Urinary Epinephrine and Norepinephrine Interrelations With Obesity, Insulin, and the Metabolic Syndrome in Hong Kong Chinese

Zoe S.K. Lee, Julian A.J.H. Critchley, Brian Tomlinson, Robert P. Young, G. Neil Thomas, Clive S. Cockram, Thomas Y.K. Chan, and Juliana C.N. Chan

The metabolic syndrome is characterized by a clustering of cardiovascular risk factors including type 2 diabetes mellitus, hypertension, dyslipidemia, and obesity. Elevated plasma insulin and urinary norepinephrine (noradrenaline) and reduced urinary epinephrine (adrenaline) excretion are associated with obesity in Caucasian populations. We examined the interrelationships between obesity, plasma insulin, and urinary catecholamine excretion in Chinese subjects with various components of the metabolic syndrome. A total of 577 Chinese subjects (aged 38 ± 10 years; 68% with type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, and/or albuminuria and 32% healthy subjects) were studied, all of whom had a plasma creatinine less than 150 μmol/L. The blood pressure, height, weight, waist and hip circumference, and fasting plasma glucose, insulin, lipid, and creatinine levels were measured. A 24-hour urine sample was collected for measurement of albumin and catecholamine excretion. The body mass index (BMI) and waist circumference were used as measures of general and central obesity, respectively. The insulin resistance index was estimated by the calculated product of fasting plasma insulin and glucose concentrations. Patients with an increasing number of components of the metabolic syndrome (type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, and/or albuminuria) were more obese, hyperglycemic, dyslipidemic, and albuminuric and had higher blood pressure, plasma insulin, insulin resistance indices, and 24-hour urinary norepinephrine excretion but lower urinary epinephrine output (all $P < .005$). Increasing quintiles of BMI in the whole population or waist circumference in both sexes were associated with increasing trends for adverse lipid profiles, plasma insulin, insulin resistance indices, and urinary norepinephrine excretion but a decreasing trend for urinary epinephrine output (all $P < .001$). There were close associations between age, obesity, blood pressure, fasting plasma glucose, lipid, insulin, insulin resistance indices, and urinary catecholamine excretion. Using stepwise multiple regression analysis (all $P < .001$), 34% of the variability of the BMI and 45% of that of the waist circumference were independently related to gender (waist higher in males and BMI higher in females), increased plasma insulin, triglyceride, and urinary norepinephrine excretion, and decreased high-density lipoprotein (HDL) cholesterol and urinary epinephrine output. In Chinese subjects with different manifestations of the metabolic syndrome, hyperinsulinemia, insulin resistance, elevated norepinephrine, and reduced epinephrine excretion were closely associated with general and central obesity. Based on these findings, we postulate that complex interactions between the insulin and sympathoadrenal systems may lead to the development of obesity and the metabolic syndrome.

THE METABOLIC SYNDROME is characterized by a clustering of cardiovascular risk factors including obesity (general or central), type 2 diabetes mellitus, hypertension, albuminuria, and dyslipidemia. The latter is specifically characterized by reduced high-density lipoprotein (HDL) cholesterol and elevated triglyceride.[1] Hyperinsulinemia enhances fat deposition by inhibiting lipolysis and enhancing lipogenesis.[2] It can also increase blood pressure by activating the sympathetic nervous system, promoting sodium retention and stimulating vascular smooth muscle cell growth.[3] There are complex interactions between insulin and the sympathetic nervous system.[4,5] For example, insulin-induced hypoglycemia is a potent stimulus for adrenal epinephrine release and sympathetic nervous system activation. Compared with norepinephrine, epinephrine is a more potent hyperglycemic agent by stimulating hepatic gluconeogenesis and triglyceride hydrolysis in adipocytes to release free fatty acids (FFAs) for energy expenditure.[6,7] In general, the vast majority of norepinephrine is secreted by the sympathetic nerve endings, while epinephrine is secreted by the adrenal glands. The 24-hour urinary excretion of norepinephrine is a fairly reliable index of the overall sympathetic activity, while the 24-hour urinary output of epinephrine specifically reflects adrenal gland activation.[8] In Caucasians, obesity expressed as the body mass index (BMI) correlates positively with the plasma insulin concentration and 24-hour urinary norepinephrine output but negatively with epinephrine output.[9,10]

Type 2 diabetes mellitus, hypertension, and dyslipidemia, the main disease entities of the metabolic syndrome, have reached epidemic proportions in Hong Kong Chinese.[11] According to a 1995 to 1996 population-based survey on 7,730 Chinese residents aged 25 to 74 years,[12] about 10% of men and women had diabetes mellitus or hypertension. Moreover, 12% of men and 13% of women had a plasma total cholesterol level of 6.2 mmol/L or greater, while 17% of men and 10% of women had plasma triglycerides of 2.0 mmol/L or greater. Using structural equation modeling, we have previously reported that obesity was a major component of the metabolic syndrome and explained most of the variance in blood pressure, lipid abnormalities, and plasma glucose in Hong Kong Chinese.[13] More recently, we have demonstrated close associations between

From the Divisions of Clinical Pharmacology and Endocrinology, Department of Medicine and Therapeutics, The Prince of Wales Hospital, The Chinese University of Hong Kong (CUHK), Shatin, New Territories, Hong Kong.

