Obesity, Independent of Insulin Resistance, Is a Major Determinant of Blood Pressure in Normoglycemic Hong Kong Chinese

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Obesity and insulin resistance are considered important links underlying the development of hypertension. In Caucasians, there have been many reports of an association between insulin resistance and hypertension. However, this relationship is not consistently found in other ethnic groups. In this study, we examined the involvement of insulin resistance (assessed as fasting insulin-glucose product, FIGP) and general and central obesity as potential links in the development of hypertension in 413 normoglycemic Hong Kong Chinese (56.9% hypertensive) subjects. Anthropometric parameters (waist circumference [WC], waist-to-hip ratio [WHR], body mass index [BMI]), surrogate measures of insulin resistance (fasting plasma glucose, insulin, FIGP), fasting lipids and systolic (SBP) and diastolic (DBP) blood pressure were measured. Both male and female hypertensives were more obese and dyslipidemic, and the females had higher indices of insulin resistance than the normotensive subjects of the same gender. Before adjustment for age, gender, and adiposity, FIGP correlated with SBP in the total ($r = .19$, $P = .009$) and low BMI ($r = .23$, $P < .05$) and low WHR ($r = .25$, $P < .01$) groups. However, after adjustment, there was no significant relationship between FIGP and blood pressure. In contrast, BMI and WC were strongly associated with blood pressure ($r \geq .41$, $P < .001$ for both DBP and SBP in the total population), although in the group with general obesity, the strength of the relationship was weaker ($r \geq .13$). These relationships persisted after adjustment for age, gender, and FIGP. Obesity, therefore, appears to have a predominant role compared with insulin resistance in determining blood pressure in these normoglycemic Chinese.

HYPERTENSION, DYSLIPIDEMIA, type 2 diabetes mellitus, and obesity are often found clustered together in the same individual.[1,2] Obesity, and in particular visceral obesity, and insulin resistance have been considered as important links underlying the close associations between hypertension, dyslipidemia, and type 2 diabetes.[3-6]

The positive relationship between body weight and hypertension is strongly supported by data gathered from epidemiologic studies.[7-9] In some studies, over 50% of hypertensive subjects were above the recommended body weight.[10] Concordance rates of 15% for dizygotic and 31% for monozygotic twins have been reported in those with both obesity and hypertension.[11] In studies of hypertension in twins, body weight has been shown to be the major 'environmental' factor influencing the level of blood pressure.[12] These observations suggest a common underlying pathogenesis for obesity and hypertension.[6,11]

Many studies in Caucasians support the involvement of hyperinsulinemia and/or insulin resistance in the pathogenesis of hypertension.[6,13-15] However, a clear relationship between insulin resistance and hypertension is not consistently found in all ethnic groups. Although there is evidence to support this relationship in Japanese,[16-18] it is not found in Pima Indians.[19] The findings in blacks, Hispanics, and Chinese are also not consistent with both positive[20-22] and negative findings reported.[7,19,23,24] Thus, only in Caucasians is there good evidence of a positive relationship between plasma insulin concentrations and blood pressure.

Differences in the blood pressure response to pharmacologic interventions between diabetic and nondiabetic hypertensive patients[2] and the finding that hypertension is more common in most diabetic groups than in the general population[25] suggest that the pathogenesis of hypertension in the presence or absence of the diabetic milieu is likely to be the result of a somewhat different interplay of genetic and environmental factors.[26] Factors, which may represent pathogenic mechanisms contributing to or which may be associations with blood pressure, may thus require investigation separately in diabetics and nondiabetics. In the present study, we investigated insulin-obesity-blood pressure relationships in normoglycemic Hong Kong Chinese, who were either normotensive or hypertensive.

SUBJECTS AND METHODS

Study Protocol

The Clinical Research Ethics Committee of the Chinese University of Hong Kong (CHUK) approved the study protocol. All of the subjects, both patients and controls, gave written informed consent and were of Han Chinese origin, unrelated, and without any known ancestors of other ethnic origin. They were living in the Hong Kong Special Administrative Region of China at the time of the study, and none were diabetic. The catchment area of the Prince of Wales Hospital has only been developed since the 1960s and serves a population of over 1 million. The majority of its inhabitants are a typical socioeconomic representation of first- or second-generation migrants from southern China now living in a westernized environment.

Subject Recruitment and Classification

Subjects were recruited from the medical outpatient clinic at the Prince of Wales Hospital. Anthropometric, seated blood pressure, and plasma biochemical parameters after an overnight fast were measured.

