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ORIGINAL ARTICLE

Effects of weight loss on renal function in overweight Japanese men

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Obesity is known as an independent risk factor for renal injury. Sympathetic nerve activation may have an important role of the pathogenesis of obesity, and hypertension may underpin the development of cardiovascular events. In the present study, we evaluated the effects of weight loss (WL) on renal function, especially focusing on sympathetic nervous activity. In 154 overweight or obese Japanese men (89 normotensive and 65 untreated mild hypertensive subjects), body weight, body mass index (BMI), total body fat mass, blood pressure (BP), serum creatinine, blood urea nitrogen, creatinine clearance (CCr) (calculated with the Cockcroft–Gault equation) and plasma norepinephrine (NE) were measured before and after a 12-month period of WL with a mild caloric-restricted diet and exercise. A significant WL was defined as 10% or more WL compared with the entry period. In total, 97 (63.0%) subjects succeeded in significant (by 14.3%) WL at 12 months, and 57 subjects (37.0%) did not succeed in significant WL but they lost 7.7% weight. At entry, levels of plasma NE, serum creatinine and fat mass were significantly lower and CCr was greater in the group with a significant WL compared with those without WL. BMI, total body fat mass and plasma NE significantly decreased, and CCr increased with WL. At both baseline and at the 12-month period, fat mass and plasma NE negatively correlated with CCr and positively correlated with creatinine at each time point. Changes in fat mass and plasma NE over 12 months correlated with changes in creatinine, and only changes in fat mass negatively correlated with changes in CCr. Basal fat mass and plasma NE correlated positively with serum creatinine at 12 months and negatively with CCr at the same time point. In multiple regression analyses, basal plasma NE and fat mass were significant determinants of serum creatinine levels and CCr at 12 months. In conclusion, WL improved renal function (as evident from measures of creatinine and CCr) in overweight individuals. Basal plasma NE levels and total body fat mass could be predictors for improvement in renal function associated with WL. Suppression of sympathetic nervous activation associated with WL may have a role in the ameliorative effects on renal function.

INTRODUCTION

Obesity is a major and growing health problem.[1,2] The presence of increased adiposity is associated with elevated risk of development of cardiovascular and renal complications.[2–4] Evidence from several studies indicates that obesity and weight gain are associated with an increased risk of hypertension and diabetes.[1,2,5,6] Furthermore, several large cohort studies have demonstrated close associations between obesity, especially abdominal obesity and the onset of chronic kidney disease (CKD)[7–11] and faster CKD progression.[10] Intentional weight loss (WL) reduced the risk of the onset and development of hypertension,[12,13] diabetes[14] and renal injury[15] in overweight or obese individuals.

The sympathetic nervous system has an important role in the regulation of energy expenditure, and reduced energy expenditure and resting metabolic rate are predictive of weight gain (obesity). In many clinical and epidemiological studies, elevated sympathetic nervous activity has been documented in obesity[16] or weight gain[17–19] and in patients with end-stage renal disease.[7,20–22] Zoccali *et al.*[20,22] reported that the degree of sympathetic nervous activation might relate to the occurrence of fatal cardiovascular events. We also observed previously that[23] higher plasma NE levels could predict future renal injury in non-obese, normotensive individuals. Thus, one could speculate that sympathetic nervous activation might be the trigger linking obesity to impairment in renal function.

Weight loss is recommended as the first-line treatment for obesity. Many large studies[24–26] have shown marked clinical benefits of lifestyle intervention, and modest WL, on the resolution of obesity-relate diseases including CKD as well as long-term benefits on all-cause mortality. In obese subjects, obesity-related glomerular hyperfiltration,[27] elevated sympathetic nervous activity,[12,13,28–30] insulin resistance and stimulation of the renin–angiotensin–aldosterone system (RAS)[30,31] are ameliorated after WL.