Submitted September 28, 1999; accepted July 9, 2000.

Supported by the Hong Kong Research Grants Committee and the CUHK Strategic Research Programs.

Address reprint requests to Professor Julian A.J.H. Critchley, MB, PhD, Division of Clinical Pharmacology, Department of Medicine and Therapeutics, 9/F, Clinical Sciences Building, The Prince of Wales Hospital, Shatin, New Territories, Hong Kong.

0026-0495/01/5002-0025$35.00/0

doi:10.1053/meta.2001.19502

anthropometric indices,[14] visceral fat accumulation as quantified by magnetic resonance imaging,[15] and various cardiovascular risk factors in Chinese subjects with or without type 2 diabetes mellitus. However, there are few data on the relationships between obesity and catecholamines in the Chinese. In the present study, we examined the interrelationships between obesity, plasma insulin, and urinary catecholamine excretion in a group of Chinese subjects with different aspects of the metabolic syndrome.

SUBJECTS AND METHODS

Subjects

The study cohort consisted of 577 Hong Kong Chinese with a mean age of 38 ± 10 years (mean ± SD), 390 (68%) of whom have various combinations of type 2 diabetes mellitus, hypertension, dyslipidemia, albuminuria, and/or obesity. They were mainly recruited from the medical outpatient clinics at The Prince of Wales Hospital and subsequently referred to the Clinical Pharmacology Studies Unit (CPSU). The other 187 (32%) were classified as healthy subjects, mainly hospital staff or friends who were volunteers and had medical examinations in the CPSU. All subjects had a plasma creatinine less than 150 μmol/L. Antihypertensive and lipid-lowering medications were discontinued for at least 4 weeks before the study day, whereas no antidiabetic agents were taken on the morning of the test. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All subjects provided written informed consent.

On the study day, the subjects attended the CPSU after an overnight fast. The height, weight, and waist (minimum circumference between the umbilicus and xiphoid process) and hip (maximum circumference around the buttocks and symphysis pubis) circumferences were recorded. The BMI was calculated as weight (kilograms) divided by height (meters) squared as an index of general obesity. The waist circumference and waist to hip and waist to height ratios were calculated as indices of central obesity. Blood pressure was taken as the mean of 3 readings separated by a 1-minute interval by a Dinamap 8100 automated blood pressure monitor (Critikon, Tampa, FL) after at least 5 minutes in the sitting position. Venous blood was sampled for measurement of fasting plasma glucose and insulin, serum lipid (total cholesterol, HDL cholesterol, and triglyceride), and plasma creatinine concentrations. A 24-hour urine sample was collected for the measurement of urinary albumin, norepinephrine, and epinephrine excretion using boric acid preservative.[16]

Biochemical Measurements

All urine samples were stored at −20°C and analyzed for urinary norepinephrine and epinephrine excretion using alumina extraction followed by high-performance liquid chromatography with electrochemical detection.[16] The plasma insulin level was measured by the DAKO insulin enzyme linked immunosorbent assay (DAKO Diagnostics, Glostrup, Denmark). Plasma glucose, lipids, and urinary albumin levels and renal function were measured by routine assays in the Department of Chemical Pathology at The Prince of Wales Hospital as previously described.[17]

Definitions

Type 2 diabetes mellitus was defined according to 1985 World Health Organization (WHO) criteria.[18] Subjects were considered hypertensive if they were on antihypertensive medication or had a blood pressure of 140/90 mm Hg or higher.[19] Subjects who had increased plasma cholesterol (total cholesterol ≥ 6.2 mmol/L or low-density lipoprotein [LDL] cholesterol ≥ 4.1 mmol/L) or triglyceride (≥2.3 mmol/L) or a total cholesterol to HDL cholesterol ratio of 5 or higher were classified as dyslipidemic.[20-22] Using the WHO definition for obesity in Asians, general obesity was defined as a BMI of at least 25 kg/m^2 in both sexes.[23] Central obesity was defined as a waist circumference ≥90 cm in men or ≥80 cm in women.[23] Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as a urinary albumin excretion less than 30, 30 to 300, and at least 300 mg/d, respectively.[24] Insulin resistance was expressed as the fasting plasma insulin (picomoles) and glucose (millimoles) product divided by 22.5. This index is numerically the same as that derived from the homeostasis model assessment equation, insulin resistance = fasting serum insulin/($22.5e^{-\ln \text{fasting plasma glucose}}$).[25] In the present study, type 2 diabetes mellitus, hypertension, dyslipidemia, obesity (general/central), and increased albuminuria (micro/macroalbuminuria) were defined as the 5 components of the metabolic syndrome.