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The anthropometric parameters required to calculate the body mass index (BMI) and waist-to-hip ratio (WHR) parameters were measured. Subjects were defined as hypertensive if, after 5 minutes of rest, seated systolic blood pressure (SBP) was ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg on at least 2 occasions while off antihypertensive treatment (after a 4-week washout period).[27] Blood pressure was based on a mean of 3 readings taken 1 minute apart. No subjects had a history of significant renal, hepatic, or cardiac disease. Normotensive (SBP was <140 mm Hg and DBP was <90 mm Hg) normoglycemic (fasting plasma glucose [FPG] <6.0 mmol/L) controls were recruited from hospital staff and their friends.

The index of insulin resistance we used is equivalent to that derived from the homeostasis model assessment (HOMA).[28] However, the relatively complex equation generated by this model (ie, insulin resistance = insulin/[22.5$e^{-\ln \text{ glucose}}$]) can be mathematically rearranged to the conceptually simpler equation: fasting insulin-glucose product (FIGP) divided by 22.5 (ie, insulin × glucose/22.5). This adjusted FIGP (FIGPa) is numerically identical to the originally published equation. We present the FIGPa so that our data can be compared with those in previous publications in other ethnic groups. However, division by a constant is not necessary for analysis of data within our study. Therefore, we also present the simpler FIGP values, which have not been divided by 22.5. As it is the product of pmol/L and mmol/L, we have omitted its units. The HOMA-derived index has been shown to correlate well with the results of the euglycemic hyperinsulinemic clamp in population-based studies.[29,30] Subjects with FPG levels less than 6.0 mmol/L were considered normoglycemic.[31] Subjects with a FPG ≥6.0 mmol/L or receiving glucose-lowering therapies were excluded from the study.

General obesity was defined as a BMI of ≥25.0 kg/m^2 or ≥27.0 kg/m^2 and central obesity as WHR ≥0.85 or ≥0.90 in females and males, respectively.[31] As there is no generally accepted definition of central adiposity using waist circumference (WC), WHR was used to classify the subjects into centrally obese and noncentrally obese groups, and WC was used for the remainder of the analyses. Dyslipidemia was classified as either a fasting plasma total cholesterol ≥6.2 mmol/L or between 5.2 and 6.2 mmol/L with the total cholesterol to high-density lipoprotein (HDL) cholesterol ratio being ≥5.0, and/or fasting plasma triglycerides being ≥2.3 mmol/L.[32,33] Of the 413 normoglycemic subjects, 235 (56.9%) were hypertensive and 178 normotensive. Fasting insulin values were available for the surrogate measure of insulin resistance (FIGP) in only 94 of the hypertensive and 107 of the normotensive subjects.

Biochemical Analyses

Fasting plasma samples were taken for measurement of electrolytes, urate, lipids (triglycerides, total cholesterol low-density lipoprotein [LDL] cholesterol, and HDL cholesterol), and glucose. Plasma electrolytes were measured by ion-selective electrodes on a parallel multichannel analyzer (DuPont Medical Products, Newark, DE; interassay coefficient of variation [CV] <1.0%). Creatinine was measured using the Jaffe method on a Beckman Astra-8 Chemistry analyzer (Beckman, Brea, CA, interassay CV <1.0%). Urate measurement, based on the uricase method, was performed using the Dade Dimension clinical chemistry system (Dade International, Deerfield, IL; interassay CV <2.0%). Plasma glucose was measured using a standard glucose oxidase method. The interassay CV for the quality control was 2.0% at a glucose level of 6.6 mmol/L. Insulin was measured in a 96-well microtiter plate enzyme-linked immunosorbent assay (ELISA) system (Dako Diagnostics, Ely, UK). There was no cross-reactivity with proinsulin. The intraassay CVs were 9.9%, 6.8%, and 2.2% for the standard concentrations of 2.1 ± 0.2, 10.9 ± 0.7, and 31.5 ± 0.7 pmol/L, and the interassay CVs for the quality controls were 7.0%, 4.4%, and 6.4% at insulin levels of 9.3 ± 0.7, 11.2 ± 0.5, and 27.3 ± 1.8 pmol/L, respectively. Plasma total cholesterol and triglycerides were measured enzymatically (Centrichem Chemistry System, Baker Instruments, Allentown, PA). The long-term imprecision of the assay was 3% at 3.3 mmol/L and 2.2% at 6.8 mmol/L for total cholesterol and 6.9% at 1.02 mmol/L and 4.6% at 2.18 mmol/L for triglycerides, respectively. HDL cholesterol was determined after fractional precipitation with dextran sulphate-$MgCl_2$, and LDL cholesterol was calculated using Friedewald's formula.[34]

Statistical Analyses

Data from normally distributed parameters are presented as mean ± SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals.