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Many epidemiological and clinical studies have shown the presence of microalbuminuria[32,33] or proteinuria[15] as a marker of cardiovascular risks, however, Farbom *et al.*[34] reported that microalbuminuria and renal function (creatinine, blood urea nitrogen and creatinine clearance (CCr)) are independently associated with future cardiovascular events. The decrease in CCr (glomerular filtration rate, GFR) was a precursor for the future cardiovascular events.[34] However, only few investigators have simultaneously taken into account the sympathetic nervous activity and renal function in the same study population, followed longitudinally to evaluate the relationships of sympathetic nervous activity with renal function during WL with life-style modifications.[30,35]

In the present study, using plasma NE levels as a marker of sympathetic activity we evaluated the role of the sympathetic nervous system on renal function (measured serum creatinine and CCr) during WL over a 12-month period with mild caloric restriction and exercise (life-style modification).

METHODS
Subjects
The WL program enrolled 154 overweight ($25 \, \text{kg m}^{-2} \leq$ body mass index (BMI) $< 30 \, \text{kg m}^{-2}$) men, consisting of 89 overweight normotensive (blood pressure (BP) $< 140/90 \, \text{mm Hg}$) and 65 overweight, untreated mildly hypertensive men ($140/90 \, \text{mm Hg} \leq \text{BP} < 160/95 \, \text{mm Hg}$) with normal renal function (serum creatinine levels $< 1.5 \, \text{mg dl}^{-1}$, CCr $> 80 \, \text{ml per min}$, negative proteinuria or negative albuminuria by dipstick test). None of the subjects had diabetes (fasting blood glucose level $< 100 \, \text{mg dl}^{-1}$ and hemoglobin A1c $< 6.0\%$) or other illnesses, including psychological or emotional problems[36] or obstructive sleep apnea.[37] No subjects were taking antihypertensive agents or other medications. Only subjects whose body weight had not changed for at least the previous 1 year (weight change $< 5\%$ provided in their biannual medical evaluation records) were enrolled in the present study.[17,29] The protocol was approved by the ethics committee of Osaka University Graduate School of Medicine, Japan, and written informed consent was obtained from all the subjects.

Study design
The WL program consisted of a mild caloric restricted diet (1800 kcal per day, 55% of calorie from carbohydrate, 30% from protein and 15% from fat), low sodium diet (7 g NaCl per day) and aerobic exercise of more than 1 h daily (e.g., walking, jogging or gym exercise). The subjects attended a 1-h private counseling session each week for 4 weeks followed by biweekly 1 h sessions for an additional 11 months. All session were led by experts in nutrition and exercise counseling. Calorie intake was calculated based on the subjects' meal diary, which was assessed by trained nutritionists. The physical activity was quantified and recorded by the use of pedometers on a daily basis. Diet and exercise compliance were measured according to the subjects' own records every 2 weeks.

Measurements
Data including height, body weight, BMI, percentage total body fat mass, waist circumference, hip circumference and urinalysis were determined in the morning after an overnight fast of 12 h. After 30 min rest in the supine position, BP, heart rate and venous blood sampling for measurements of blood urea nitrogen, creatinine, glucose, plasma norepinephrine (NE) were obtained. Samples were taken at baseline and at 12 months during the study. BP and heart rate were measured more than three times in the supine position by an automated sphygmomanometer (TM-2713, A&D, Tokyo, Japan) using an adjusted cuff size, based on arm circumference. Recorded BP levels and heart rates were averaged. The percentage body fat mass was determined by impedance measurements (BF-102, Tanita, Tokyo, Japan). Total body fat mass (kg) was calculated according to the following formula: (percentage body fat mass (%)/100) × body weight (kg). Plasma NE was measured by the methods previously reported.[29] Creatinine clearance was calculated by the Cockcroft–Gault equation as an estimated GFR: (140–age) × (weight in kg)/72 × (creatinine in mg dl^{-1}).[38]

Statistical analyses
Values are shown as mean ± s.d. All data analyses were performed with SPSS 8.0 for Windows program (SPSS Inc., Chicago, IL, USA). Changes in measured parameters within each group and differences among groups were examined by two-way analysis of variance. When these differences were significant, *post hoc* analysis was performed using Dunnett's test. Prevalence of hypertension was estimated using the χ^2-test. Associations between selected variables were analyzed with Pearson product-moment correlations. Multiple linear regression analyses were used to examine relations among variables using serum creatinine levels or CCr at the 12-month period as independent variables *vs.* changes in BMI, total body fat mass, waist circumference, waist-to-hip ratio, BP changes and hormonal measurements as dependent variables.

