Reduction in Resting Metabolic Rate and Ratio of Plasma Leptin to Urinary Nitric Oxide: Influence on Obesity-Related Hypertension

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Abstract

Background: Multiple factors are involved in the pathogenesis of hypertension in the obese individual.

Objective: To evaluate the role of a decrease in sympathetically mediated thermogenesis and the effect of the correlation between the plasma leptin and daily urinary nitric oxide levels on obesity-related hypertension.

Methods: We evaluated three groups: 25 obese hypertensive patients (age 45.7±1.37 years, body mass index 34.2±1.35 kg/m^2, systolic/diastolic blood pressure 155±2.9/105±1.3, mean arterial pressure 122±1.50 mmHg); 21 obese normotensive patients (age 39.6±1.72, BMI 31.3±0.76, SBP/DBP 124±2.1/85.4±1.8, MAP 98.2±1.80); and 17 lean normotensive subjects (age 38.1±2.16, BMI 22.1±0.28, SBP/DBP 117±1.7/76.8±1.5, MAP 90.1±1.50). We determined basal resting metabolic rates, plasma insulin (radioimmunoassay), norepinephrine (high performance liquid chromatography) in all subjects. Thereafter, 14 obese hypertensives underwent a weight reduction diet. At weeks 6 (n = 14) and 14 (n = 10) of the diet the above determinations were repeated. Plasma leptin (enzyme-linked immunosorbent assay) and UNOx (spectrophotometry) were assayed in 17 obese hypertensives and 17 obese normotensives, and in 19 obese hypertensives versus 11 obese normotensives, respectively.

Results: Obese hypertensive patients had significantly higher basal RMR and plasma NE levels. Insulin levels were lower in the lean group, with no difference between the hypertensive and normotensive obese groups. At weeks 6 and 14, BMI was significantly lower, as were insulin and NE levels. RMR decreased to values of normotensive subjects. MAP normalized but remained significantly higher than in obese normotensives. Leptin blood levels and the leptin/UNOx ratio were significantly higher in the obese hypertensive compared to the obese normotensive patients. Both these parameters were strongly correlated to BMI, MAP, RMR, and plasma NE and insulin. Obese hypertensive patients excreted less urinary NO metabolites. A strong correlation was found between MAP and the leptin/UNOx ratio.

Conclusions: A reduction in sympathetically mediated thermogenesis, as reflected by RMR, results in normalization of obesity-related hypertension. In contrast, insulin does not seem to play a major role in the pathogenesis of hypertension associated with obesity. Increased leptin levels in conjunction with decreased NO production in the presence of enhanced sympathetic activity may contribute to blood pressure elevation in the obese.

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BMI = body mass index
SBP/DBP = systolic blood pressure/diastolic blood pressure
MAP = mean arterial pressure
UNOx = urinary nitric oxide
RMR – resting metabolic rate
NE = norepinephrine
NO = nitric oxide

Hypertension, whether in the obese or non-obese patient, is frequently associated with glucose intolerance, insulin resistance and hyperinsulinemia. These metabolic abnormalities have been hypothesized to play a role in the pathogenesis of hypertension [1–3]. Insulin is known as a potent stimulator of the sympathetic nervous system. Both the plasma insulin concentration and urinary norepinephrine excretion were significantly correlated with blood pressure in the Normative Aging Study [2]. Obesity is a consequence of prolonged disequilibrium between energy intake and output.

Thermogenesis is an important contributor to energy output. According to Landsberg [4], in obese individuals, increased sympathetic activity due to hyperinsulinism and recruited for increasing thermogenesis will eventually lead to an elevation of blood pressure. However, studies examining this issue have yielded conflicting results [5].

Plasma leptin levels have been found to be raised in both obese and non-obese essential hypertension [6]. The possible hypertensive effect of chronic hyperleptinemia may be mediated by the peptide's stimulatory action on the sympathetic nervous system [7]. Leptin has also been shown to induce endothelial nitric oxide-mediated vasorelaxation [8]. However, in lean essential hypertensive patients, urinary nitric oxide excretion is reduced [9]. The association in the obese of an increase in plasma leptin coupled with a decrease of UNOx may play a contributory role in obesity-related hypertension.