Studies using the insulin-glucose product as a surrogate estimate of insulin resistance have not described dichotomous criteria to define an insulin-resistant state, but regard the measure as a continuous variable.[28,35] Therefore, to provide an indication of the prevalence of insulin resistance in the hypertensive population, arbitrary cut offs for insulin resistance based on the 95th, 90th, and 75th percentiles of FIGPa of the normotensive group were used. Differences in distribution between the hypertensive and normotensive groups for both males and females were then assessed using the χ^2-test.

For the correlation and stepwise multiple regression analyses, gender was coded 0 and 1 for male and female, respectively. WC, BMI, FIGP, and age were also included in the analyses. The variables included in the analyses were linearly related to the dependent variables. For the stepwise multiple regression, the appropriateness of the regression model was judged from the Durbin-Watson statistic (testing for serial correlation of adjacent error terms) and partial plots of the residuals. The tolerance and variance inflation factors (VIF) were taken as measures of collinearity with low tolerance and high VIF being signs of collinearity that indicate that a variable should not be included in the model. The Statistics Package for Social Sciences (SPSS for Windows, version 7.5.1, 1996, SPSS, Chicago, IL) was used for the above analyses.

RESULTS

The hypertensive population was slightly older ($P < .001$) than the normotensive subjects (Table 1). Both the male and female hypertensives were more obese with increased BMI waist circumference and WHR compared with gender-matched normotensive controls (all $P < .01$). Furthermore, in both sexes compared with the controls, the hypertensives had a higher prevalence of dyslipidemia with elevated triglycerides and lower HDL cholesterol, and additionally plasma sodium, urate, and creatinine were also elevated (Table 1). The female hypertensives had a significantly higher plasma glucose and were more insulin-resistant in terms of their elevated fasting plasma insulin and consequently their FIGP, unlike their male counterparts.

When compared with the arbitrary cut offs for insulin resistance based on the 95th, 90th, and 75th percentiles of FIGPa of the normotensive group in the combined male and female group, 7%, 16%, and 34% of the hypertensives were insulin-resistant, respectively (P = not significant [NS]). When gender-specific groups were analyzed, there was no difference between the distribution of the FIGPa in the males (Fig 1) with 4%, 14%, and 22% (P = NS) being insulin-resistant using male-specific cut offs, respectively. In the females, the overlap was not as great as in the males, but the dichotomy in the distribution was less than that seen for either BMI or waist circumference (Fig 1). Using equivalent female-specific cut offs, 11%, 17%, and 44% were insulin-resistant, respectively.

Table 1. Anthropometric, Blood Pressure, and Plasma Biochemical Characteristics of the Male and Female Normotensive and Hypertensive Populations

Cohort	Males		Females	
	Normotensive	Hypertensive	Normotensive	Hypertensive
No.	67	117	111	118
Age (yr)	38.0 ± 8.6	46.5 ± 9.1§	42.0 ± 9.7	49.0 ± 10.9§
SBP (mm Hg)	116 ± 9	147 ± 17§	112 ± 9	151 ± 18§
DBP (mm Hg)	70 ± 9	92 ± 11§	64 ± 9	87 ± 11§
Mean arterial pressure (mm Hg)	101 ± 8	128 ± 14§	96 ± 8	130 ± 14§
Pulse (beats/min)	70 ± 10	73 ± 14	70 ± 9	74 ± 10¶
Sodium (mmol/L)	141 ± 1	142 ± 2‖	140 ± 1	142 ± 2§
Potassium (mmol/L)	4.1 ± 0.5	4.0 ± 0.4	3.9 ± 0.4	3.9 ± 0.5
Creatinine (μmol/L)	76.7 (73.6-79.4)	84.7 (81.3-87.1)§	57.5 (54.2-60.0)	61.4 (58.9-64.6)‖
Urate (mmol/L)	0.32 (0.31-0.34)	0.37 (0.36-0.39)§	0.24 (0.23-0.25)	0.29 (0.27-0.30)§
Total cholesterol (mmol/L)	5.5 ± 1.6	5.6 ± 1.2	5.5 ± 1.7	5.8 ± 1.5
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3‖	1.5 ± 0.4	1.2 ± 0.3§
LDL-cholesterol (mmol/L)	3.6 ± 0.4	3.7 ± 1.1	3.5 ± 1.5	3.7 ± 1.4
Triglyceride (mmol/L)	1.08 (0.91-1.27)	1.72 (1.52-1.95)§	0.89 (0.79-1.01)	1.74 (1.51-2.00)§
Fasting glucose (FPG, mmol/L)	5.1 (5.0-5.2)	5.2 (5.1-5.2)	5.0 (4.9-5.1)	5.2 (5.1-5.3)§
Fasting insulin (FPI, pmol/L)*	43.4 (35.7-52.6)	45.0 (38.9-52.5)	38.6 (33.1-45.1)	53.2 (42.7-66.1)‖
Insulin-glucose product (FIGP)*	221 (185-270)	229 (195-268)	196 (167-229)	279 (222-349)¶
Adjusted FIGP (FIGPa)*	9.8 (8.0-12.0)	10.1 (8.6-11.9)	8.7 (7.4-10.2)	12.4 (9.9-15.5)¶
BMI (kg/m^2)	23.8 ± 3.9	25.9 ± 3.6¶	22.9 ± 3.4	25.8 ± 4.0§
WC (cm)	79.8 ± 9.3	88.1 ± 9.1§	72.4 ± 8.5	82.5 ± 7.7§
WHR	0.85 ± 0.06	0.89 ± 0.05§	0.78 ± 0.05	0.84 ± 0.06§
Dyslipidemia (%)	37.3	57.3‖	32.7	54.3¶
Increased central adiposity (%)†	16.4	44.4§	10.8	47.1§
Increased general adiposity (%)‡	21.5	32.9	25.7	51.9§
Increased general/central adiposity combined (%)†‡	28.3	52.1¶	29.4	76.5§