RESULTS
Prevalence of significant weight loss at 6 and 12 months
When significant WL was defined as a 10% or more reduction in BMI from baseline, 97 subjects (63.0%) succeeded in achieving significant WL, with the WL being 14.3%. Fifty-seven subjects (37.0%) did not succeed in significant WL at 12 months, but all of them lost weight by 7.7%, and all subjects lost weight more than 5%. The group with significant WL included 60 normotensive and 37 hypertensive subjects at the baseline period, and 85 normotensive and 12 hypertensive subjects at 12 months. The group that did not lose weight significantly at 12 months included 29 normotensive and 28 hypertensive subjects at the baseline period and 39 normotensive and 18 hypertensive subjects at 12 months. There was no statistical significance in the prevalence of hypertension between the groups with and without significant WL at the baseline period ($\chi^2 = 1.774$, not significant); however at 12 months, after WL, the group who succeeded in significant WL contained higher frequency of normotensive subjects ($\chi^2 = 8.445$, $P < 0.01$) (Table 1).

Calorie intake and physical activity
Diet compliance (calorie intake), physical activity (steps per day), behavior (alcohol intake, cigarette smoking) and socioeconomic status were similar between the two study groups throughout the study (Table 1). Diet and exercise compliance were assessed from the subjects' own records every 2 weeks, which were recorded at private counseling sessions. Compliance to diet and exercise was considered excellent and consistent, based on those records over the 12-month period. There were no significant differences in these confounders between the groups with and without significant WL at 12 months.

Characteristics of subjects with significant weight loss
Subjects who succeeded in significant WL ($\geq 10\%$) compared with baseline BMI had significantly lower total body fat mass amounts, lower levels of plasma NE and serum creatinine and greater CCr at the baseline period compared with those without significant WL, although BMI, lean body mass, waist-to-hip ratio, BP levels and blood urea nitrogen at the baseline period were similar (Table 1). Importantly, calorie intake and physical activity, as assessed using pedometers were similar between the two groups at both baseline and at 12 months. All parameters, except CCr, significantly decreased at 12 months compared with those at the baseline period in both groups, and CCr increased significantly even in the group without significant WL. Even in subjects who did not succeed in significant WL, those parameters changed significantly from the baseline values, although absolute and percent changes in these parameters in the group without significant WL were smaller than those with significant WL (Table 1).

Table 1 Characteristics of subjects with and without significant weight loss at 12 months

