Obesity is the key determinant of cardiovascular risk factors in the Hong Kong Chinese population: cross-sectional clinic-based study

ZSK Lee, JAJH Critchley, JCN Chan, PJ Anderson, GN Thomas, GTC Ko, RP Young, TYK Chan, CS Cockram, B Tomlinson

Objectives. To examine the interrelationships between obesity and various cardiovascular risk factors, and to investigate the relative importance of insulin and obesity in their associations with various pathophysiologies.
Design. Cross-sectional clinic-based study.
Setting. Medical clinics at a university teaching hospital, Shatin, Hong Kong.
Participants. A heterogeneous cohort of 767 Hong Kong Chinese subjects with a mean age of 43 (standard deviation, 14) years.
Main outcome measures. Body mass index, waist circumference, plasma insulin, insulin resistance index, fasting plasma glucose and lipid levels, blood pressure, and 24-hour urinary albumin excretion.
Results. Pathophysiological abnormalities and risk factors are frequently clustered to varying degrees. Compared with the control subjects, patients with at least one component of the metabolic syndrome were more obese, hyperinsulinaemic, insulin resistant, hyperglycaemic, hypertensive, dyslipidaemic, and albuminuric (all variables, $P<0.001$). Increasing degrees of body mass index, waist circumference, plasma insulin level, and insulin resistance index were associated with an increasing number of risk factors after adjusting for age and sex (all variables, $P <0.02$). Multiple regression analysis showed that obesity, as reflected by either the body mass index or waist circumference, had a closer association than plasma insulin with the fasting plasma glucose concentration, blood pressure, and high-density lipoprotein–cholesterol and triglyceride concentrations. Using 19.0-20.9 kg/m^2 as the reference body mass index interval, the lowest cardiovascular risk was associated with a body mass index of <23.0 kg/m^2. There was an increased risk of 3.1 and 5 times when the body mass index was 23.0-24.9 kg/m^2 and ≥25 kg/m^2, respectively.
Conclusions. Obesity, hyperinsulinaemia, and insulin resistance are characteristic features of Hong Kong Chinese patients who have various components of the metabolic syndrome. Obesity has a greater effect than plasma insulin on the various associated pathophysiologies.

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Key words: Cardiovascular diseases; Hong Kong; Insulin resistance; Obesity; Risk factors; Syndrome

Divisions of Clinical Pharmacology and Endocrinology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
ZSK Lee, BSc, PhD
JAJH Critchley, PhD, FRCP
JCN Chan, MD, FRCP
PJ Anderson, MPhil, PhD
GN Thomas, MPhil, PhD
RP Young, DPhil, MRCP
TYK Chan, MB, ChB, FRCP
CS Cockram, MD, FRCP
B Tomlinson, MD, FRCP
Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, 11 Chuen On Road, Tai Po, Hong Kong
GTC Ko, MB, ChB, MRCPI

Correspondence to: Prof JAJH Critchley

Introduction

In light of its close association with various health-threatening diseases[1] and rising prevalence throughout the world,[2] obesity has recently been classified as a global epidemic disease.[3] In addition, obesity has been grouped with other cardiovascular risk factors such as diabetes, hypertension, and dyslipidaemia under the term 'metabolic syndrome'. The syndrome is characterised by various pathophysiologies such as hyperinsulinaemia, insulin resistance, hyperglycaemia, high blood pressure, abnormal lipid profiles,[4] and albuminuria.[5]

Based on the diverse effects of insulin, the 'insulin hypothesis' emphasises the importance of insulin resistance and hyperinsulinaemia in a multifaceted causal chain that leads to the various components of the metabolic syndrome.[4,6] Insulin resistance has been demonstrated in Caucasian patients with glucose intolerance or type 2 diabetes mellitus,[7] hypertension,[8,9] and dyslipidaemia.[10] Apart from promoting glucose storage or utilisation, insulin also inhibits lipolysis and promotes lipogenesis. Resistance to the antilipolytic action of insulin can lead to an elevated concentration of free fatty acids in the blood, which in turn promotes gluconeogenesis, reduces glucose uptake because free fatty acids compete with glucose for oxidation,[11] decreases insulin clearance, and further increases insulin resistance.[12] These processes are compensated for progressively by an increase in insulin secretion, thereby leading to hyperinsulinaemia, which in turn downregulates the insulin receptors.[13] The subsequent hyperinsulinaemia may increase the blood pressure by enhancing the activity of the sympathetic nervous system, renal tubular sodium reabsorption, and vascular smooth muscle cellular hypertrophy, as well as by modulating transcellular cation transport.[14] Insulin resistance can also result in decreased activity of lipoprotein lipase and increased activity of triglyceride hydrolase[15] and cholesteryl ester transfer protein,[16] thereby elevating triglyceride levels and reducing high-density lipoprotein (HDL)–cholesterol levels. The combination of these events will set up a vicious cycle of increasing hyperinsulinaemia, insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia.[4] In the presence of severe insulin resistance, even a slight relative insulin deficiency will fail to maintain the hyperinsulinaemic state and will lead to a loss of blood glucose control and hence diabetes mellitus.[4]