The purpose of this study therefore was to assess: a) the influence of a reduction in resting metabolic rate (as an indicator of thermogenesis), and b) the postulated correlation of plasma leptin to nitric oxide and its effect on hypertension in the obese individual.

Patients and Methods

Definitions

Obesity was defined using the body mass index, calculated as weight/height^2 (kg/m^2). A participant was considered to be obese if his BMI was >28 kg/m^2. A BMI of 23 kg/m^2 was the upper limit for acceptance to the non-obese control group [10].

Hypertension was defined as blood pressure 140/90 mmHg. The upper limit for normal blood pressure was set at an MAP of 108 mmHg.

Subjects

Sixty-three male volunteers were enrolled in the study. They were divided into three groups consisting of 25 obese hypertensive subjects, 21 obese normotensive, and 17 non-obese normotensive subjects. The main characteristics and mean blood pressure values of the three groups are depicted in Table 1. Only subjects with established essential hypertension participated in the study. Exclusion criteria included smoking, any chronic medication, or having taken part in a nutritional intervention program during the year prior to enrollment.

The local and national review committee on human investigation approved the study protocol. All participants gave written informed consent prior to their enrollment.

Study protocol

The study protocol comprised three phases: In phase 1, RMR was measured in all 63 participants (as detailed below). In the second phase, 14 subjects from the obese hypertensive group were placed on a weight reduction diet for 6 weeks. In phase 3, 10 of these latter patients who were able to maintain their reduced weight were followed for an additional 8 weeks. Measurement of RMR was repeated at the completion of phases 2 and 3. The weight reduction diet (60% carbohydrate, 20% fat, 20% protein) was planned to provide 60–70% of the pre-diet RMR with no change in the sodium content.

Plasma insulin, NE, lipid profiles and standard laboratory tests were determined at baseline and at the completion of each phase. Plasma leptin and UNOx were determined only at baseline.

Methods

Blood pressure measurements were determined as recommended in the Joint National Committee (JNC VI) report [11]. Anthropometric measurements (height, weight, triceps, supra-ileal and subscapular skin folds) were performed on each subject before every RMR measurement. Skinfold thickness was determined using a caliper, and lean body weight was calculated as described by Durnin and Womersley [12]. The blood sample for plasma NE was drawn from a canula placed in an antecubital vein of the arm contralateral to that used for blood pressure measurements. Twenty-four hour urinary collections for creatinine and nitric oxide metabolites were performed. Blood and urine samples were stored at –70°C until assayed.

Table 1. Age, body mass index, and blood pressure values of the three groups

	Study		Control
	Obese hypertensive	**Obese normotensive**	**Lean normotensive**
N	25	21	17
Age (yr)	45.7 ± 1.37*	39.6 ± 1.72	38.1 ± 2.16
(range)	(27–59)	(25–58)	(23–53)
BMI (kg/m^2)	34.2 ± 1.35	31.3 ± 0.76	22.1 ± 0.28*
SBP (mmHg)	155 ± 2.9	124 ± 2.1	117 ± 1.7
DBP (mmHg)	105 ± 1.3	85.4 ± 1.8	76.8 ± 1.5
MAP (mmHg)	122 ± 1.50*	98.2 ± 1.80	90.1 ± 1.50