	Subjects with significant weight loss (⩾10%)		Subjects without significant weight loss (<10%)	
Time point	Baseline	12 months	Baseline	12 months
Subjects (n)	97	97	57	57
Normotensives vs. hypertensives	NT=60, HT=37	NT=85, HT=12	NT=29, HT=28	NT=39, HT=18
BMI (kg m^{-2})	27.3 ± 1.4	23.4 ± 1.9## (85.7 ± 2.2%)	27.2 ± 1.3	25.1 ± 1.8*,# (92.3 ± 1.9%)
Total body fat mass (kg)	23.9 ± 5.0	18.9 ± 4.1## (79.1 ± 7.8%)	26.9 ± 5.1*	22.2 ± 3.7**,# (82.5 ± 6.1%)
Body weight (kg)	87.5 ± 4.7	74.9 ± 5.5# (85.6 ± 2.2%)	88.1 ± 4.3	81.3 ± 5.6# (92.3 ± 2.3%)
Lean body mass (kg)	63.6 ± 5.4	56.2 ± 6.9# (88.3 ± 7.8%)	61.2 ± 5.7	59.1 ± 4.9 (96.6 ± 8.0%)
Waist-to-hip ratio	1.01 ± 0.13	0.82 ± 0.14** (81.2 ± 10.7%)	1.05 ± 0.15	0.92 ± 0.13*,# (87.6 ± 11.7%)
Systolic BP (mm Hg)	134 ± 10	126 ± 7# (94.0 ± 3.7%)	138 ± 10	133 ± 6*,# (96.3 ± 2.1%)
Diastolic BP (mm Hg)	78 ± 9	72 ± 7# (92.3 ± 4.5%)	77 ± 9	74 ± 6 (96.1 ± 2.3%)
Heart rate (beats per min)	68 ± 7	64 ± 7 (94.1 ± 2.7%)	71 ± 7	69 ± 7* (97.1 ± 3.5%)
Plasma NE (pmol ml^{-1})	2.09 ± 0.45	1.49 ± 0.46## (71.3 ± 10.5%)	2.45 ± 0.44*	2.07 ± 0.41*,# (84.5 ± 7.5%)
BUN (mg ml^{-1})	16.9 ± 2.4	15.8 ± 2.8 (93.5 ± 7.9%)	17.4 ± 2.7	16.2 ± 2.9 (93.1 ± 8.3%)
Creatinine (mg ml^{-1})	0.91 ± 0.13	0.84 ± 0.08 (92.3 ± 7.7%)	1.15 ± 0.12*,#	1.01 ± 0.09*,# (87.8 ± 7.1%)
Creatinine clearance (ml min^{-1})	108.3 ± 7.8	121.3 ± 9.5## (112.0 ± 8.3%)	98.6 ± 8.2*	104.0 ± 10.1**,# (105.4 ± 10.4%)
Calorie intake (×1000 kcal per day)	2.45 ± 0.62	1.72 ± 0.28## (70.2 ± 10.4%)	2.41 ± 0.52	1.79 ± 0.19## (74.3 ± 8.6%)
Physical activity (×1000 steps per day)	9.9 ± 4.7	21.9 ± 4.1## (212.2 ± 22.4%)	10.1 ± 3.5	19.9 ± 3.5## (197.2 ± 17.6%)

Abbreviations: BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; HOMA–IR, homeostasis model of insulin resistance; HT, hypertensive subjects; NE, norepinephrine; NT, normotensive subjects; WL, weight loss.
(%) Percent in parenthesis shows percent changes compared with the values at the baseline period in each group.
*$P<0.05$, **$P<0.01$ vs. values in subjects with significant weight loss; #$P<0.01$, ##$P<0.01$ vs. values at entry period.

Correlations between total body fat mass, plasma NE, serum creatinine and creatinine clearance

At both periods, total body fat mass and plasma NE levels significantly were positively correlated with serum creatinine levels (Figure 1), and negatively with CCr (Figure 2). Changes in total body fat mass correlated positively with changes in serum creatinine levels over 12 months and negatively with changes in CCr over 12 months (Figure 3). Creatinine clearance did not improve in several subjects, although serum creatinine decreased in all subjects. Furthermore, decreases in plasma NE over 12 months with WL correlated with decreases in serum creatinine levels, but there was no correlation between changes in plasma NE and changes in CCr (Figure 3). Basal (i.e., on admission to the study) total body fat mass and basal plasma NE correlated with serum creatinine levels at 12 months ($R=0.4503$, $P<0.05$; $R=0.4467$, $P<0.05$; respectively), and negatively with CCr at 12 months ($R=-0.3386$, $P<0.05$; $R=-0.3399$, $P<0.05$; respectively) (Figure 4).

Multiple regression analyses

In multiple linear regression analyses, using serum creatinine level at a 12-month period as an independent variable, basal total body fat-mass ($R^2=0.3158$, $P<0.05$), basal plasma NE ($R^2=0.2944$, $P<0.05$) and basal serum creatinine ($R^2=0.3542$, $P<0.05$) were significant determinant variables. When CCr at 12 months was used as an independent variable, basal total body fat mass ($R^2=0.3675$, $P<0.05$), basal plasma NE levels ($R^2=0.3327$, $P<0.05$), basal CCr ($R^2=0.4579$, $P<0.05$), changes in total body fat mass ($R^2=0.4123$, $P<0.05$) and changes in plasma NE levels ($R^2=0.3656$, $P<0.05$) were significant predictive variables.