Despite the close associations of plasma insulin with blood pressure,[8,9] hypertriglyceridaemia, and decreased HDL-cholesterol levels,[17] these relationships are considerably weakened or become insignificant after adjusting for obesity.[18] In the 1940s, Jean Vague indicated the importance of body fat distribution in cardiovascular morbidity.[19] Numerous studies have also confirmed the close relationships of visceral fat mass with cardiovascular related risk factors[20] and death.[21] There is now an array of studies confirming that central (visceral) obesity has relatively greater adverse effects than peripheral fat accumulation. In fact, visceral obesity is now considered an important component of the metabolic syndrome,[22] and it may play a key role in the induction of insulin resistance in patients who exhibit features of the metabolic syndrome.[23]

There are increasing trends of obesity in most parts of the world,[24] although data in Hong Kong remain relatively scarce. Two large-scale population-based studies, which used different sampling methods, have shown the prevalence of being overweight (body mass index [BMI] $\geq$25 kg/m^2) to have increased from 28% to 38% in men and from 28% to 34% in women during the period 1990 to 1997.[25-28] Although these figures are not directly comparable, they are in keeping with the rising trend of childhood obesity (>120% of mean body weight adjusted for body height), which has been reported to range from 10% to 15%.[29] Besides, an epidemic proportion of at least 10% prevalence of diabetes mellitus, hypertension, and adverse lipid profiles had been reported in the survey of 1995.[27] Using data collected from 1513 Hong Kong Chinese subjects in the 1990 survey, the BMI was found to be one of the predictors for glucose intolerance.[25] Obesity, as assessed by measuring the BMI or waist to hip ratio, also explained most of the variance of the various components of the metabolic syndrome, including blood pressure, plasma glucose, triglycerides, insulin, and to a lesser extent microalbuminuria.[26,30] The close relationships between visceral fat mass, as measured by magnetic resonance imaging, and various cardiovascular risk factors have also been confirmed in patients with type 2 diabetes mellitus.[31] Furthermore, we have recently shown that central obesity is associated with endocrine perturbations such as hypercortisolaemia and reduced growth hormone levels in young Chinese patients with type 2 diabetes mellitus.[32] These hormonal changes are compatible with a sedentary lifestyle and a high level of psychosocial stress.[32]

In this study, we examined the relationships between obesity, various pathophysiologies, and cardiovascular risk factors in a heterogeneous cohort of 767 Hong Kong Chinese individuals who were aged between 18 and 60 years. We also investigated the relative importance of insulin and obesity in their associations with various pathophysiologies by using stepwise multiple regression analyses. Furthermore, the degrees of odds ratios associated with risk factors across different categories of BMI were estimated.

Methods

Participants

The study cohort, recruited from 1995 through 1997, consisted of 767 Hong Kong Chinese individuals whose mean age was 42 years (standard deviation [SD], 13 years). Four hundred and sixty-six (60.9%) of the participants had type 2 diabetes and/or hypertension

and/or dyslipidaemia and/or albuminuria. These patients were selected at random from the medical out-patient clinics at the Prince of Wales Hospital (PWH) on the basis of having one or more features of the metabolic syndrome. They were classified as being diabetic, hypertensive, or dyslipidaemic. The other 301 (39.1%) participants were healthy volunteers—most were hospital staff or friends who did not have clinical evidence of diabetes, hypertension, dyslipidaemia, or a history of a major illness. All participants had normal renal function (plasma creatinine, <150 μmol/L) and were studied following an overnight fast, at the Clinical Pharmacology Studies Unit of the PWH. The hypertensive or dyslipidaemic patients had been free of medication for at least 4 weeks before the study. None of the diabetic patients received insulin treatment or lipid-lowering drugs, and their treatments were omitted on the morning of the study day. The study was approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong. All participants gave informed oral and written consent.

Height, weight, waist circumference (the minimum circumference between the umbilicus and xiphoid process), and hip circumference (the maximum circumference around the buttocks and symphysis pubis) were recorded. The BMI (in kg/m^2) was calculated as weight divided by the square of the height and was used as an index of general obesity. The waist circumference and waist to hip ratio were used as the indices of central obesity. The blood pressure was taken as the mean of three readings separated by a 1-minute interval by using a Dinamap 8100 automated blood pressure monitor (Critikon Inc., Florida, United States) after the individual had been in the sitting position for at least 5 minutes. Venous blood was sampled for routine investigations, which included the fasting plasma glucose level, serum lipid (total cholesterol, HDL-cholesterol, and triglyceride) concentrations, and plasma creatinine level. A 24-hour urine sample was collected, using boric acid as a preservative, to measure the urinary albumin excretion rate.[33] These routine assays were performed in the Department of Chemical Pathology at the PWH as previously described.[34] The plasma insulin level was measured by using a commercially available enzyme-linked immunosorbent assay (DAKO Diagnostics Ltd., Glostrup, Denmark).