* $P < 0.05$ vs. other groups

- *Measurement of RMR*. All subjects were studied after an overnight (14 hour) fast. The measurement was performed in the morning, after 20 minutes of complete rest, with the subject barefoot, seated comfortably in an armchair and wearing light indoor clothes. The indirect calorimetric method was used [13], which measures heat production in calories per day. The subject was covered by a head mask, with airflow of 60–80 L/min produced by a suckling pump. Airflow was measured by a mass flow meter model 8160 (Matheson, East Rutherford, NJ, USA). After drying, a sample of 100 ml/min was passed serially through an oxygen analyzer model S-3a/I (Applied Electronics, Sunnyvale CA, USA) and a carbon dioxide analyzer (Ametek Thermox instruments Division, Pittsburgh, PA, USA). The voltage was translated to digital output and the data were calculated by a personal computer. Values of heat production, respiratory quotient and airflow were presented graphically and numerically during measurements. Calibration of heat production and respiratory quotient was made by burning and weighing absolute alcohol. LBW was calculated from the anthropometric measurements [12] and RMR was then corrected for the lean body weight (corrected RMR=RMR/LBW cal/day/kg).
- *Plasma and urine parameters*. Plasma NE was determined by a high powered liquid chromotographic electrochemical detection method [14]. Insulin was measured using a commercial radioimmunoassay kit (INSIK-5, SORIN Biomedica, Saluggia, Italy). Plasma leptin was assayed using a commercial ELISA kit (Diagnostic System Laboratories Inc., Webster, TX, USA). Total triiodothyronine, free thyroxine and thyroid-stimulating hormone were assayed using commercial RIA kits (C.A.C from DPC, Los Angeles, CA, USA, for TT3 and FT4) and DELFIA RIA kit (Wallac, Turku, Finland, for TSH, respectively). Sodium, potassium, calcium, phosphorus, urea, creatinine, total cholesterol, triglycerides and high density lipoprotein were measured by an automatic autoanalyzer (Hitachi 747) using standard laboratory techniques. Low density lipoprotein was calculated using the formula: LDL = total cholesterol – HDL – (triglycerides/5). Urinary NO metabolites were determined by a spectrophotometric assay [15].

Statistical analysis

Spearman-rank correlation was used to determine relations among variables. Differences between study groups were analyzed by analysis of variance. The effect of intervention was tested with a paired *t*-test where subjects served as their own controls. The subjects' age was adjusted and used as a confounding variable in a multidimensional model that tested differences among treatments.

LBW = lean body weight
ELISA = enzyme-linked immunosorbent assay
RIA = radioimmunoassay
TT3 = total triiodothyronine
FT4 = free thyroxine
TSH = thyroid-stimulating hormone
LDL = low density lipoprotein
HDL = high density lipoprotein

SAS software was employed throughout. Results are expressed as mean ± standard error, unless otherwise stated.

Results

Anthropometric measurements showed that all obese subjects had centrally distributed adipose tissue (central obesity). The mean age of the obese hypertensive group was significantly higher than that of the other groups. However, statistical analysis (as detailed above) showed that age did not influence the measured variables.

Phase I

In all subjects, electrolytes, renal and thyroid function tests were within normal limits and did not differ between groups. RMR, cRMR and plasma NE levels were significantly higher in the obese hypertensive compared to the two normotensive groups [Table 2]. Plasma insulin, blood glucose and lipid levels were significantly lower in the non-obese group with, however, no difference between the hypertensive and normotensive obese groups. SBP, DBP and MAP correlated significantly with RMR (r = 0.56, 0.55, 0.58, respectively, $P < 0.01$), BMI (r = 0.54, 0.51, 0.54, $P < 0.01$), NE (r = 0.40, 0.46, 0.45, $P < 0.01$), and insulin (r = 0.29, 0.32, 0.32, $P < 0.05$). cRMR was found to strongly correlate with plasma NE (r = 0.81, $P < 0.002$) and less so with insulin (r = 0.56, $P = 0.04$).

Phase II and III

Compared to baseline, the BMI of the intervention group decreased significantly after 6 weeks and remained so after 14 weeks. The RMR and cRMR declined, in parallel, to levels equal to those found in the control normotensives. At 14 weeks, plasma insulin and NE levels decreased significantly [Table 3]. At both 6 and 14 weeks, SBP, DBP and MAP were significantly lowered but remained significantly higher than that of the obese normotensives [Table 3]. Electrolytes, renal and thyroid function tests remained within normal limits throughout the study period. Following weight reduction, a statistically significant improvement in the lipid profile was seen. The correlation between cRMR and both plasma NE and insulin disappeared when weight reduction was achieved.