DISCUSSION

The main findings in the present report were that: (1) subjects who succeed with significant WL (⩾10%) over a 12-month period have initial lower total body fat mass, plasma NE and serum creatinine levels and greater CCr compared with subjects who failed to lose significant weight, (2) even in subjects who failed to lose weight significantly, serum creatinine and CCr improved in response to WL

as did plasma NE levels, (3) initial total body fat mass and plasma NE levels correlated with serum creatinine levels and CCr at the 12-month follow-up period and (4) changes in plasma NE with WL over 12 months correlated with reductions in creatinine levels, whereas reductions in total body fat mass correlated with reductions in serum creatinine levels and improvement in CCr. These findings demonstrate that WL improves renal function, as evident from measures of serum creatinine and CCr, even in subjects whose WL was modest and who initially had normal renal function. The improvement in CCr was predicted by initial total body fat mass and plasma NE levels. In overweight subjects with normal renal function, CCr (calculated with the Cockcroft–Gault equation) was, at least partially, determined by adiposity and sympathetic nervous activity.

Obesity, which is frequently associated with sympathetic nervous activation, is an important factor in the progression and perhaps even in the initiation of CKD,[39,40] and abdominal obesity is a relevant risk factor for death and cardiovascular complications in those with CKD.[20,41] Obesity, itself, contributes to the development and progression of CKD, independent of elevated BP or diabetes.[42] The risk for end-stage renal disease is progressively higher at increasing BMI levels and in extremely obese individuals in which such risk is much higher than that in persons with normal BMI.[41] Elevated sympathetic nervous activity has been observed in patients with CKD, regardless of obesity, hypertension or diabetes.[11,16,20] Our earlier study showed that high plasma NE levels could predict future renal injury even in non-obese, normotensive subjects.[23] In addition, we reported in a recent study that WL might contribute to the improvement in renal function that accompanies suppression of muscle sympathetic nerve activity in obese subjects with metabolic syndrome.[30] In the present study, we observed that long-term WL, even mild or moderate, was associated with a reduction in sympathetic activity with concomitant improvement in renal function, as assessed from measures of serum creatinine and estimated CCr. Taken together, activation of the sympathetic nervous system is an important factor in the onset and development of obesity-related renal injury,[7,20,22,23] and hence WL
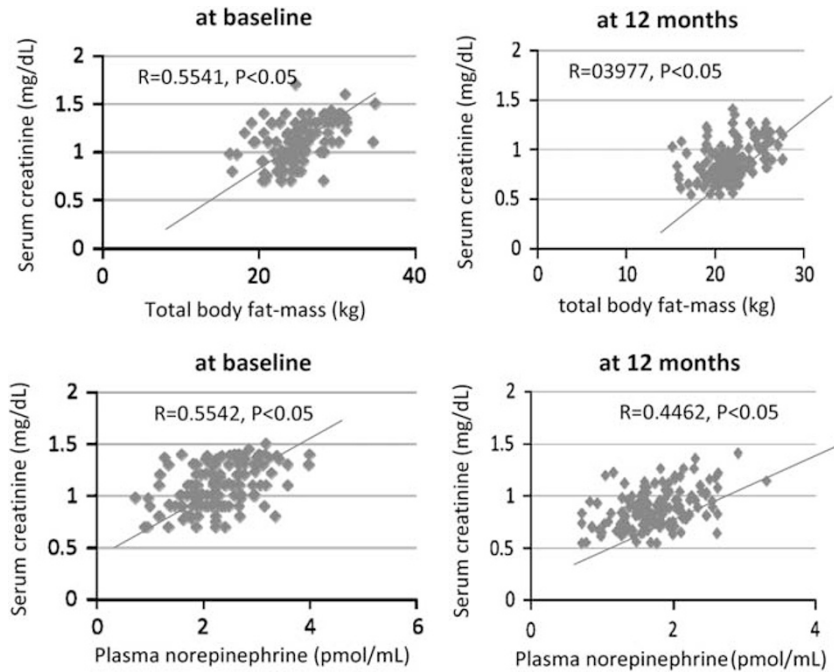
Figure 1 Upper panels, correlations between total body fat mass and serum creatinine levels at the baseline period (upper-left panel) and at 12 months (upper-right panel). Lower panels, correlations between plasma norepinephrine levels and serum creatinine levels at the baseline period (lower-left panel) and at 12 months (lower-right panel).
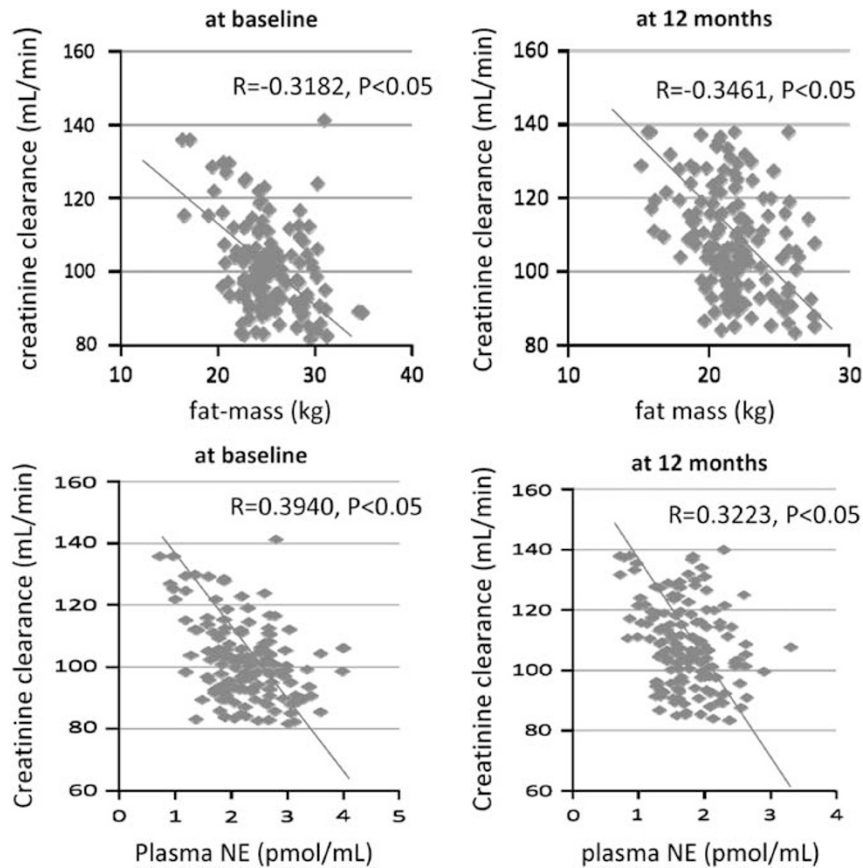