Statistical Analysis

Plasma insulin, serum triglyceride, 24-hour urinary albumin, norepinephrine, and epinephrine values were logarithmically transformed due to their skewed distribution. All data are expressed as the mean ± SD or geometric mean ×/÷ antilog SD as appropriate. χ^2 and unpaired *t* tests were used to compare variables between 2 groups. Quintile analysis was performed by dividing the study population into 5 groups according to the BMI or waist circumference. ANOVA with a polynomial approach was used to determine the significance of any trends across quintiles. Analysis of covariance (ANCOVA) was used to compare variables between groups after controlling for the confounding effects of age and sex. The Pearson product-moment correlation was used to examine relationships between variables. Stepwise multiple regression analysis was used to examine the independent relationships among different variables. Significance was indicated at a *P* value less than .05 (2-tailed). All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 6.0; SPSS, Chicago, IL).

RESULTS

Clinical Characteristics

Descriptive statistics for the study participants are shown in Table 1. Forty-one percent of the subjects (237 of 577) had general obesity as defined by a BMI of at least 25 kg/m^2, 29% (168 of 577) had central obesity as defined by a waist circumference of 90 cm or greater for men and 80 cm or greater for women, and 43% had either general or central obesity. Twenty-two percent (125 of 577), 24% (140 of 577), 27% (157 of 577), and 16% (89 of 577) had type 2 diabetes mellitus, hypertension, dyslipidemia, and increased albuminuria, respectively. Among the diabetic patients, 47% (59 of 125) were treated with oral antidiabetic agents, which were only omitted on the morning of the test. None of the patients were treated with insulin. There were no significant differences in the hormonal parameters including plasma insulin (geometric mean ×/÷ antilog SD, 57.0 ×/÷ 1.9 *v* 67.6 ×/÷ 2.4 pmol/L), the insulin resistance index (21.8 ×/÷ 2.2 *v* 25.6 ×/÷ 2.6), and 24-hour urinary norepinephrine (167 ×/÷ 2 *v* 175 ×/÷ 2 nmol/d) and epinephrine (52 ×/÷ 2 *v* 57 ×/÷ 2 nmol/d) between those treated and not treated by oral agents (all $P > .05$).

Considering type 2 diabetes mellitus, hypertension, dyslipidemia, obesity (general/central), and increased albuminuria as the 5 components of the metabolic syndrome, 32% (187 of 577), 28% (159 of 577), 22% (128 of 577), and 18% (103 of 577) the subjects had 0, 1, 2, and 3 or more components, respectively. Men had a higher mean waist circumference and

Table 1. Clinical, Biochemical, and Hormonal Features of Chinese Subjects With a Varying Number of the Components of the Metabolic Syndrome

