Turkish Journal of Endocrinology and Metabolism, (2004) 2 : 49-56 **ORIGINAL ARTICLE**

The Effects of Body Mass Index on the Cardiovascular Risk Factors in the Patients with Essential Hypertension

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To examine effects of body mass index on cardiovascular risk factors in hypertensive women. Study Design: Retrospective, cross-sectional study Subjects: 446 hypertensive subjects attending the endocrinology outpatient Measurements: Height, weight, resting blood pressure, pulse pressure, fasting glucose, insulin, total cholesterol, triglyceride, and HDL cholesterol concentrations, insulin resistance with HOMA, medical history of type 2 diabetes mellitus and smoking status. Results: Obese hypertensive patients had significantly higher systolic and diastolic blood pressure, pulse pressure, fasting glucose, insulin, triglyceride, and LDL-C concentrations. Total / HDL-C ratio and HOMA were significantly higher in obese patients compared with non-obese patients. No significant differences were observed with respect to total cholesterol and HDL-C levels. Insulin resistance, hyperinsulinemia and high total / HDL-C ratio were highly prevalent in the obese hypertensive patients. There were significant relationships between obesity and blood pressure, pulse pressure, insulin resistance. Conclusions: Hypertensive subjects with BMI>30 kg / m2 carry a burden of common coronary risk factors such as insulin resistance, dyslipidemia, hyperinsulinemia, hypertension and wider pulse pressure.

Keywords: Hypertension, obesity, insulin resistance, women, cardiovascular disease, BMI

Introduction

About 45 % of deaths in the western world are related to cardiovascular disease (CVD). Among all cardiovascular risk factors, obesity and hypertension emerge today with epidemic proportion and will probably be the worst killers of 21st century (1). Obesity is closely related to several known cardiovascular risk factors, such as hypertension, lipid abnormalities, and impaired glucose metabolism (2). The individual and independent effect of obesity on the risk of CVD is difficult to estimate because obesity exerts much of its effect through the enhancement of other risk factors.

The effect of obesity on the development of CVD in a hypertensive subject is controversial. Some studies suggested that lean hypertensive patients might have a higher risk of CVD than obese hypertensive patients (3, 4).

The aim of the present retrospectively designed study is to evaluate the association between BMI and the other cardiovascular risk factors: systolic and diastolic blood pressure, pulse pressure, serum lipid levels (total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total/HDL-C, triglyceride] fasting glucose, insulin resistance, hyperinsulinemia, and smoking in hypertensive women.

Material and Methods

Age matched obese and non-obese hypertensive women were retrospectively selected from recorded data file of outpatient endocrinology clinic of Trakya University, Medical Faculty from 1999

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to 2003. 778-hypertensive women were admitted to our hypertension clinic between in this period. After age matching, the study cohort consisted of 221 obese-hypertensive women and 225 non-obese hypertensive subjects. Clinical and laboratory data were obtained at the time of initial visit. Secondary causes of hypertension were excluded, as much as possible, in all patients by measurement of serum urea, creatinine, electrolytes, TSH and free T_4 concentrations, urinary metanephrine, over-night 1 mg dexamethasone suppression test. Height and weight were measured with vertical ruler and standard scale. Subject's shoes were removed and results were rounded down for 0.5 cm and 0.5 kg. Body mass index (BMI) was calculated as weight/ height^2 (kg/m^2). Obesity was defined according to the World Health Organization technical report, with the cut point of BMI: Non-obese patients (BMI < 30 kg/m^2) and obese patients (BMI ≥ 30 kg/m^2) (5). Blood pressure (BP) was measured 2 times in the seated position after about 10 minutes rest by use of a standard manual mercury sphygmomanometer (for non-obese subjects) and an 18 x 42 cm extra large cuff (for obese subjects). The recorded pressure was the average of the two measurements. Women with systolic and diastolic BP equal to or exceeding 140/90 mmHg and women who used BP lowering medications were considered to have hypertension (6). Pulse pressure (PP) was calculated as the difference between the systolic and diastolic blood pressure.