Definitions

The four cardiovascular risk factors were defined as type 2 diabetes mellitus, hypertension, dyslipidaemia, and increased albuminuria (microlbuminuria or macroalbuminuria). Type 2 diabetes mellitus was defined as a fasting plasma glucose concentration of ≥7.8 mmol/L and/or 2-hour post–glucose loading plasma glucose concentration of ≥11.1 mmol/L using the 1985 World Health Organization (WHO) criteria.[35] Patients were considered to be hypertensive if they were taking antihypertensive drugs or had a blood pressure of ≥140/90 mm Hg, as stipulated in the criteria of the Joint National Committee.[36] Patients who had an increased cholesterol concentration (total cholesterol, >6.2 mmol/L or low-density lipoprotein [LDL]-cholesterol, >4.1 mmol/L) or a triglyceride concentration of >2.3 mmol/L, or a total cholesterol/HDL-cholesterol ratio of >5 were classified as being dyslipidaemic.[37,38] Control subjects were defined as those having a blood pressure of <120/80 mm Hg,[36] and the following values: fasting plasma glucose, ≤6.1 mmol/L[37]; total cholesterol, <5.2 mmol/L; LDL-cholesterol, <3.4 mmol/L; triglyceride, <2.0 mmol/L; and HDL-cholesterol >1.2 mmol/L for women and >1.0 mmol/L for men.[37] Albuminuria was defined as a urinary albumin excretion rate of ≥30 mg/d.[39]

Overweight was defined as a BMI of ≥25 kg/m^2, whereas central obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women.[3,40] Insulin resistance was expressed as the product of the fasting plasma insulin concentration (in pmol/L) and glucose concentration (in mmol/L) divided by 22.5. The resulting figure was equivalent to that derived from the homeostasis model assessment equation.[41]

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 9.0; SPSS Inc., Chicago, United States). All P values were two-tailed. The insulin resistance index, concentrations of plasma insulin and serum triglycerides, and urinary albumin excretion rate were logarithmically transformed because of skewed distributions. Data were expressed as mean (SD) or geometric mean (antilog SD), as appropriate. The Chi squared test and unpaired Student's *t* test were used to compare the metabolic variables between the two groups. The analysis of covariance (ANCOVA) was used to compare groups after adjusting for confounding factors such as age and sex. The polynomial analysis of variance (ANOVA), ANCOVA, and the Chi squared test for trend were used to determine the significance of trends across ascending BMI categories (<19.0, 19.0-20.9, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-28.9, and >28.9 kg/m^2). Ninety-five percent confidence intervals (CIs) were calculated for the odds ratios using logistic regression models with or without adjustment for age and sex. In all analyses, the

category of 19.0-20.9 kg/m^2 instead of <19.0 kg/m^2 was used as the reference interval. The latter value was not chosen because it was far below the recommended BMI range stated in the current WHO guidelines[3] and might be associated with excess risks due to cigarette smoking, malnutrition, or subclinical disease,[42] which were not assessed in this study. To test for a linear trend across BMI categories, the seven BMI categories were entered as an ordinal variable in the logistic regression models.

Results

Clinical characteristics

The clinical and biochemical characteristics of the 767 study participants are shown in Table 1. Men were heavier and had a higher waist circumference, waist to hip ratio, serum triglyceride concentration, systolic and diastolic blood pressures, as well as a lower HDL-cholesterol level than women (all variables P<0.01). A total of 466 (60.9%) participants were identified as having at least one feature of the metabolic syndrome (type 2 diabetes mellitus, hypertension, or dyslipidaemia) [Fig 1]. Approximately 38% (89/232) of diabetic patients were hypertensive, whereas dyslipidaemia was detected in 40% (93/232) of diabetic patients and 45% (106/235) of hypertensive patients. Approximately 10% (48/466) of the participants with at least one feature of the metabolic syndrome had diabetes, hypertension, and dyslipidaemia concomitantly. In addition, approximately 51% (236/466), 33% (153/466), and 20% (88/446) of patients had general obesity, central obesity, or albuminuria, respectively.

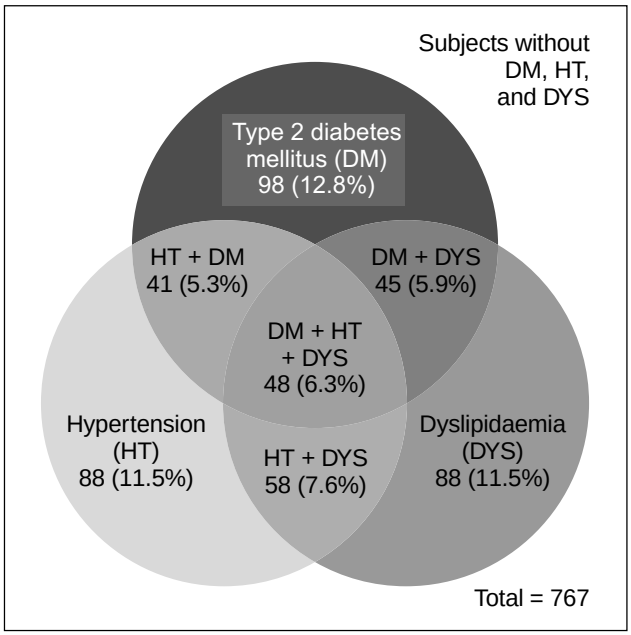

Fig 1. Venn diagram of the characteristics of the study participants

Comparisons between control subjects and patients

The mean BMI of the whole study population was 24.4 kg/m^2 (range, 14.2-38.3 kg/m^2). Patients who had at least one component of the metabolic syndrome had a mean BMI of 26.2 (SD, 4.1) kg/m^2, which was significantly different from that of the control subjects—that is, 20.8 (2.2) kg/m^2 (P<0.001). These patients also had a higher waist circumference of 84 (11) cm when compared with 68 (6) cm in the control subjects (P<0.001).