Figure 2 Upper panels, correlations between total body fat mass and creatinine clearance (CCr) at the baseline period (upper-left panel) and at 12 months (upper-right panel). Lower panels, correlations between plasma norepinephrine (NE) levels and CCr at the baseline period (lower-left panel) and at 12 months (lower-right panel).
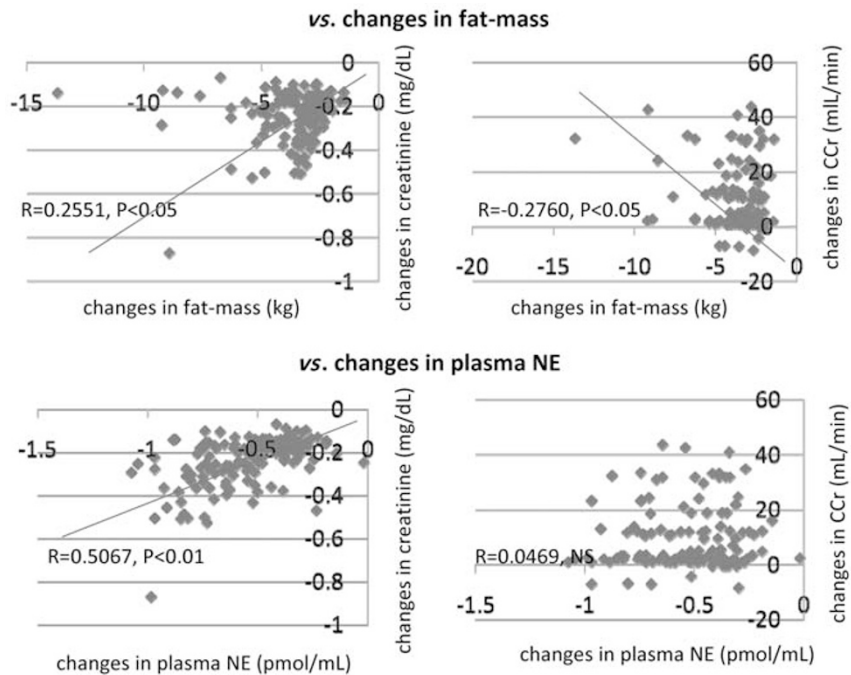
Figure 3 Upper panels, correlations between changes in total body fat mass over 12 months and changes in serum creatinine levels over 12 months (upper-left panel) and between changes in total body fat mass over 12 months and changes in creatinine clearance (CCr) over 12 months (upper-right panel). Lower panels, correlations between changes in plasma norepinephrine (NE) levels over 12 months and changes in serum creatinine levels over 12 months (lower-left panel), and between changes in plasma NE levels over 12 months and changes in CCr over 12 months (lower-right panel).
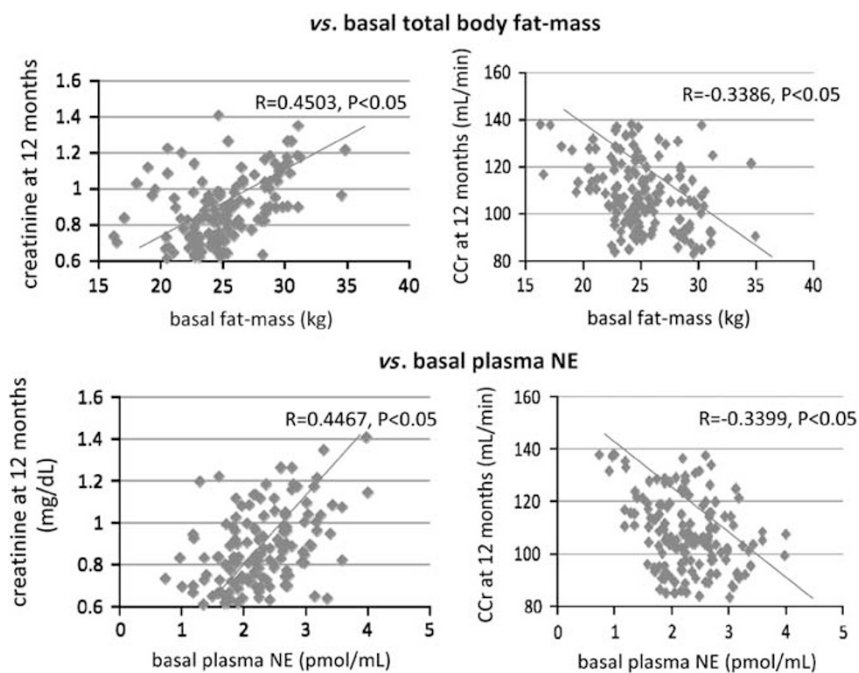