NOTE. Mean ± SD, geometric mean (geometric 95% confidence intervals of the mean). For comparison both FIGP and FIGPa are shown (FIGPa = FPI × FPG/22.5), *n = 201; †increased central adiposity = WHR ≥0.85 or ≥0.90; and ‡increased general obesity = BMI ≥25.0 kg/m^2 or ≥27.0 kg/m^2 in females and males, respectively.

§$P < .001$.

¶$P < .01$.

‖$P < .05$.

The proportion with insulin resistance in the female hypertensives when compared with the cut off for the FIGPa of the normotensive population was only significantly higher at the 75th percentile ($P = .04$).

Partial correlation analyses were used to assess the relationships of adiposity (WC and BMI) and FIGP with blood pressure, both before (0 order correlation coefficients) and after the removal of the effects of age and gender and the other parameter (adiposity or FIGP) in the subgroup with fasting insulin values available (Table 2). The relationships were examined in this subgroup as a whole and after division into further subgroups with or without increased BMI or those with or without increased WHR.

Before adjustment for age, gender, and adiposity, the only significant relationships were seen between FIGP and SBP in the total ($r = .19$, $P = .009$) and low BMI ($r = .23$, $P < .05$) and low WHR ($r = .25$, $P < .01$) groups. However, after adjustment, no significant relationships between FIGP and SBP or DBP were identified in any of the subgroups (Table 2). There was a strong relationship between FIGP and BMI or WC after adjustment for age and gender. Furthermore, there was also a strong relationship between SBP and DBP and BMI or WC after adjustment for age, gender, and FIGP (Table 2). Unlike the weak relationship between FIGP and blood pressure, the relationships between the anthropometric measures and SBP and DBP after adjustment for age, gender, and FIGP were strong in all groups, except for a weak relationship between BMI and SBP in the low BMI group.

In the stepwise multiple regression analyses performed in the population for whom insulin levels were available, the parameters were normally distributed and linearly related to the dependent variables, DBP and SBP. Of the variables included (age, gender, WC, BMI, and FIGP) in the analyses, WC was the strongest independent predictor of both DBP ($\beta = 0.53$) and SBP ($\beta = 0.47$). Age was also significantly associated with DBP ($\beta = 0.13$) and SBP ($\beta = 0.24$; DBP = $[0.20 \cdot \text{age}] + [0.75 \cdot \text{waist}] + 33.1$, $R^2 = .32$, $P < .001$; SBP = $[0.50 \cdot \text{age}] + [0.94 \cdot \text{waist}] + 33.1$, $R^2 = .32$, $P < .001$). The FIGP was not an independent predictor for either DBP or SBP and was eliminated from the regression equation, as was BMI.