Table 2 shows various metabolic indices and pathophysiologies of the 104 control subjects and the

Table 1. Clinical and biochemical characteristics of the study population

	Characteristics*		
	Total, n=767	Male, n=297	Female, n=470
Age (years)	43 (14)	42 (14)	44 (13)
Height (m)	1.59 (0.08)	1.67 (0.06)	1.54 (0.06)‖
Weight (kg)	61.8 (12.0)	67.6 (12.0)	58.1 (10.4)‖
Body mass index (kg/m^2)	24.4 (4.1)	24.4 (4.1)	24.4 (4.1)
Waist circumference (cm)	81 (12)	84 (10)	79 (12)‖
Waist to hip ratio	0.84 (0.09)	0.87 (0.07)	0.82 (0.11)‖
Fasting glucose (mmol/L)	6.2 (2.6)	6.4 (3.2)	6.1 (2.2)
Plasma insulin (pmol/L)†	45.7 (2.0)	45.6 (2.0)	45.7 (1.9)
Insulin resistance†	12.0 (2.3)	12.2 (2.3)	11.9 (2.2)
Total cholesterol (mmol/L)	5.3 (1.4)	5.2 (1.2)	5.3 (1.4)
LDL‡-cholesterol (mmol/L)	3.3 (1.2)	3.3 (1.0)	3.3 (1.2)
HDL§-cholesterol (mmol/L)	1.3 (0.3)	1.2 (0.3)	1.4 (0.3)‖
Triglyceride (mmol/L)†	1.1 (2.0)	1.2 (2.0)	1.1 (2.0)¶
Systolic blood pressure (mm Hg)	126 (22)	128 (19)	125 (23)¶
Diastolic blood pressure (mm Hg)	75 (15)	78 (14)	73 (15)‖
Plasma creatinine (μmol/L)	70 (22)	84 (20)	61 (18)‖
24-hour urinary albumin (mg/d)†	11.9 (3.4)	12.2 (3.2)	11.7 (3.5)

* Data are expressed as the mean (SD) except where indicated
† Geometric mean (antilog SD)
‡ LDL low-density lipoprotein
§ HDL high-density lipoprotein
‖ P<0.001, unpaired Student's *t* test
¶ P<0.001, unpaired Student's *t* test

Table 2. Comparisons of metabolic indices and pathophysiologies between control subjects and patients*

	Control subjects, n=104	Patients with: Only type 2 diabetes mellitus, n=98	Only hypertension, n=88	Only dyslipidaemia, n=88
Age (years)	32 (9)	32 (7)	45 (10)‖	43 (10)‖
Sex ratio (M:F)	39:61	42:58	38:62	48:52
Height (m)	1.61 (0.09)	1.61 (0.07)	1.57 (0.08)	1.60 (0.09)
Weight (kg)	54.2 (7.9)	66.0 (14.1)‖	65.0 (13.5)‖	63.5 (11.5)‖
Body mass index (kg/m^2)	20.8 (2.2)	25.4 (4.7)‖	26.3 (4.4)‖	24.7 (3.3)‖
Waist circumference (cm)	68 (6)	82 (11)‖	84 (10)‖	81 (10)‖
Waist to hip ratio	0.76 (0.05)	0.84 (0.06)‖	0.85 (0.08)‖	0.84 (0.07)‖
Fasting glucose (mmol/L)	4.8 (0.4)	7.8 (3.3)‖	5.2 (0.6)‖	5.2 (0.6)‖
Plasma insulin (pmol/L)†	32.3 (1.8)	58.7 (2.4)‖	44.1 (1.8)‖	48.2 (1.9)‖
Insulin resistance†	6.9 (1.8)	20.0 (2.7)‖	10.5 (1.9)‖	11.3 (2.0)‖
Total cholesterol (mmol/L)	4.2 (0.5)	4.6 (0.7)‖	4.9 (0.6)‖	6.7 (1.4)‖
LDL‡-cholesterol (mmol/L)	2.4 (0.5)	2.8 (0.6)‖	3.1 (0.6)‖	4.7 (1.4)‖
HDL§-cholesterol (mmol/L)	1.5 (0.3)	1.2 (0.3)‖	1.3 (0.3)‖	1.2 (0.4)‖
Triglyceride (mmol/L)†	0.6 (1.5)	1.1 (1.5)‖	1.0 (1.5)‖	1.5 (1.9)‖
Systolic blood pressure (mm Hg)	109 (7)	110 (10)	151 (13)‖	118 (12)‖
Diastolic blood pressure (mm Hg)	61 (7)	69 (7)‖	93 (15)‖	71 (10)‖
Plasma creatinine (μmol/L)	67 (16)	64 (15)	69 (19)	70 (15)
24-hour urinary albumin (mg/d)†	6.9 (1.9)	17.5 (3.9)‖	14.3 (3.2)‖	10.9 (2.5)‖