Parameter	Whole	Male	Female
No. of subjects	577	239	338
Age (yr)	38 ± 10	38 ± 11	39 ± 10
Weight (kg)	62.8 ± 12.3	68.0 ± 12.0	59.1 ± 11.2‡
BMI (kg/m^2)	24.5 ± 4.2	24.4 ± 4.0	24.6 ± 4.3
Waist circumference (cm)	80 ± 11	83 ± 11	77 ± 11‡
Waist to hip ratio	0.83 ± 0.07	0.86 ± 0.07	0.80 ± 0.07‡
Waist to height ratio	0.50 ± 0.07	0.50 ± 0.07	0.50 ± 0.07
Systolic blood pressure (mm Hg)	123 ± 20	127 ± 19	120 ± 20‡
Diastolic blood pressure (mm Hg)	74 ± 15	78 ± 15	72 ± 14‡
General obesity (n)	237 (41%)	100 (42%)	137 (41%)
Central obesity (n)	168 (29%)	56 (23%)	112 (33%)*
General and/or central obesity (n)	250 (43%)	104 (44%)	146 (43%)
Type 2 diabetes mellitus (n)	125 (22%)	52 (22%)	73 (22%)
Hypertension (n)	140 (24%)	64 (27%)	76 (23%)
Dyslipidemia (n)	157 (27%)	80 (34%)	77 (23%)†
Microalbuminuria (n)	68 (12%)	30 (13%)	38 (11%)
Macroalbuminuria (n)	21 (4%)	9 (4%)	12 (4%)
Biochemical parameters			
Fasting glucose (mmol/L)	5.8 ± 2.3	5.9 ± 2.4	5.7 ± 2.2
Total cholesterol (mmol/L)	5.1 ± 1.2	5.1 ± 1.2	5.1 ± 1.2
LDL cholesterol (mmol/L)	3.1 ± 1.0	3.2 ± 1.0	3.1 ± 1.0
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.4 ± 0.3‡
Serum triglyceride (mmol/L)	1.0 ×/÷ 2.0	1.2 ×/÷ 2.0	0.9 ×/÷ 2.0‡
Plasma creatinine (μmol/L)	68 ± 16	81 ± 14	58 ± 10‡
24-h urinary albumin excretion (mg/d)	12.3 ×/÷ 3.4	12.6 ×/÷ 3.5	12.1 ×/÷ 3.4
Hormonal parameters			
Fasting insulin (pmol/L)	45.7 ×/÷ 2.0	46.6 ×/÷ 2.0	45.1 ×/÷ 2.0
Insulin resistance index	11.1 ×/÷ 2.3	11.5 ×/÷ 2.3	10.9 ×/÷ 2.3
24-h urinary norepinephrine (nmol/d)	184 ×/÷ 2	206 ×/÷ 2	170 ×/÷ 2†
24-h urinary epinephrine (nmol/d)	58 ×/÷ 2	70 ± 2	50 ± 2‡

NOTE. Data are expressed as the mean ± SD, number (%), or geometric mean ×/÷ antilog SD.
* $P < .05$, † $P < .01$, ‡ $P < .001$: χ^2 or unpaired t tests.

waist to hip ratio, blood pressure, serum triglyceride, and 24-hour urinary norepinephrine and epinephrine excretion but a lower mean HDL cholesterol than women ($P < .001$).

Comparisons Between Subjects With a Different Number of Components of the Metabolic Syndrome

Table 2 shows the clinical, biochemical, and hormonal characteristics of subjects with a different number of components of the metabolic syndrome. There were no significant age and sex differences among the 4 groups. An increasing number of components of the metabolic syndrome were associated with greater obesity (both general and central), higher blood pressure and fasting plasma glucose, a more adverse lipid profile, higher insulin concentration and insulin resistance, and higher 24-hour urinary albumin and norepinephrine excretion but lower 24-hour urinary epinephrine output (all $P < .005$).

Relationships Between Obesity, 24-Hour Urinary Catecholamine Excretion, Plasma Insulin, and Lipid Profile

Tables 3, 4, and 5 summarize the clinical, biochemical, and hormonal characteristics among subjects divided into quintiles of BMI in the whole study population, males divided into quintiles of waist circumference, and females divided into quintiles of waist circumference, respectively. In all 3 analyses, increasing quintiles of obesity were associated with increasing blood pressure, hyperglycemia, adverse lipid profiles, and 24-hour urinary albumin excretion (all $P < .001$). Twenty-four-hour urinary epinephrine excretion declined while the plasma insulin concentration, insulin resistance index, and urinary norepinephrine excretion increased progressively with increasing adiposity (all $P < .005$).

Table 6 shows the correlation matrix between the age, obesity, lipid profile, plasma insulin, insulin resistance index, and 24-hour urinary catecholamine excretion in the whole study population. Obesity indices, either the BMI or waist circumference, were closely associated with increasing age, serum triglyceride, plasma insulin, insulin resistance index, and 24-hour urinary norepinephrine but decreasing plasma HDL cholesterol and urinary epinephrine excretion (all $P < .001$). There were also positive correlations between urinary norepinephrine and epinephrine excretion ($P < .001$) and negative associations between urinary epinephrine excretion and the triglyceride concentration ($P < .001$).

