± 1	11.2 ± 2
PWTd (mm)	9 ± 1	9.9 ± 1	10.3 ± 2
RWT [(PWTd/LVIDd)×2]	0.37 ± 0.05	0.42 ± 0.07	0.44 ± 0.07
LVM (g)	158 ± 21	174 ± 31	188 ± 48 ^a
LVM/h ^{2.7} (g/m ^{2.7})	41 ± 7	45 ± 10	55 ± 17 ^a
LVEF (%)	62 ± 5	64 ± 6	63 ± 5
%LVH	5/16 (31%)	6/16 (37%)	14/26 (54%) ^b

^a*p* < 0.05 vs A.

^bChi square test.

LVIDd, left ventricular internal diastolic diameter; IVSTd, interventricular septum thickness diastolic; PWTd, posterior wall thickness; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVM/h^{2.7}, left ventricular mass normalized to height^{2.7}; %LVH, percentage of subjects with left ventricular hypertrophy.

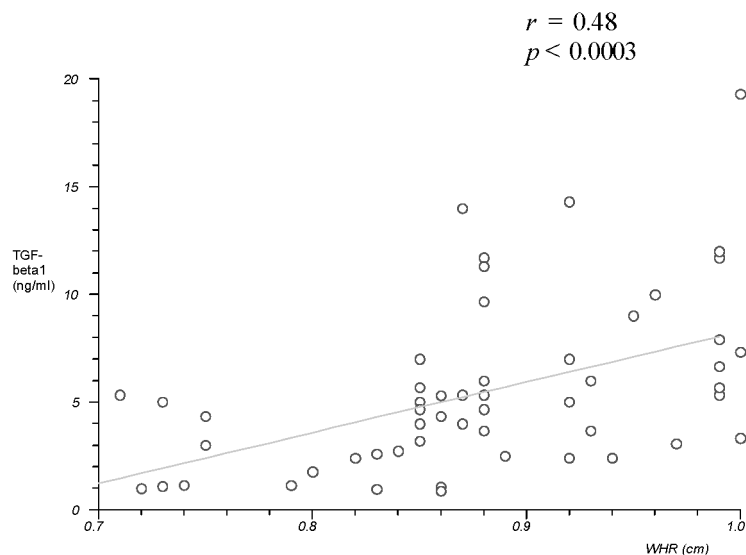
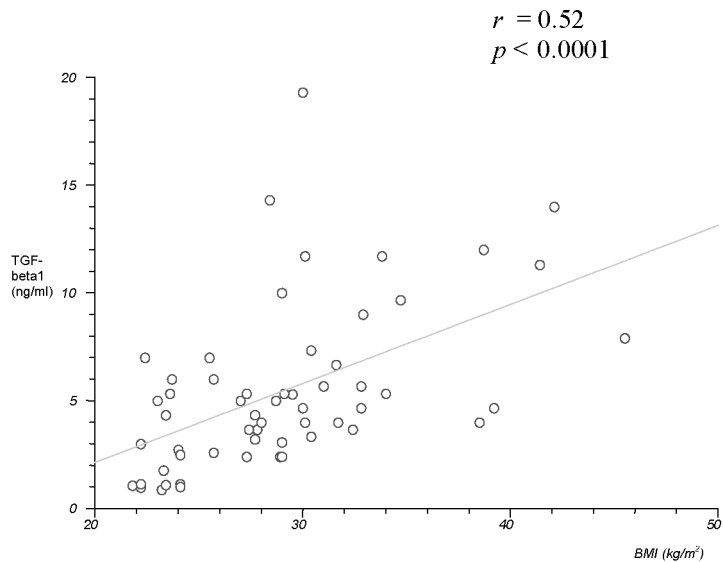


Fig. 1. Relationship between transforming growth factor β_1 , body mass index (BMI) and waist-hip ratio (WHR) in all the subjects studied.

way analysis of variance and the post-hoc Newman-Keuls test. Since an asymmetry of TGF β_1 data distribution was evident (high skewness), the difference in TGF β_1 values among the groups were analysed by a non-parametric test, i.e. Kruskal-Wallis test and by the Conover-Inman procedure post-hoc test. Differences among hypertrophic patients' prevalence of three groups were analysed by chi-square test. Relationship among TGF β_1 and the other parameters were analysed by univariate and multiple regression analysis. Data are expressed as mean value \pm standard deviation (SD). A $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of study groups are reported in Tables I and II. There were no significant differences among the groups in age and blood pressure values (Table I).