DISCUSSION

In this study, both the male and female hypertensive subjects were more obese and dyslipidemic, whereas only the females had higher surrogate indices of insulin resistance than the gender-matched normotensive groups (Table 1). Both obesity and insulin resistance have been proposed to be important factors linking the clustering of these metabolic abnormalities.[6,13-15] However, these parameters are closely interrelated (Table 2), with obesity being postulated as leading to the

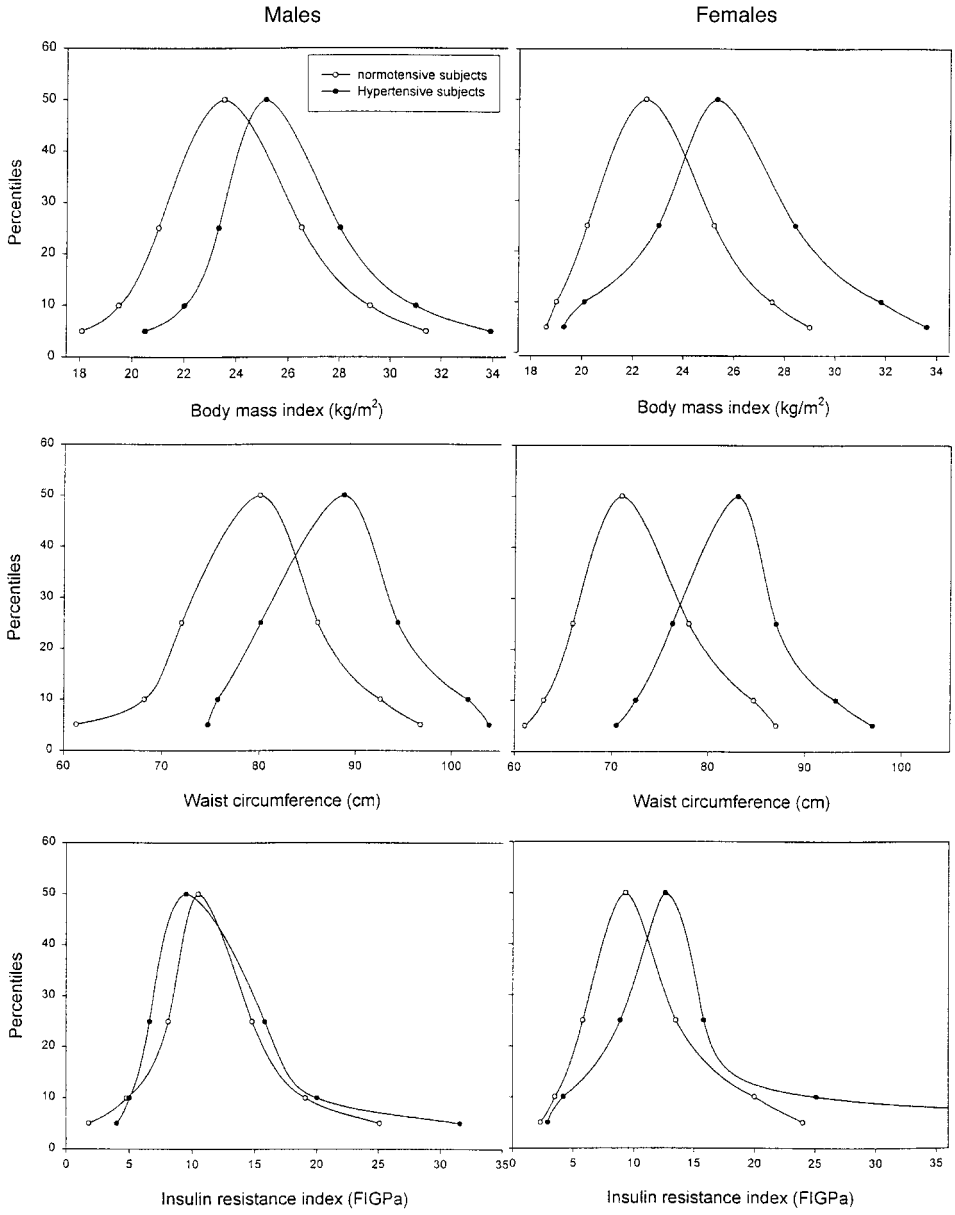

Fig 1. Distribution of the BMI, WC, and FIGPa between normotensive and hypertensive groups for males and females. The values of these parameters at specific percentiles of the population and, hence, the degree of overlap of the normotensive and hypertensive groups are shown.

development of insulin resistance.[5] In this study, we attempted to dissect the relationship between these 2 closely associated variables and determine which is the more important determinant of blood pressure in Hong Kong Chinese.