* Data are expressed as the mean (SD) except where indicated
† Geometric mean (antilog SD)
‡ LDL low-density lipoprotein
§ HDL high-density lipoprotein
‖ P<0.001, when comparing controls with patients; unpaired Student's *t* test

following patient cohorts: those with only type 2 diabetes mellitus (n=98), only hypertension (n=88), and only dyslipidaemia (n=88). In general, all patient cohorts were significantly heavier and more obese than the controls. In addition, they had a higher fasting plasma glucose concentration, insulin concentration, and insulin resistance index; a more unfavourable lipid profile; higher blood pressures; and a higher urinary albumin excretion rate than did the controls. Despite the age differences between the control and patient cohorts, the results remained significant following ANCOVA with adjustment for age (all variables, P<0.001).

Comparisons between patients with increasing numbers of cardiovascular risk factors

The effects of various cardiovascular risk factors in patients with type 2 diabetes mellitus (n=232), hypertension (n=235), and dyslipidaemia (n=239) were investigated by comparing the characteristics of patients who had no other risk factor with those who had an increasing number of other risk factors (Table 3). The potential risk factors for diabetic patients included hypertension, dyslipidaemia, and albuminuria; those for hypertensive patients included diabetes, dyslipidaemia, and albuminuria; and those for dyslipidaemic patients included diabetes, hypertension, and albuminuria. In general, patients who had the greater number of other risk factors were more obese (both general and central obesity), and had higher plasma insulin levels and higher insulin resistance indices after adjusting for age and sex (all variables, P<0.02; Table 3).

Relationships between obesity, insulin resistance, and various pathophysiologies

After excluding diabetic patients who were receiving treatment, because of the possible influence of medications on the blood glucose level or insulin resistance, multiple regression analysis was performed using age, sex (male=0, female=1), BMI, waist circumference, and plasma insulin concentration as the independent variables. Analysis showed that obesity had closer relationships with various pathophysiologies than it had with the plasma insulin concentration (Table 4). The fasting plasma glucose concentration was positively associated with age, plasma insulin concentration, and waist circumference. Blood pressures correlated with increasing age and waist circumference, and were higher in males than in females. Both total cholesterol and LDL-cholesterol concentrations were associated with age and waist circumference. The HDL-cholesterol concentration correlated negatively with male sex, plasma insulin level, and BMI. Serum triglyceride concentrations were positively associated with age, male sex, plasma insulin level, and waist circumference.

Odds ratios of cardiovascular risk factors

The odds ratios of at least one cardiovascular risk factor according to different BMI categories (<19.0,

Table 3. Clinical and biochemical characteristics of (a) type 2 diabetic, (b) hypertensive, and (c) dyslipidaemic patients with different numbers of other cardiovascular risk factors*

	No other risk factor	One other risk factor	Two or more other risk factors	Polynomial ANOVA† P for trend	Polynomial ANCOVA‡ P for trend
(3a) Type 2 diabetes mellitus (other cardiovascular risk factors defined as hypertension, dyslipidaemia, and albuminuria)					
n	98	85	49	-	-
Age (years)	32 (7)	50 (15)	52 (15)	<0.001	-
Sex ratio (M:F)§	42:58	46:54	33:67	-	-
Body mass index (kg/m^2)	25.4 (4.7)	25.5 (4.5)	27.2 (3.6)	<0.001	<0.001
Waist circumference (cm)	82 (11)	87 (15)	89 (7)	<0.001	<0.001
Waist to hip ratio	0.84 (0.06)	0.89 (0.15)	0.90 (0.06)	<0.001	<0.005
Plasma insulin (pmol/L)‖	58.7 (2.4)	53.6 (2.1)	74.0 (1.9)	<0.002	<0.001
Insulin resistance index‖	20.0 (2.7)	20.9 (2.1)	29.1 (1.9)	<0.001	<0.005
(3b) Hypertension (other cardiovascular risk factors defined as type 2 diabetes mellitus, dyslipidaemia, and albuminuria)					
n	88	100	47	-	-
Age (years)	45 (10)	51 (11)	55 (13)	<0.001	-
Sex ratio (M:F)§	38:62	46:54	32:68	-	-
Body mass index (kg/m^2)	26.3 (4.4)	26.0 (4.2)	26.6 (3.2)	ns	<0.02
Waist circumference (cm)	84 (10)	88 (13)	89 (8)	<0.002	<0.001
Waist to hip ratio	0.85 (0.08)	0.90 (0.15)	0.91 (0.07)	<0.002	<0.01
Plasma insulin (pmol/L)‖	44.1 (1.8)	49.0 (1.8)	73.1 (1.9)	<0.001	<0.001
Insulin resistance index‖	10.5 (1.9)	13.9 (1.9)	27.2 (2.0)	<0.001	<0.001
(3c) Dyslipidaemia (other cardiovascular risk factors defined as type 2 diabetes mellitus, hypertension, and albuminuria)					
n	88	97	54	-	-
Age (years)	43 (10)	48 (12)	51 (14)	<0.001	-
Sex ratio (M:F)§	48:52	60:40	32:68	-	-
Body mass index (kg/m^2)	24.7 (3.3)	25.4 (4.3)	27.4 (3.5)	<0.001	<0.001
Waist circumference (cm)	81 (10)	86 (10)	89 (8)	<0.001	<0.001
Waist to hip ratio	0.84 (0.07)	0.88 (0.07)	0.90 (0.07)	<0.001	<0.001
Plasma insulin (pmol/L)‖	48.2 (1.9)	55.5 (2.0)	74.4 (1.9)	<0.001	<0.001
Insulin resistance index‖	11.3 (2.0)	17.7 (2.2)	27.4 (2.0)	<0.001	<0.001