Overweight and obese vs lean hypertensives

Overweight and obese hypertensive patients had significantly ($p < 0.05$) higher BMI, WHR, UAE and TGF β_1 than did lean hypertensives. BUN and creatinine levels were not significantly different among the groups studied (Table I).

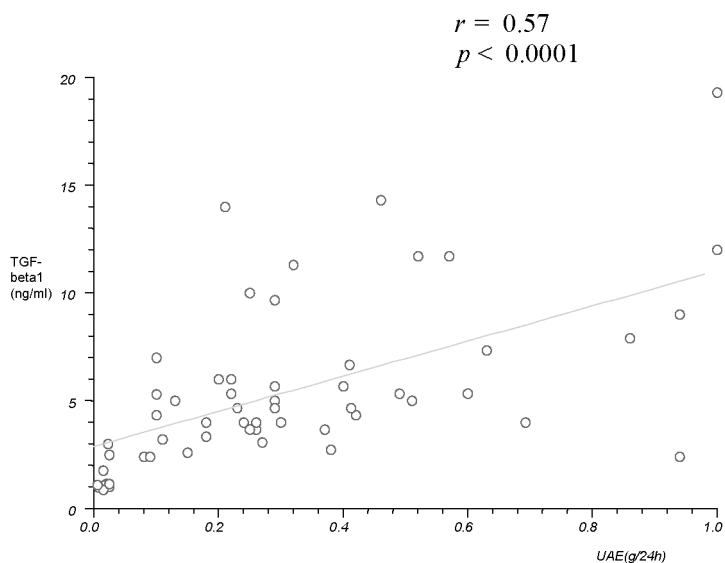
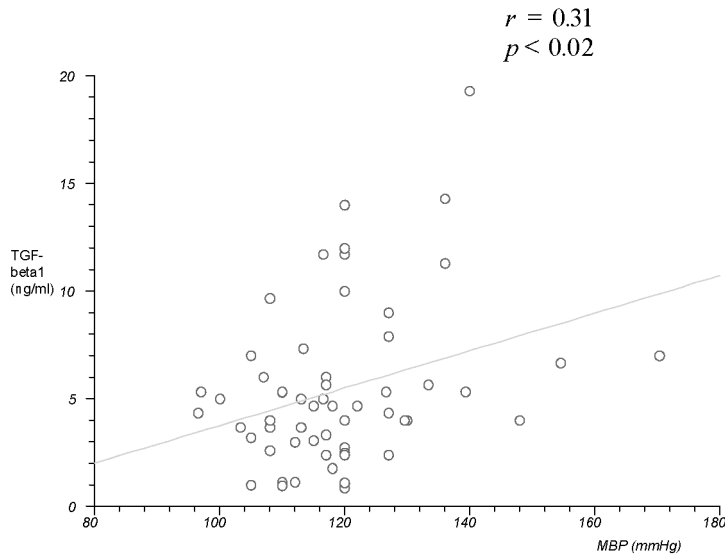


Fig. 2. Relationship between transforming growth factor β1, mean blood pressure (MBP) and urinary albumin excretion (UAE) in all the subjects studied.

In addition, obese hypertensive patients had significantly ($p < 0.05$) higher total and indexed LVM values than those detectable in lean hypertensives. An evident, but not significant, higher prevalence of LVH has been found only in obese than lean hypertensives (54% vs 31%; Table II).