There was no evidence in this study to suggest a relationship between insulin resistance and blood pressure in the male subjects, as similar levels of glucose, insulin, and FIGP were seen in the hypertensive and normotensive males, and there was no difference in the proportion with insulin resistance between these groups. In females, despite the indices of insulin resistance being higher in hypertensives than controls (Table 1), the distribution of FIGP overlapped in the 2 populations considerably (Fig 1) and only at the 75th percentile was there any significant difference in the proportion with insulin resistance. The proportion of combined male and female hypertensives above the 95th percentile of the FIGPa criterion derived from the normotensive population and thus defined as insulin-resistant was only 7%. Using an equivalent cut off criterion, the prevalence of insulin resistance (FIGPa) was higher at 27% in a similar group of male and female Caucasian hypertensives[36] than in our hypertensive group. The percentage of the variance in blood pressure that is explained by the FIGP in our study was small ($<4\%$ for 0 order correlations, $<1\%$ after adjustment for age, gender, and BMI, Table 2). Only in the low BMI group was there any significant correlation between FIGP and SBP, and this was greatly diminished after adjusting for WC. Furthermore, FIGP was not an independent predictor of blood pressure when indices of obesity were included in the analyses. Together, these data suggest that insulin resistance per se, as assessed by FIGP, is unlikely to play a key role in the development of

Table 2. Partial Correlation Analyses of Relationships Between DBP and SBP and the Insulin-Glucose Product (FIGP), BMI and WC

Obesity Criteria	All Subjects	BMI§		WHR Ratio‖	
		High	Low	High	Low
No.	201	75	126	49	152
r for FIGP*					
BMI	.42¶	.36#	.31¶	.28**	.44¶
WC	.36¶	.24	.24**	.24	.41¶
r for FIGP					
DBP	−.08	−.13	.04	−.14	.04
SBP	.02	−.11	.14	−.10	.10
r for body mass index†					
DBP	.36¶	.29**	.22**	.26	.33¶
SBP	.33¶	.32#	.13	.22	.28#
r for WC‡					
DBP	.46¶	.31**	.30#	.30**	.34¶
SBP	.42¶	.29**	.32¶	.17	.32

NOTE. Partial correlations are adjusted for *age and gender or age, gender and †body mass index and waist circumference, or ‡FIGP. §High general obesity (BMI) = BMI ≥25.0 kg/m² or ≥27.0 kg/m² and ‖high central adiposity (WHR) = WHR ≥0.85 or ≥0.90 in females and males, respectively.

¶$P \leq .001$.

#$P \leq .01$.

**$P \leq .05$.

hypertension in our normoglycemic Chinese, particularly in the male subjects.

Although there is evidence to support the relationship between insulin resistance and hypertension in Caucasians, the situation in other ethnic groups is less clear. Hispanic Americans have 3 times more type 2 diabetes than in non-Hispanic whites, yet the rate of hypertension is similar.[7] Furthermore, the nondiabetic Hispanics were younger, more obese, and insulin-resistant. Pima Indians have one of the highest rates of obesity, insulin resistance, and type 2 diabetes in the world, yet they have a lower frequency of hypertension (14%) than non-Hispanic whites (22%).[7,19] Insulin levels were significantly associated with blood pressure in the whites, even after adjustment for age, sex, percentage body fat, and body weight, but not in the Pima Indians or blacks.[19] However, other studies in blacks, as well as Hispanics, have found positive associations between insulin resistance and blood pressure.[20,21]

Although 3 Japanese studies reported significant relationships between fasting hyperinsulinemia and hypertension,[16-18] findings in Chinese subjects are less clear. A positive relationship between FPI and blood pressure was reported in 2 studies on Chinese,[3,22] but in 1, much of the variance in FPI levels was attributed to obesity.[3] Furthermore, obesity contributed additionally to blood pressure in a manner independent of insulin resistance.[3] In a Chinese Mauritian population, there was a significant relationship in the females between blood pressure and both FPI and 2-hour post 75-g glucose load insulin levels.[24] However, the relationships were much weaker after adjustment for age and BMI and not found in males.[24] These findings support the current study, which only found a weak relationship in the female subjects. This was predominantly determined by obesity, particularly when the fat was centrally deposited. Some of the discrepancies between the races may be methodological regarding the assessment of insulin resistance. Clear criteria for defining insulin resistance are needed to enable direct comparisons between populations and the simplicity of FIGP is advantageous.

Mykkanen et al[14] found that insulin resistance was independently associated with DBP, but only in non-obese Caucasian subjects. Non-obese, normoglycemic Caucasian hypertensives have lower whole-body glucose disposal than their non-obese normotensive counterparts, suggesting a relationship between insulin resistance and hypertension in the non-obese.[13] Only in our low BMI and low WHR Chinese groups was there any evidence of a relationship between FIGP and blood pressure (SBP), accounting for 4% of the variance and then only before adjustment for age, gender, and adiposity. In contrast to data reported in obese Caucasians,[37] in our obese Chinese subjects, no relationship between insulin resistance and blood pressure was identified, even before adjustment (Table 2). This is despite a large proportion of the obese subjects being insulin-resistant as determined by FIGP. The high prevalence of insulin resistance in the obese subjects may result in a loss of linearity between insulin resistance and blood pressure and may explain why a weak relationship was found only in the non-obese subjects.