* Data are expressed as the mean (SD) except where indicated
† ANOVA analysis of variance
‡ ANCOVA analysis of covariance; age- and sex-adjusted
‖ Geometric mean (antilog SD)
§ Chi squared test used
ns not significant

19.0-20.9, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-28.9, and >28.9 kg/m^2), using the second group as the reference interval (odds ratio = 1.0) is shown in Figure 2. There was an increasing trend of odds ratios across the increasing intervals of BMI values (P<0.001). Subjects with a BMI of <23.0 kg/m^2 had the lowest risk whereas those in the BMI categories of 23.0-24.9, 25.0-26.9, 27.0-28.9, and >28.9 kg/m^2 had a significantly higher odds ratio risk of 3.1 (95% confidence interval, 1.7-5.4), 5.0 (2.7-9.1), 8.4 (4.1-16.9) and 17.8 (8.1-39.2) times, respectively. The rising trend remained significant after adjusting for age and sex (P<0.001).

Discussion

Frequent clustering of cardiovascular risk factors

Since type 2 diabetes mellitus, hypertension, and dyslipidaemia occur frequently in the general population, it is not surprising that any given individual might manifest two or more of these disorders. In agreement with data from a study of Caucasian populations,[8] this study found overlapping patterns of cardiovascular risk factors in Hong Kong Chinese patients. Approximately 58% of the diabetic patients were also hypertensive and/or dyslipidaemic; 45% of the hypertensive patients were dyslipidaemic; and 10% of the patients had diabetes mellitus, hypertension, and dyslipidaemia concomitantly. These findings are consistent with the results of previous studies performed in Hong Kong.[43] Chan et al[43] reported that about half of the type 2 diabetic patients attending a hospital clinic were hypertensive (49%) or albuminuric (47%). Furthermore, there were intimate relationships between these cardiovascular risk factors, insulin resistance, and dyslipidaemia.[34] Drug utilisation surveys that had been conducted in public hospital medical clinics have also shown a high prevalence of hypertension and albuminuria: more than 50% of patients receiving antidiabetic treatment were also receiving antihypertensive drugs.[44,45] Similarly, the clustering of these risk factors have been observed in population-based surveys performed in 1990[25,26] and 1995.[27]

We have previously confirmed in young patients with type 2 diabetes mellitus the high prevalence of

Table 4. Standardised regression coefficients for the relationships between age, sex, obesity, plasma insulin, and various pathophysiologies*

	Fasting glucose	Systolic blood pressure	Diastolic blood pressure	Total cholesterol	LDL†-cholesterol	HDL‡-cholesterol	Triglyceride
R^2	0.16	0.34	0.32	0.15	0.14	0.12	0.30
F test	25.8§	99.8§	61.1§	36.1§	33.3§	32.2§	42.9§
Independent variables							
Age	0.24§a	0.26§	0.25§	0.33§a	0.30§a	ns	0.20§
Sex (M=0, F=1)	ns	ns	-0.12§	ns	ns	0.21§	-0.11¶
Body mass index	ns	ns	ns	ns	ns	-0.23§a	ns
Waist circumference	0.18§	0.45§a	0.39§a	0.14‖	0.16§	ns	0.31§a
Plasma insulin	0.16‖	ns	ns	ns	ns	-0.19§	0.21§

* Patients who were receiving treatment for type 2 diabetes mellitus were excluded from analysis
† LDL low-density lipoprotein
‡ HDL high-density lipoprotein
§ P<0.001
‖ P<0.01
¶ P<0.05
a The first independent variable entered into the equation using stepwise multiple regression analysis
ns not significant

obesity and its close association with hyperinsulinaemia.[32] In this study, the majority of patients with hypertension and dyslipidaemia were also obese, hyperinsulinaemic, and insulin-resistant. Furthermore, with an increasing number of risk factors, there were increasing degrees of hyperinsulinaemia, obesity (in the form of either general or central adiposity), and insulin resistance. The frequent occurrence of these risk factors in the same individual is probably more than a chance association, although the nature of the common linking factor requires further elucidation.