Obese vs overweight hypertensives

Obese hypertensives had significantly ($p < 0.05$) higher

BMI, UAE and TGFβ1 than did overweight hypertensives. No significant change in the remaining measurements was found between the two groups (Tables I and II).

Correlations

In the univariate analysis, there was a positive correlation between plasma TGFβ1 concentration and UAE ($r = 0.57$;

$p < 0.0001$), BMI ($r = 0.52$; $p < 0.0001$), WHR ($r = 0.48$; $p < 0.003$) and MBP ($r = 0.31$; $p < 0.02$) (Figs 1 and 2).

No correlation between TGF β 1 and total and indexed LVM was found. Multiple regression analysis was used to investigate relationships between TGF β 1, UAE and the other variables. Firstly, for selection of variables, we analysed the correlation matrix and then TGF β 1, UAE, BMI, WHR, LVM/h^{2.7}, MBP, age and gender were entered into the model. The best subset selection by examination of all possible regressions was used computing the minimum Mallow's Cp statistics. We also controlled for collinearity and this confirmed the selection of the variables. Finally, TGF β 1, UAE, BMI and MBP were the best variables to fit the model. A regression equation and the multiple correlation coefficients were computed. We both controlled for autocorrelation using the Dubin–Watson test statistic and examined the scatter plot of the residuals against fitted TGF β 1 and UAE values to investigate distributions of data for deviation from normality. This analysis indicated that BMI, MBP and UAE were able to explain the 47.9% of TGF β 1 variability ($r = 0.69$; $p < 0.0001$; Table IIIA) and that TGF β 1 was the best predictor of UAE changes explain the 36.5% of UAE variability ($r = 0.60$; $p < 0.0001$; Table IIIB).

DISCUSSION AND CONCLUSION

The main finding of the current study was the association among TGF β 1, UAE and BMI in hypertensive patients. We found higher TGF β 1 circulating levels in hypertensive patients with increased BMI as compared with TGF β 1 levels in hypertensive patients with normal BMI. Our findings may indicate that an excess of circulating levels of TGF β 1 is associated with albumin excretion rate in central obese hypertensives patients, adding clinical support to the notion that it plays a role in the pathophysiology of hypertensive renal disease. This fact is also supported by a direct relationship between TGF β 1 levels and one of the most important measurements of progressive renal damage such as albumin excretion rate. In our opinion, it is possible to hypothesize that TGF β 1 overproduction may be considered a pathogenetic mechanism for the excess burden of hypertension and hypertensive renal damage in central obese subjects. In this context, overproduction of TGF β 1 has been experimentally linked to the sequelae of chronic hypertension, including vascular remodelling and progressive renal disease [27, 28].

In the present study, TGF β 1 circulating levels were associated not only with UAE but also with BMI and WHR, and this strong association was still present after stepwise multivariate analysis. In addition, our data seem to indicate that TGF β 1 may be considered the most important factor to explain higher UAE levels in central

Table III. Multiple regression analysis

(A)			
Intercept	$b_0 = -14.507853$	$t = -2.673679$	$p = 0.01$
MBP	$b_1 = 0.049135$	$t = 1.720436$	$p = 0.09$
WHR	$b_2 = 7.859432$	$t = 1.339088$	$p = 0.18$
BMI	$b_3 = 0.192599$	$t = 2.316731$	$p = 0.02$
UAE	$b_4 = 5.063598$	$t = 3.123374$	$p = 0.002$

$$\text{TGF}\beta 1 = -14.507853 + 0.049135 \text{ MBP} + 7.859432 \text{ WHR} + 0.192599 \text{ BMI} + 5.063598 \text{ UAE}.$$

Analysis of variance from regression: $F = 12.194276$; $p < 0.0001$.

Multiple correlation coefficient: $R = 0.69$; $R^2 = 47.9\%$; $Ra^2 = 44\%$.