It is noteworthy that in the multiple regression analyses, WC was found to be the major determinant of blood pressure accounting for more than 20% of the variance. There is now increasing evidence showing the pivotal role of central adiposity in linking dyslipidemia, insulin resistance, and blood pressure, possibly mediated through the release of free fatty acids.[38,39]

Several mechanisms may contribute to increases in blood pressure resulting from increasing levels of adiposity in a manner independent of insulin resistance. Leptin, produced by adipocytes, has been reported to have sympathetic and cardiovascular actions in animal models[40] with its chronic action purported to have an overall pressor effect.[41] In addition to the proposed action of leptin, sympathetic activation associated with obesity[42] and adipocyte release of angiotensinogen[43] both promote the formation of angiotensin II and aldosterone, which have direct pressor and antinatriuretic effects.[44] Thus, there are several possible mechanisms by which obesity, independently of insulin resistance, may influence blood pressure.

In conclusion, although our data do not exclude the involvement of insulin resistance in the pathogenesis of hypertension, particularly in the female subjects, our findings emphasize the important influence of obesity. Central adiposity assessed by WC was the strongest determinant of blood pressure in this normoglycemic population.

REFERENCES

1. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

2. Chan JCN, Critchley JAJH, Tomlinson B, et al: Antihypertensive and antialbuminuric effects of Losartan potassium and felodipine in Chinese elderly hypertensive patients with or without non-insulin-dependent diabetes mellitus. Am J Nephrol 17:72-80, 1997

3. Chan JCN, Cheung JCK, Lau EMC, et al: The metabolic syndrome in Hong Kong Chinese. The interrelationships among its components analyzed by structural equation modeling. Diabetes Care 19:953-959, 1996

4. Després JP, Moorjani S, Lupien PJ, et al: Regional distribution of body fat, plasma lipoproteins and cardiovascular disease. Arteriosclerosis 10:497-511, 1990

5. Abate N: Insulin resistance and obesity. Diabetes Care 19:292-294, 1996

6. Modan M, Halkin H, Almog S, et al: Hyperinsulinaemia: A link between hypertension, obesity and glucose intolerance. J Clin Invest 75:809-817, 1985

7. Haffner SM, Mitchell BD, Valdez RA, et al: Eight-year incidence of hypertension in Mexican-Americans and non-Hispanic whites. The San Antonio Heart Study. Am J Hypertens 5:147-153, 1992

8. Saad MF, Knowler WC, Pettitt D, et al: Insulin and hypertension. Relationship to obesity and glucose intolerance in Pima Indians. Diabetes 39:1430-1435, 1990

9. Tyroler HA, Hayden S, Hames CG: Weight and hypertension: Evans County studies of blacks and whites, in Oglesby P (ed): Epidemiology and Control of Hypertension. New York, NY, Stratton Intercontinental, 1975, pp 177-201

10. MacMahon SW, Blacket RB, Macdonald GJ, et al: Obesity, alcohol consumption and blood pressure in Australian men and women: The National Heart Foundation of Australia Risk Factor Prevalence Study. J Hypertens 2:85-91, 1984

11. Carmelli D, Cardon LR, Fabitz R: Clustering of hypertension, diabetes and obesity in adult male twins: Same genes or same environments? Am J Hum Genet 55:566-573, 1994

12. Feinleib M: Genetics and familial aggregation of blood pressure, in Onesti G, Klimt C (eds): Hypertension Determinants, Complications and Intervention. New York, NY, Grune & Stratton, 1979, pp 35-48

13. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

14. Mykkanen L, Haffner SM, Ronnemaa T, et al: Relationship of plasma insulin concentration and insulin sensitivity to blood pressure. Is it modified by obesity. J Hypertens 14:399-405, 1996

15. Fontbonne A, Charles MA, Thibult N, et al: Hyperinsulinaemia as a predictor of coronary heart disease mortality in a healthy population: The Paris Prospective Study, 15 year follow-up. Diabetologia 34:356-361, 1991

16. Ohmori S, Kiyohara Y, Kato I, et al: Hyperinsulinaemia and blood pressure in a general Japanese population: The Hisayama study. J Hypertens 12:1191-1197, 1994

17. Tsuruta M, Hashimoto R, Adachi H, et al: Hyperinsulinaemia as a predictor of hypertension: An 11-year follow-up study in Japan. J Hypertens 14:483-488, 1995