Figure 4 Upper panels, correlations between basal total body fat mass and serum creatinine levels at 12 months (upper-left panel), and between basal total body fat mass and creatinine clearance (CCr) at 12 months (upper-right panel). Lower panels, correlations between basal plasma norepinephrine (NE) levels and serum creatinine levels at 12 months (lower-left panel), and between basal plasma NE levels and CCr at 12 months (lower-right panel).

programs should be initiated and convey some degree of renal protection in the overweight/obese patient.

Glomerular hyperfiltration,[41] hyperleptinemia,[43,44] insulin resistance[30] and stimulation of the RAS,[21,45] accompanying heightened sympathetic nervous activity, may contribute to renal injury in obesity. It has been documented that the RAS is linked to obesity and its activity is reduced in association with WL.[46,47] Such reduction in RAS is important for renal protection.[48,49] A recent study by our group in

Caucasian subjects demonstrated that exercise, but not calorie restriction, contributed more to improvements in renal function and suppression of plasma renin activity.[30] In the present study, we did not measure RAS parameters, and hence cannot unequivocally assess the contributions of the RAS on renal function improvement. In addition, we previously reported that only plasma NE, but not homeostasis model assessment–insulin resistance or leptin,[23] could predict future renal injury in non-obese, normotensive subjects. It would seem, therefore, that the contributions of insulin resistance or hyperleptinemia on renal function seem not to be as strong as the influence of sympathetic nervous activation.

Many studies have shown that the early increases in GFR that occur with weight gain (obesity) are compensatory.[48] The decrease in GFR and arterial pressure after WL is comparable with this hypothesis. Chagnac *et al.*,[15] however, reported that obesity-related glomerular hyperfiltration was improved after WL in morbidly obese subjects as assessed using insulin and p-aminohippuric acid clearance. In the present study, we also observed that several subjects did not improve CCr as calculated using the Cockcroft–Gault equation, even though their creatinine levels decreased with WL. This might be related to irreversible glomerular hyperfiltration, due to obesity or hypertension, but we cannot exclude that it occurs as result of limitations of the Cockcroft–Gault equation (as discussed in the next paragraph).

In the present study, we used serum creatinine concentration and CCr with the Cockcroft–Gault equation as markers of renal function. The National Kidney Foundation in the United States currently recommends using a CCr, based estimate of GFR (i.e., Modification of Diet in Renal Disease formula), and has advocated the use of a standardized classification for CKD. Furthermore, Cockcroft *et al.*[38] assessed the accuracy of the equation to be in around 70% agreement in subjects with normal CCr (normal renal function), although, particularly in patients with a CCr below $50\,\mathrm{ml\,min}^{-1}$, overall accuracy of the equation is substantially diminished, because creatinine is removed not only by glomerular filtration but also by renal tubular secretion.[50] Thus, CCr with the Cockcroft–Gault equation may obscure the genuine association between renal function and WL (adiposity) in subjects with normal renal function,[51] although CCr with the Cockcroft–Gault equation in mild-to-moderate renal injury cannot reflect renal functions accurately. In this study all subjects had $>80\,\mathrm{ml\,min}^{-1}$ of CCr without proteinuria or $>1.5\,\mathrm{mg\,dl}^{-1}$ of serum creatinine (normal renal function).

Serum creatinine and estimated CCr were ameliorated with WL in the present study. Estimation of renal function is better using a serum creatinine-based formula than individual serum creatinine values,[52] because serum creatinine levels are more dependent on creatinine production, mainly in muscle. However, when we analyzed the relationships with renal function using lean body mass, which is more related with muscle than fat mass, serum creatinine and creatinine clearance did not correlate significantly with lean body mass, suggesting that adiposity accompanying high plasma NE might relate to renal function observed in serum creatinine and CCr. One of the limitations in the present study, however, was that we did not obtain measurements of cystatin C, which is documented as a marker of renal function that is less sensitive to changes in muscle mass.[50]

CONCLUSION

The present study demonstrated that a WL program with mild caloric restriction diet and exercise had an ameliorative effect on renal function in overweight subjects, with initially normal renal function. Initial total body fat mass and plasma NE were predictors of renal function (CCr and serum creatinine) and WL (total body fat mass loss) over a 12-month period. Furthermore, it should be noted that even in subjects with mild WL over 12 months, renal function, as seen in serum creatinine and CCr, and plasma NE levels improved significantly.

Weight loss has been shown to benefit renal function,[14,30,33] however the precise mechanisms by which this occurs has not been fully clarified. There are few longitudinal studies of sufficient duration aimed to address the relationships between renal function and the sympathetic nervous activity with WL. Furthermore, previous studies have relied on measures of albuminuria or proteinuria as an index of renal function. This study emphasizes the pivotal role that the sympathetic nervous system has in renal function and highlights its role in ameliorating the effects of WL in obesity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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