- *Plasma leptin.* Levels were determined in 17 obese hypertensive and 17 obese normotensive subjects, and were significantly higher in the former compared to the latter: 13,212 ± 2,920 vs 7,021 ± 1,096 pg/ml ($P < 0.05$). Correcting plasma leptin for BMI (leptin/BMI) yielded similar statistical significance. Leptin blood levels significantly correlated with BMI ($r = 0.89$, $P < 0.001$), MAP (r = 0.45, $P < 0.01$), RMR (r = 0.50, $P < 0.01$), NE (r = 0.40, $P < 0.01$), and insulin (r = 0.53, $P < 0.01$).
- *Urinary nitric oxide.* Levels were measured in 19 obese hypertensive and 11 obese normotensive subjects, with the former excreting 983 ± 196 mol/day compared to 1,544 ± 385 in the obese normotensives (P = 0.06). Correcting for creatinine excretion (UNOx/creatinine) resulted in a similar P value. MAP was found to significantly correlate with the leptin/UNOx ratio (r = 0.56, $P < 0.05$).

Table 2. Results of phase I

	Study		Control
	Obese hypertensive	Obese normotensive	Lean normotensive
RMR (W)	132.8 ± 7.9*	100.5 ± 5.8*	78.3 ± 4.2*
cRMR (W/kg)	1.94 ± 0.09*	1.56 ± 0.09	1.41 ± 0.06
NE (nmol/L)	3.77 ± 0.44*	2.35 ± 0.3	2.07 ± 0.14*
Insulin (pmol/L)	147 ± 13	119 ± 13	70 ± 8*
Glucose (mmol/L)	5.8 ± 0.09	5.6 ± 0.1	5.2 ± 0.13*

* $P < 0.05$ vs. other groups

Table 3. Results of phases II and III

		Baseline	6 weeks	14 weeks
BMI	kg/m^2	35.6 ± 2.3*	32.6 ± 1.9	30.2 ± 1.3
SBP	mmHg	157 ± 3.4*	136.7 ± 3.6	138 ± 3.4
DBP	mmHg	108 ± 1.6*	93.5 ± 3.1	91.3 ± 2
MAP	mmHg	124 ± 2.1*	108 ± 3.1	107 ± 2.4
RMR	W	142.2 ± 8.3*	109.3 ± 6.8	104.5 ± 6.6
cRMR	W/kg	1.98 ± 0.12*	1.66 ± 0.09	1.56 ± 0.09
NE	nmol/L	4.09 ± 0.57	3.17 ± 0.40	2.89 ± 0.40**
Insulin	pmol/L	162 ± 19*	103 ± 9	121 ± 24

* $P < 0.05$ vs. 6 and 14 weeks
** $P < 0.05$ vs. baseline and 6 weeks

Discussion

Many surveys have documented the association between hypertension and obesity. The frequency of obesity-related hypertension depends upon age, gender, and genetic and environmental factors. Obesity is a leading risk factor for chronic hypertension. It has been reported that up to 50% of the overweight population is hypertensive [16]. However, despite its commonality and clinical implications, the fundamental nature of this association is, as yet, unclear. Obesity may be viewed as an imbalance between energy intake and output. The capacity to dissipate excess calories as heat (dietary thermogenesis) is an important physiologic defense against obesity. Diet-induced thermogenesis is regulated by the sympathetic nervous system. It is conceivable that, at least in some obese subjects, increased SNS activity recruited to maintain adequate energy expenditure will give rise to hypertension [2,4]. Ample evidence has documented enhanced sympathetic activity – as reflected by increased NE levels – in essential hypertension [17,18]. Despite its limitations, measurement of plasma catecholamine levels, in particular NE, has been the method most frequently used to assess SNS function. NE levels have been found to be significantly higher in the obese compared to the non-obese [17].