Relationships between insulin, obesity, and cardiovascular risk factors

In view of the controversial roles of insulin in the development of hypertension and dyslipidaemia,[18,46] stepwise multiple regression analysis was used to identify the most significant determinant of risk

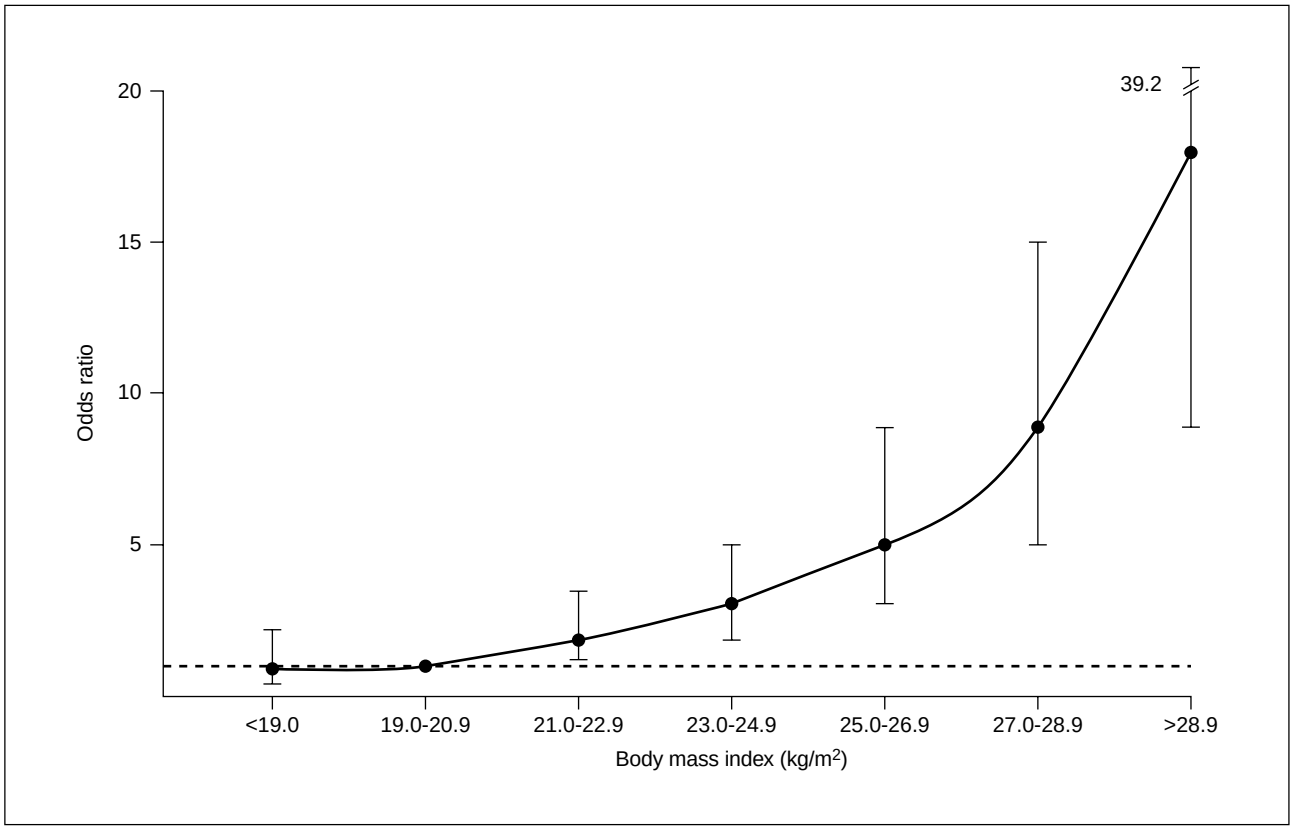

Fig 2. Odds ratios of the occurrence of at least one cardiovascular risk factor (type 2 diabetes mellitus, hypertension, dyslipidaemia, or albuminuria)
The bars represent 95% confidence intervals; in all cases, the body mass index reference interval was 19.0-20.9 kg/m²; P for trend <0.001

factors in this study. The results showed that the fasting plasma glucose concentration was independently associated with increased plasma insulin levels and central obesity. Obesity has been consistently reported to be a major predictor of type 2 diabetes mellitus.[47] In concordance with other studies,[18] there was no significant relationship between blood pressures and the plasma insulin concentration when the confounding effects of obesity were controlled. The relationship between the plasma insulin concentration and an adverse lipid profile, however, remained after adjusting for obesity. These findings suggest that insulin resistance, hyperinsulinaemia, and obesity can all contribute to the development of the various components of the metabolic syndrome.

Overall analyses showed that obesity (in particular, the central form) was a more important correlate with various pathophysiologies than plasma insulin levels. It has been well established that insulin resistance correlates with obesity.[48] Longitudinal studies have also shown that weight loss is associated with a reduction in plasma insulin levels.[49] Using the euglycaemic insulin clamp technique, it has been shown that tissue sensitivity to insulin declines by approximately 30% to 40% when there is an increase of 35% to 40% over the ideal body weight.[50] The causal relationships between obesity and hyperinsulinaemia, however, remain unclear. Some studies have shown that insulin resistance increases when a non-diabetic individual consumes excessive calories and gains weight. Consequently, insulin secretion increases to offset the insulin resistance.[23] Animal and human studies have shown that loss of appetite regulation can lead to chronic overfeeding[51] and can result in the hypersecretion of insulin.[52] Based on these findings, it can be argued that insulin resistance and its compensatory hyperinsulinaemia might be a consequence of obesity.