Self-administered questionnaire containing dichotomous (yes or no) questions regarding smoking and personal history of type 2 diabetes mellitus (DM) was administered.

Analytical Procedures

Samples for the measurement of plasma glucose, insulin, and serum total cholesterol, HDL-C, triglyceride levels were drawn after an overnight fast. Plasma glucose was measured by the glucose oxidase technique (Synchron Systems, record number: 472500). Plasma concentration of insulin was measured by the immunoradiometric assay (Immulite, DPC, Los Angeles, USA). Fasting insulin levels, higher than 12.2 mUI/l, were chosen as an indicator of insulin resistance and hyperinsulinemia (7). In each subject, the degree of insulin resistance was estimated by homeostasis model assessment [HOMA, fasting glucose (mmol/l) fasting insulin (mUI/l)]/22.5 (8). The cutoff point of HOMA, which defines insulin resistance in Turkish population, was accepted as 2.24 (9).

Spectrophotometric method (Beckman Coulter LX20, Ireland) was used to determine serum levels of total cholesterol (Synchron Systems, record number: 467825) triglycerides (Synchron Systems, record number: 445850) and HDL-C (Cholesterol HDL Liquid, Sentinel CH, Milan-Italy). LDL-C was calculated with Friedewald's equation [Total Cholesterol – (triglyceride/5 + HDL-C)] (10). Total/ HDL cholesterol ratio > 4.5 was accepted as a cardiovascular risk factor (11).

Statistical Analysis

Subjects were divided into two groups (obese and non-obese) according to body mass index (BMI) ≥ 30 kg/m^2 and < 30 kg/m^2 respectively. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 10.0; SPSS Inc., Chicago, IL).

All continuous variables were compared with unpaired Student's t-test. The Pearson correlation analysis was used to test the bivariate associations between different variables in the entire population. Multiple regression analyses (Stepwise) were performed to evaluate the potential influences of BMI, insulin resistance, fasting insulin, and glucose on the systolic and diastolic BP, PP, and serum lipids levels.

The study population was dichotomized into smokers and non-smokers, diabetic or non-diabetic. Population was also divided into groups according to insulin resistance, insulinemia, and total/HDL-C ratio. χ^2 was used to estimate differences of the prevalence of smoking habit, DM, insulin resistance, hyperinsulinemia, and high total/HDL-C ratio between the obese hypertensive and non-obese hypertensive group. Since it is well recognized that some anti-hypertensive drugs may influence body weight, insulin sensitivity, and lipid profile, both favorably (e.g., alpha1-antagonists, angiotensin converting enzyme-inhibitors, angiotensin II type 1 receptor-antagonists) and unfavorably (e.g., not selective beta-blockers, some calcium channel blockers), we evaluated the distributions of these agents in obese and non-obese hypertensive patients by χ^2 test.

Two-tailed P values were used and statistical significance was considered at $P < 0.05$. Data were expressed as mean ± standard deviation.

Results

The main characteristics of the obese and non-obese groups are presented in Table 1. Both groups were well matched for age. Obese patients had significantly higher systolic and diastolic BP, PP, fasting glucose, insulin, triglyceride, and LDL-C concentrations. Total / HDL-C ratio and HOMA were significantly higher in obese patients compared with non-obese patients. No significant differences were observed with respect to total cholesterol and HDL-C levels.