18. Ogihara T, Rakugi H, Ikegami H, et al: Enhancement of insulin sensitivity by troglitazone lowers blood pressure in diabetic hypertensives. Am J Hypertens 8:316-320, 1995

19. Saad MF, Lillioja S, Nyomba BL, et al: Racial differences in the relation between blood pressure and insulin resistance. N Engl J Med 324:733-739, 1991

20. Falkner B, Hulman S, Tannenbaum J, et al: Insulin resistance and blood pressure in young Black men. Hypertension 16:706-711, 1990

21. Haffner SM, Ferrannini E, Hazuda HP, et al: Clustering of cardiovascular risk factors in confirmed prehypertensive individuals. Hypertension 20:38-45, 1992

22. Chen CH, Tsai ST, Chaung JH, et al: Population-based study of insulin, c-peptide and blood pressure in Chinese with normal glucose tolerance. Am J Cardiol 76:585-588, 1995

23. Shetterly SM, Rewers M, Hamman R, et al: Patterns and predictors of hypertension incidence among Hispanics and non-Hispanic whites: The San Luis Valley Diabetes Study. J Hypertens 12:1095-1102, 1994

24. Dowse GK, Collins VR, Alberti KGMM, et al: Insulin and blood pressure levels are not independently related in Mauritians of Asian Indian, Creole or Chinese origin. J Hypertens 11:297-307, 1993

25. Chan JCN, Cheung CK, Swaminathan R, et al: Obesity, albuminuria and hypertension among Hong Kong Chinese with non-insulin-dependent diabetes mellitus (NIDDM). Postgrad Med J 69:204-210, 1993

26. Thomas GN, Tomlinson B, Chan JCN, et al: The Trp64Arg polymorphism of the β3-adrenergic receptor gene and obesity in Chinese subjects with components of the metabolic syndrome. Int J Obesity 24:545-551, 2000

27. JNC-VI: The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. Arch Intern Med 157:2413-2446, 1997

28. Mathews DR, Hoskers JP, Rudenski AS, et al: Homeostasis model assessment of insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-419, 1985

29. Alberti KGMM: Insulin resistance: Rewards and fairies, in Baba S, Kaneko T, (eds): Diabetes 1994. Proceedings of the 15th International Diabetes Federation Congress. New York, NY, Elsevier, 1995, pp 52-61

30. Dowse GK, Qin H, Collins VR, et al: Determinants of estimated insulin resistance and beta-cell function in Indian, Creole and Chinese Mauritians. The Mauritius NCD Study Group. Diabetes Res Clin Pract 10:265-279, 1990

31. The Expert Committee on the Diagnosis and Classification of Diabetes mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus. Diabetes Care 20:1183-1197, 1997

32. Wong SP, Cockram CS, Janus ED, et al: Guide to plasma lipids and lipoproteins for Hong Kong doctors. J Hong Kong Coll Cardiol 4:81-89, 1996

33. Expert panel on detection evaluation and treatment of high blood cholesterol in adults: Summary of the second report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. JAMA 269:3015-3023, 1993

34. Freidewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

35. Haffner SM, Miettinen H, Stern MP: The homeostatic model in the San Antonio Heart Study. Diabetes Care 20:1087-1092, 1997

36. Lind L, Berne C, Lithell H: Prevalence of insulin resistance in essential hypertension. J Hypertens 13:1457-1462, 1995

37. DeFronzo RA: The effect of insulin on renal sodium metabolism: A review with clinical implications. Diabetologia 21:165-171, 1981

38. Fujimoto WY, Abbate SL, Kahn SE, et al: The visceral adiposity syndrome in Japanese-American men. Obesity Res 2:364-371, 1994

39. James RW, Brulhart-Meynet MC, Lehman T, et al: Lipoprotein distribution and composition in obesity: Their association with central adiposity. Int J Obesity 21:1115-1120, 1997

40. Mark AL, Correia M, Morgan DA, et al: Obesity-induced hypertension: New concepts from the emerging biology of obesity. Hypertension 33:537-541, 1998

41. Shek EW, Brands MW, Hall JE: Chronic leptin infusion increases arterial pressure. Hypertension 31:409-414, 1998

42. Rosenbaum M, Leibel RL, Hirsch H: Obesity. N Engl J Med 337:396-407, 1987

43. Cooper R, McFarlane-Anderson N, Bennett FI, et al: ACE, angiotensinogen and obesity: A potential pathway leading to hypertension. J Hum Hypertens 11:107-111, 1997

44. Dzau VJ, Pratt RE: Renin-angiotensin system, in Fozzard H (ed): The Heart and Cardiovascular System, vol 2. New York, NY, Raven, 1992, pp 1817-1849