It has been shown that central obesity is more closely associated with insulin resistance than is general obesity.[53] This effect may be because of certain unique metabolic features of visceral fat. The proximity of this adipose tissue to the portal circulation enhances its responsiveness to the activities of lipolytic hormones, as compared with fat cells in the gluteal region.[54] Consequently, high concentrations of free fatty acids are produced in the portal circulation, which in turn can inhibit the hepatic clearance of insulin. These events will lead to hyperinsulinaemia, insulin resistance, and ultimately diabetes mellitus, hypertension, and dyslipidaemia.[4] In this study, most of the variance in various pathophysiologies was explained by waist circumference, thus suggesting that this type of body fat distribution is particularly relevant in the development of the metabolic syndrome.

Odds ratio of cardiovascular risk factors associated with the body mass index

The BMI is the most common anthropometric index that is used to assess overweight or obesity.[2,3] Using the criterion of a BMI of ≥25 kg/m^2 to define overweight,[3] more than 50% of Europeans are considered to be overweight.[55] This contrasts with the 30% prevalence of being overweight in the Hong Kong Chinese population, as reported in 1997.[27] In our study, the mean BMI of the control subjects was approximately 21 kg/m^2, whereas that of the patients (with diabetes mellitus, hypertension, dyslipidaemia, and/or albuminuria) was approximately 26 kg/m^2. The latter figure is lower than the BMI that has been reported for Caucasian patients (>28 kg/m^2)[56] but almost corresponds to the average BMI values of Caucasian general populations.[2] Due to these differences in the prevalence of obesity and BMI distribution, the Chinese population is often considered as a non-obese one. Nevertheless, the direct relationships between obesity, various pathophysiologies, and cardiovascular risk factors hold true in this relatively lean population, as demonstrated in this study and in those of other local investigators.[26]

The World Health Organization's criteria of obesity and its relevance to the Hong Kong Chinese population

In keeping with the WHO-recommended arbitrary cut-off BMI value for being overweight,[3] our study showed that a BMI of ≥25 kg/m^2 was significantly associated with greatly increased risks of type 2 diabetes mellitus, hypertension, dyslipidaemia, and/or albuminuria. Although the WHO classification has included a BMI range of 23.0 to 24.9 kg/m^2 in the recommended normal range of values that are associated with minimum risks, this BMI category was associated with a three-fold increase in odds ratio compared with the reference group (19-21 kg/m^2) in our study. These results are similar to those reported in Japan, where a health risk was clearly apparent when the BMI was 23 kg/m^2; above this value the risk increased—especially when the BMI exceeded 25 kg/m^2.[57] A lower BMI value should thus be used for the Chinese population to estimate the prevalence of obesity and to identify the high-risk groups. Interestingly, despite the aforementioned WHO recommendations[3] regarding a BMI of 23 to 24.9 kg/m^2, several reports show that even in Caucasian populations, a BMI of more than 22 to 23 kg/m^2 is associated with adverse health risks and increased mortality.[58,59]

Maladaptation to westernised lifestyles

Obesity appears to be a result of a long-term positive energy balance. The effect of a westernised lifestyle and high personal affluence on the development of obesity is clearly demonstrated by the marked variations in the prevalence of diabetes mellitus. The prevalence is less than 1% in some rural areas in mainland China,[60] between 6% and 12% in affluent societies such as Hong Kong[25,26] and Singapore,[60] and 16% in a small inbred Chinese population living in Mauritius.[61] It has been widely accepted that the availability of excess food, particularly an energy-concentrated high-fat diet, results in 'passive consumption' because of its weak satiating capacity.[61] Sedentary lifestyles that are characterised by, for example, the increased use of motor vehicles, motorised lifts and escalators, remote control devices, and mobile telephones are now dominant features of modern living.[62] In a recent local survey, 50% of the respondents were taking more than the recommended dietary fat intake (defined as <30%) and more than 50% were considered to be physically inactive.[27] Furthermore, the highly urbanised and overcrowded living conditions, the low emphasis on regular sports activities for children, the high frequencies of eating out, and the high levels of psychosocial stress due to the high demands for performance and productivity further increase the risk of Hong Kong people developing obesity and insulin resistance.

Given the lipogenic effects of insulin, the development of insulin resistance has been proposed to represent a physiological adaptation to decrease the storage of excess fuel and thus limit further weight gain through the decreased uptake and storage of glucose by skeletal muscle, and through the decreased storage of triglycerides in adipose tissue.[54] The consequent increase in the level of insulin may be accompanied by increased activities of the sympathetic nervous system, which may promote lipolysis and increased energy expenditure.[54] The toxic effects of high concentrations of glucose and free fatty acids in the blood and the pluripotent effects of persistently elevated levels of plasma insulin may all contribute to the subsequent development of the metabolic syndrome (or components thereof) as discussed previously.[4]

Conclusion

Obesity—in particular, central adiposity—insulin resistance, and hyperinsulinaemia are characteristic features of Hong Kong Chinese patients who have various components of the metabolic syndrome. Furthermore, obesity has a closer association with the clustering of cardiovascular risk factors (including hyperglycaemia, high blood pressure, and adverse lipid profiles) than it has with the plasma insulin concentration.

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