Table 1. Characteristics of Obese and non-obese patients

	Obese Patients	Non-Obese Patients	P
Age (y)	56.31 ± 10.17	56.47 ± 10.16	> 0.05
BMI (kg / m^2)	33.94 ± 3.46	27.18 ± 1.99	< 0.001
Systolic BP (mmHg)	165.70 ± 24.28	158.54 ± 26.02	<0.01
Diastolic BP (mmHg)	65.47 ± 17.74	62.05 ± 19.29	< 0.01
Pulse Pressure (mmHg)	5.56 ± 0.81	5.35 ± 0.84	< 0.05
Fasting Glucose (mmol / L)	5.58 ± 1.55	5.05 ± 0.67	< 0.001
Fasting Insulin (mU / L)	12.36 ± 3.52	8.40 ± 1.49	< 0.001
HOMA	3.07 ± 1.36	2.02 ± 0,69	< 0.001
Serum Triglycerides (mmol / L)	1.74 ± 0.79	1.56 ± 0.65	< 0.05
Serum Cholesterol (mmol / L)	5.67 ± 1.23	5.60 ± 1.19	> 0.05
Serum LDL-cholesterol (mmol / L)	3.89 ± 1.05	3.54 ± 1.01	< 0.05
Serum HDL-cholesterol (mmol / L)	1.27 ± 0.28	1.28 ± 0.28	> 0.05
Total / HDL-C	4.82 ± 1.26	4.43 ± 1.14	< 0.05

Pearson correlation coefficients in both obese and non-obese populations are shown in Table 2. BMI was positively correlated with systolic and diastolic BP, fasting glucose, insulin, triglyceride, and HOMA. HOMA was positively correlated with systolic BP, PP, triglyceride, and total/HDL-C ratio. Fasting glucose was positively correlated with systolic BP and PP. Multiple linear regression analysis revealed that BMI was the independent predictor for diastolic BP. HOMA was most powerful predictor of systolic BP and total / HDL-C. Fasting glucose was the independent predictor for PP. The data of regression analysis are shown in Table 3.

The prevalence of smoking and DM was comparable between non-obese and obese hypertensive women. 18.4 % of non-obese and 16.7 % of obese patients currently used cigarettes. The prevalence of DM was % 14.6 in non-obese patients, and % 19.8 in obese patients. The prevalence of hyperinsuline-mia, insulin resistance and high total / HDL-C ratio were significantly higher in the obese group than in the non-obese group. The results are given in Table 4.

Table 5 shows the percentages of anti-hypertensive agents, which were used in the treatment of patients. The percentages of the medications were comparable between two groups.

Table 2. Pearson's correlations among BMI, fasting insulin, HOMA, fasting glucose, BPs, PP, and serum lipid concentrations

	R	P
BMI		
Systolic BP	0.147	< 0.01
Diastolic BP	0.146	< 0.01
Fasting Insulin	0.507	< 0.001
HOMA	0.405	< 0.001
Fasting Glucose	0.226	< 0.001
Triglyceride	0.154	< 0.01
HOMA		
Systolic BP	0.165	< 0.001
PP	0.176	< 0.001
Triglyceride	0.141	< 0.01
Total Cholesterol / HDL-C	0.156	< 0.05
Fasting Glucose		
Systolic BP	0.132	< 0.01
PP	0.207	< 0.001

Table 3. Relationship between variables evaluated using stepwise multiple regression analysis

Dependent Variable	Independent Variable	P- value	Beta	% 95 CI
Systolic BP	HOMA	< 0.001	0.165	1.439 - 5.842
	Fasting glucose			
	Fasting Insulin			
	BMI			
Diastolic BP	BMI	< 0.01	0.138	0.132 - 0.834
	Fasting glucose			
	Fasting Insulin			
	HOMA			
PP	Fasting glucose	< 0.0001	0.209	0.095 – 0.266
	BMI			
	Fasting Insulin			
	HOMA			
Total / HDL-C	HOMA	< 0.05	0.156	0.006 – 0.322
	BMI			
	Fasting Insulin			
	Fasting glucose			

Table 4. Prevalence of smoking, DM, total/HDL-C, hyperinsulinemia, and insulin resistance in obese and non-obese hypertensive patients

	Non-Obese Patients	Obese Patients	P
Smoking %	18.4	16.7	> 0.05
DM %	14.6	19.8	> 0.05
Total / HDL-C %	12.9	31.8	< 0.01
Hyperinsulinemia %	12,4	43.4	< 0.001
Insulin resistance %	27.6	71.8	< 0.001

Table 5. The prevalence of antihypertensive medication in both groups.