(B)			
Intercept	$b_0 = -0.574068$	$t = -1.295463$	$p = 0.20$
WHR	$b_1 = 0.55713$	$t = 1.215573$	$p = 0.22$
BMI	$b_2 = 0.004673$	$t = 0.691017$	$p = 0.49$
TGF β 1	$b_3 = 0.0307$	$t = 3.123374$	$p = 0.003$
MBP	$b_4 = 0.000796$	$t = 0.348741$	$p = 0.72$

$$\text{UAE} = -0.574068 + 0.55713 \text{ WHR} + 0.004673 \text{ BMI} + 0.0307 \text{ TGF}\beta 1 + 0.000796 \text{ MBP}.$$

Analysis of variance from regression: $F = 7.620798$; $p < 0.0001$.

Multiple correlation coefficient: $R = 0.60$; $R^2 = 36.5\%$; $Ra^2 = 31.7\%$.

MBP, mean blood pressure; WHR, waist–hip ratio; BMI, body mass index; UAE, urinary albumin excretion; TGF β 1, transforming growth factor β 1.

obese hypertensive subjects. In our opinion, this represents an interesting finding with relevant clinical implications, considering the potential role of TGF β 1, hypertension, central obesity and UAE rate on cardiovascular and tissue organ damage. The exact mechanism by which TGF β 1 is enhanced in obese associated hypertension is not clear, but in this context, it has been hypothesized that many factors may contribute to TGF β 1 overproduction. They include a genetic TGF β 1 DNA polymorphism [29], angiotensin II activity [30] and shear stress [31]. Our data extend these studies by demonstrating an increase of circulating TGF β 1 in hypertensive, overweight and obese patients, and suggest a possible relationship between adipose tissue and TGF β 1 *in vivo* expression. In fact, in our model of multiple regression analysis, BMI, MBP and UAE globally explain the 48% of TGF β 1 variability and TGF β 1 remained independently associated with these variables. In our opinion, this strong association might increase our knowledge of the factors implicated in the pathophysiology of hypertensive renal disease in central obese subjects. The progressive increase of circulating TGF β 1 levels and UAE in lean, overweight and obese hypertensive subjects might also suggest an important role of the degree of obesity for the production

of TGF β 1 and for the development of hypertensive renal disease by a TGF β 1-dependent pathway. This was supported by our model of multiple regression analysis indicating that higher UAE found in obese than lean hypertensives is largely explained by elevated TGF β 1 values. This hypothesis is in agreement with previous experimental data indicating an elevated expression of TGF β 1 in the adipose tissue from obese mice [32] and a direct relationship between BMI and TGF β 1 in human adipose tissue [33]. Furthermore, recent data from Porreca *et al.* [16] suggest that TGF β 1 levels are independently associated with increased BMI and leptin levels in hypertensive patients. The marked reduction of TGF β 1 levels after weight loss induced these authors to attribute a pivotal role of obesity on TGF β 1 *in vivo* expression.

The biological actions of TGF β 1 and association with renal pathology might induce us to speculate that increased frequency of TGF β 1 overproduction is a candidate mechanism for progression of hypertensive renal disease to end-stage renal function impairment [27].

On the contrary, even if total and normalized LVM values were significantly higher in obese than lean hypertensives, no relationship between TGF β 1 and LVM was found. In addition, a mild but not significant, higher prevalence of left ventricular hypertrophy was observed in obese than in lean hypertensives. This might indicate a selective role of TGF β 1 in the pathophysiology of hypertensive target organ damage [4].

In conclusion, our data are consistent with the hypothesis that circulating TGF β 1 overproduction might be considered an important pathophysiological factor of hypertensive renal disease above all in central obese subjects. In view of this, hypertensive subjects with higher BMI values, central fat distribution and higher levels of TGF β 1 may be considered a particular subset of patients at higher risk of progressive impairment of renal function. Further longitudinal studies are necessary to confirm the role of these links on obesity-related renal consequence of hypertension.

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