In the present study, RMR and cRMR were used as an indicator of thermogenesis (energy expenditure). In the obese hypertensive group, the metabolic rate was significantly increased and was associated with elevated NE blood levels. As plasma NE increases with age, the significantly higher mean age of this group might introduce a confounding variable. However, statistically, age was not found to influence our results. Upon weight reduction, both the

cRMR = corrected RMR

SNS = sympathetic nervous system

metabolic rate and plasma NE markedly decreased to levels found in normotensive subjects concomitant with a drop in MAP. These data confirm previously published reports showing that a fall in blood pressure with weight loss in the obese is correlated with a reduction in plasma NE [2,17].

The postulated link between dietary intake and the SNS is believed to be insulin. Insulin resistance and consequently hyperinsulinemia are more severe and more closely associated with hypertension in overweight patients compared to their lean counterparts [18]. Despite a substantial decrease in insulin-mediated muscle glucose uptake, obese individuals demonstrate similar SNS responses to insulin as do lean insulin-sensitive subjects. Insulin stimulates the SNS by increasing glucose uptake and metabolism in the regulatory cells of the ventromedial nucleus of the hypothalamus. The increase in sympathetic activity leads to increased energy expenditure (dietary thermogenesis) in an attempt to restore energy balance. However, the effects of the enhanced sympathetic drive on the heart, vasculature and kidney (increased heart rate, vasoconstriction and increased tubular sodium re-absorption) may result in hypertension [4].

In none of the subjects throughout the study were we able to demonstrate a direct correlation between insulin and plasma NE. In phase I, both insulin and plasma NE correlated significantly with cRMR, although that of insulin was much weaker than that of NE. Weight reduction fully normalized the RMR and plasma NE but had no appreciable effect on insulin levels, which did not differ significantly between the two obese groups. These findings do not support a direct causal role of insulin in the pathogenesis of hypertension. In fact, infusions of insulin in dogs and humans have a vasodilating action [2]. The frequent association of hypertension and insulin resistance probably requires other physiologic mechanisms, such as the SNS, to offset insulin's vasodepressor effect.

The RMR was markedly elevated in hypertensive obese subjects. This high energy expenditure is even more impressive when taking into account the lower metabolic rate of adipose tissue. After weight loss, RMR and cRMR decreased to levels equivalent to that of normotensive obese subjects in parallel to normalization of blood pressure values. However, despite no difference in plasma NE, insulin levels, RMR, cRMR, thyroid function tests and lipids between the two obese groups at the end of the intervention and follow-up period, MAP was significantly higher, even if within the normal range, in the hypertensive group. It might be that if, as formulated, obesity-related hypertension is partly neurogenic, the remaining blood pressure increase is due to structural cardiovascular changes induced by the preceding neurogenic vasoconstriction. Alternatively, other physiologic systems could play a role [19].

Leptin is a peptide hormone, produced mainly by adipose tissue, which acts in the central nervous system through a specific receptor to decrease appetite and increase energy expenditure. It has been shown to stimulate sympathetic nerve activity to kidney, adrenal and brown adipose tissue [7], to attenuate several insulin-induced activities [20], and to induce endothelial NO-mediated vasorelaxation [8]. Whereas the acute administration of leptin, in rats, did not raise blood pressure probably due to its diuretic and natriuretic effects, chronic infusion led to increased arterial pressure [21,22]. Transgenic mice over-expressing leptin developed hypertension [23]. In humans, plasma leptin levels were found to be elevated in both obese and non-obese essential hypertension [6]. Thus, despite leptin's anti-hypertensive actions, long-standing hyperleptinemia appears to be associated with elevated blood pressure.