	Non-Obese Patients	Obese Patients	P
Angiotensin converting enzyme-inhibitors	43.3	38.1	> 0.05
Angiotensin II type-1 receptor-antagonists %	9.5	11.1	> 0.05
Calcium-channel blockers %	35.2	42.3	> 0.05
Beta-Blockers %	14.8	15.8	> 0.05
Alpha1-antagonists %	10.0	12.0	> 0.05
Diuretics %	27.1	33.5	> 0.05

Discussion

In various epidemiological studies, strong positive relationship between CVD and BP has been reported (12, 13). Also during the last years, a large number of studies have suggested PP is a major indicator of CVD (14-17). However, the role of obesity as a risk factor for CVD in hypertension is controversial. Some studies showed increasing CVD mortality rate in lean hypertensive patients unexpectedly (3, 4). In addition, some studies hypothesized a protective effect of obesity with respect to the cardiovascular risk associated with hypertension (18).

According to our results, the obese hypertensive group had high levels of fasting glucose, insulin, LDL-C, triglyceride, and total/HDL-C ratio. In addition, their systolic and diastolic BP, PP, and HOMA were higher than the non-obese group. Our results clearly indicated that obesity could rise the diastolic BP directly and, systolic and PP indirectly, through enhancement of HOMA and fasting glucose in the hypertensive patients.

Both primary and secondary prevention strategies for CVD revolve around the concept that a concerted management of major risk factors. One of these factors is growing epidemic of obesity (2, 11, 19, 20). Obesity is a major modifiable risk factor for CVD, and certainly increases the risk of the other risk factors, such as DM, hypertension, insulin resistance, and dyslipidemia (21). Framingham data suggest that obesity exert much of its adverse influence on development of CHD through the major risk factors (22). Certainly it is possible that some of the increased risk imparted by obesity results from mechanisms unrelated to the major risk factors. However, these mechanisms are not well understood, and it is difficult to define the risk imparted by this factor independent of their influence on the major risk factors.

Both cross-sectional and prospective studies have reported an association between obesity and hypertension (23, 24). Risk estimates from population studies suggested that % 75 of hypertension can be attributed to obesity (2). Framingham Heart Study documented that obesity increases the prevalence of hypertension substantially (25). In Turkish population-based study, Onat et al showed that the relation was significant between BMI and BP in women (26). The result of our analysis of the relationship between obesity and BP is consistent with these findings. When analyzed as continuous variables, BMI was correlated with systolic and diastolic BP. In multivariate analysis, BMI was independently related to diastolic BP. The relationship between BMI and PP is unclear. Some studies indicated that hypertensive patients with higher BMI had wider PP (27-29). It has been reported that the higher BMI is associated the higher PP in the normotensive subjects, but changes in BMI do not seem to be accompanied by changes in PP during a long time follow-up (30). On the other hand, Martins et al showed that PP is wider in lean hypertensive patients (31). In our study, patients with higher BMI had higher PP values compared to patients with lower BMI. In addition, BMI was positively associated with PP.

Obesity- associated hypertension has a complex, multifactorial mechanism. Much of our knowledge is based on correlations between body weight and various factors thought to increase BP and the basic physiological mechanism that link body weight and BP are not yet fully understood. Mark et al suggested that the genetic-neurobiological mechanism of obesity may critically influence the effect of obesity on BP (32). Insulin resistance that is a major confounding factor has a pivotal role in

the development of hypertension in obese individuals. Several case-control studies have clearly shown that lower insulin sensitivity is associated with BP in non-diabetic individuals (33, 34). Insulin resistance can stimulate renal sodium re-absorption; enhance sympathetic activation and up-regulate angiotensin II type 1 receptors (35). Many studies have documented that there is direct relationship between obesity and insulin resistance (36, 37). The result of our analysis of relationship between BMI and insulin resistance confirmed these findings. A HOMA level that defines the insulin resistance varies among different populations and ethnic groups. Gokcel et al reported that HOMA level that indicates the insulin resistance in Turkish people was 2.24 (9). According to this cutoff point of HOMA, % 71.8 of the obese hypertensive patients had insulin resistance, whereas % 27.6 of the non-obese hypertensive patients had insulin resistance. The present study demonstrated that HOMA was associated with systolic and diastolic BP, and PP. In addition HOMA was a strong predictor for systolic BP.

Obesity-related insulin resistance is associated not only with hypertension but also with others cardiovascular risk factors, such as high fasting insulin and glucose values. Although hyperinsulinemia has been considered in a recent meta-analysis as a weak risk indicator for the occurrence of CVD (38), some studies indicated that hyperinsulinemia contributed in the development of CVD (39-41). Elevated insulin levels may stimulate the proliferation of smooth muscle cells in the arterial wall and are also associated with atherogenic lipid patterns and increased sympathetic system activity (42). It is generally agreed that the relationship between hyperinsulinemia and cardiovascular risk is modified by ethnic background (43). It has been showed that hyperinsulinemia is an important risk factor for CVD in Turkish population (44). In this study, we observed that obese hypertensive patients were significantly more likely to have higher fasting insulin levels than non-obese hypertensive patients. Fasting insulin concentration higher than 12.2 mU/L is considered to be a risk factor for CVD. According to this cutoff value, we found that significantly high percentage of obese hypertensive patients had hyperinsulinemia compared to non-obese hypertensive patients. But we could not find any association between fasting insulin and BP. Our findings correspond with those reported by Ferrannini (34), Omaira (45), and Masuo (46). Ferrannini et al recently showed that the effect of obesity on BP elevation appeared to be mediated by insulin resistance rather than hyperinsulinemia. Omaira et al concluded that obese hypertensives behave as hyperinsulinemic but without being able to conclude that hyperinsulinemia is associated with hypertension. The results of prospective longitudinal study of Masuo et al documented that weight gain-induced sympathetic over-activity is more tightly linked to weight gain-induced BP elevation than the changes in plasma insulin that also accompany weight gain.

Fasting blood glucose values in the upper normal range are considered to independent predictor of CVD in non-diabetics (47). Hoogwerf et al (48) reported that the percentage of patients with CVD increased progressively across the range of normal glucose values in non-diabetic subjects. Also systolic and diastolic BP was significantly associated with increasing glucose concentration in the same study. The present study documented that fasting glucose levels were significantly higher in the obese hypertensive group than the non-obese hypertensive group. Fasting glucose levels were positively associated with systolic and diastolic BP and were an independent predictor for PP. There was no difference in the prevalence of DM between the obese and non-obese hypertensive groups in this cohort.

Many cross-sectional and prospective studies confirmed that hypertriglyceridemia, high level of LDL-C, low-HDL-C and high total / HDL-C ratio were associated with CVD (49-52). Obesity has a strong effect on lipoprotein metabolism. Increased weight is a determinant of higher levels of triglyceride, elevated LDL-C, and low HDL-C (2). The underlying mechanism is thought to be attributable to the insulin resistance. We found that obese hypertensive patients had higher triglyceride, LDL-C levels and total/HDL-C ratio. HDL-C level tended to be lower in the obese hypertensive patients than the non-obese hypertensive patients but there was no significant difference between these groups. BMI and HOMA were positively associated with triglyceride levels. Also HOMA was a strong predictor for total / HDL-C ratio.

Although some previous data indicated that smoking was positively related to obesity (53), most cross-sectional studies showed that the prevalence of

smoking was higher in non-obese subjects (54-56). Rasmussen et al. (57) investigated the effect of smoking on changes in BMI during the 16-yr follow-up period and found that longitudinal BMI increases were smaller among smokers than non-smokers. Self-reported smoking was comparable between the obese and non-obese groups in the present study.

In conclusion, this cross-sectional study showed that obesity had important effects on the other cardiovascular risk factors. Obesity was signifycantly associated with blood pressure, PP, fasting glucose, insulin, triglyceride, LDL-C levels, insulin resistance and high total / HDL-C.

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