Lembo et al. [8] demonstrated that leptin possesses direct vasorelaxant properties mediated by endothelial NO release. However, urinary NO excretion was diminished in lean essential hypertensive patients [9]. In our study, leptin blood levels were higher and the 24 hour urinary excretion of NOx lower in the hypertensive obese compared to the normotensive obese group. Although dietary nitrate may influence the measurement of UNOx, both obese groups consumed a similar diet. MAP was seen to positively correlate with the leptin/UNOx ratio. It is tempting to speculate that the combination of increased vasoconstrictive activity induced by leptin, coupled with decreased vasodilatation due to reduced NO production, may contribute to the development of hypertension in the obese, particularly in the presence of enhanced SNS activity.

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References

1. Modan M, Karasik A, Halkin H, et al. Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response. *Diabetologia* 1986;29:82–9.
2. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities – the role of insulin resistance and the sypathetoadrenal system. *N Engl J Med* 1996;334:374–81.
3. Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone. *Circulation* 1997;96:4104–13.
4. Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. *Q J Med* 1986;61:1081–90.
5. Gudbjornsdottir S, Lonnroth P, Bergmann Sverrisdottir Y, et al. Sympathetic nerve activity and insulin in obese normotensive and hypertensive men. *Hypertension* 1996;27:276–80.
6. Agata J, Masuda A, Takada M, et al. High plasma immunoreactive leptin level in essential hypertension. *Am J Hypertens* 1997;10:1171–4.
7. Haynes WG, Morgan DA, Walsh SA, et al. Receptor mediated regional sympathetic nerves activation by leptin. *J Clin Invest* 1997;100:270–8.
8. Lembo G, Vecchione C, Fratta L, et al. Leptin induces nitric oxide mediated vasorelaxation in aortic-rings of WKY rats [Abstract]. *Hypertension* 1998;32:599.
9. Forte P, Copland M, Smith LM, et al. Basal nitric oxide synthesis in essential hypertension. *Lancet* 1997;349:837–42.
10. Rosenbaum M, Leibel RL, Hirsch J. Obesity. *N Engl J Med* 1997;337:396–407.
11. The sixth report of the Joint National Committee on Detection,

Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;157:2413–46.
12. Durnin JVGA, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements in 481 men and women aged from 16 to 72 years. *Br J Nutr* 1974;32:77–97.
13. Schutz Y, Jequier E. Resting energy expenditure, thermic effect of food, and total energy expenditure. In: Bray GA, Bouchard C, James WPT, eds. Handbook of Obesity. New York: Marcel Dekker, 1997:443–74.
14. Blum I, Vered Y, Graff E, et al. The influence of meal composition on plasma serotonin and NE concentrations. *Metabolism* 1992;41:137–40.
15. Gilliam MB, Sherman MP, Griscavage JM, Ignarro LJA. A spectrophotometric assay for nitrate using NADPH oxidation by Aspergillus nitrate reductase. *Anal Biochem* 1993;212:359–65.
16. Berchtold P, Jorgens V, Fuike C, Berger M. Epidemiology of obesity and hypertension. *Int J Obes* 1981;5(Suppl 1):1–5.
17. Tuck ML. Obesity, the sympathetic nervous system, and essential hypertension. *Hypertension* 1992;19:I67–77.
18. Landsberg L. Hyperinsulinemia: possible role of obesity induced hypertension. *Hypertension* 1992;19(Suppl I):I-61–6.
19. Mark AL, Correia M, Morgan DA, et al. Obesity induced hypertension, new concepts from the emerging biology of obesity. *Hypertension* 1999;33(part II):537–41.
20. Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. *Science* 1996;274:1185–8.
21. Jackson EK, Li P. Human leptin may function as a diuretic/natriuretic hormone [Abstract]. *Hypertension* 1996;28:517.
22. Shek EW, Brand MW, Hall JE. Chronic leptin infusion increases arterial pressure. *Hypertension* 1998;31:409–14.
23. Ogawa Y, Masuzah H, Aizawa M, et al. Blood pressure elevation in transgenic mice over-expressing leptin, the obese gene product [Abstract]. *J Hypertens* 1998;16:57.

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