Since most of these variables were interrelated, stepwise multiple regression analyses were used to identify the most significant predicators for obesity (BMI and waist circumference) using the age, sex (male = 0 and female = 1), lipid profile (HDL cholesterol and triglyceride), plasma insulin, and

Table 2. Comparison of Clinical, Biochemical, and Hormonal Parameters Between Subjects Stratified Into Groups by the Number of Components of the Metabolic Syndrome

Parameter	No Component	1 Component	2 Components	≥3 Components	Polynomial ANOVA for the Trend	Polynomial ANCOVA for the Trend (adjustment for age and sex)
No. of subjects	187	159	128	103	—	—
Sex ratio (male:female)*	36:64	42:58	45:55	47:53	NS	—
Obesity (general and/or central, n)†	0	50 (31%)	100 (78%)	100 (97%)	<.0001	<.0001
Diabetes mellitus (n)†	0	44 (28%)	37 (29%)	44 (43%)	<.0001	<.0001
Hypertension (n)†	0	33 (21%)	49 (38%)	58 (56%)	<.0001	<.0001
Dyslipidemia (n)†	0	28 (18%)	50 (39%)	65 (63%)	<.0001	<.0001
Albuminuria (n)†	0	4 (3%)	20 (16%)	65 (63%)	<.0001	<.0001
Age (yr)	36 ± 10	40 ± 10	39 ± 10	40 ± 11	NS	—
Weight (kg)	54.4 ± 7.3	59.8 ± 9.5	69.2 ± 10.9	74.4 ± 11.9	<.0001	<.0001
BMI (kg/m^2)	21.1 ± 2.1	23.5 ± 3.1	26.8 ± 3.5	28.9 ± 3.5	<.0001	<.0001
Waist circumference (cm)	70 ± 6	76 ± 9	85 ± 7	92 ± 9	<.0001	<.0001
Waist to hip ratio	0.78 ± 0.06	0.82 ± 0.06	0.84 ± 0.07	0.89 ± 0.06	<.0001	<.0001
Waist to height ratio	0.44 ± 0.04	0.48 ± 0.05	0.52 ± 0.05	0.57 ± 0.05	<.0001	<.0001
Systolic blood pressure (mm Hg)	112 ± 9	122 ± 18	129 ± 21	138 ± 23	<.0001	<.0001
Diastolic blood pressure (mm Hg)	65 ± 9	75 ×/÷ 15	80 ± 13	85 ± 14	<.0001	<.0001
Biochemical parameters						
Fasting glucose (mmol/L)	4.9 ± 0.4	5.8 ± 2.2	5.8 ± 1.8	7.4 ± 3.8	<.0001	<.0001
Total cholesterol (mmol/L)	4.5 ± 0.7	5.0 ± 1.0	5.3 ± 1.1	6.0 ± 1.7	<.0001	<.0001
LDL cholesterol (mmol/L)	2.7 ± 0.7	3.1 ± 1.0	3.5 ± 0.9	3.7 ± 1.0	<.0001	<.0001
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	<.0001	<.0001
Serum triglyceride (mmol/L)	0.7 ×/÷ 1.6	0.9 ×/÷ 1.7	1.2 ×/÷ 1.7	2.2 ×/÷ 2.3	<.0001	<.0001
Plasma creatinine (μmol/L)	66 ± 15	67 ± 15	71 ×/÷ 18	69 ± 18	NS	NS
24-h urinary albumin excretion (mg/d)	7.9 ×/÷ 1.6	8.3 ×/÷ 1.9	13.0 ×/÷ 2.5	56.3 ×/÷ 5.8	<.0001	<.0001
Hormonal parameters						
Fasting insulin (pmol/L)	32.8 ×/÷ 1.8	45.9 ×/÷ 2.0	51.7 ×/÷ 1.9	78.0 ×/÷ 1.8	<.0001	<.0001
Insulin resistance index	7.1 ×/÷ 1.8	11.5 ×/÷ 2.1	12.7 ×/÷ 2.1	23.2 ×/÷ 2.3	<.0001	<.0001
24-h urinary norepinephrine (nmol/d)	167 ×/÷ 2	182 ×/÷ 2	194 ×/÷ 2	211 ×/÷ 2	<.0001	.003
24-h urinary epinephrine (nmol/d)	69 ×/÷ 2	60 ×/÷ 2	51 ×/÷ 2	45 ×/÷ 2	<.0001	<.0001

NOTE. Data are expressed as the mean ± SD or geometric mean ×/÷ antilog SD.

* χ^2 test for comparisons of frequency between groups.

† χ^2 test for the trend.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; NS, nonsignificant.

24-hour urinary catecholamine excretion as independent variables (Table 7). We found that 34% of the variability of BMI and 45% of that of waist circumference were explained by increased plasma insulin, serum triglyceride, and 24-hour urinary norepinephrine excretion, as well as decreased HDL cholesterol and 24-hour urinary epinephrine excretion. However, female gender had a greater effect on the BMI, whereas male gender had more impact on the waist circumference.

DISCUSSION

Obesity and Other Components of the Metabolic Syndrome

Chronic overfeeding is associated with obesity, insulin resistance, and hyperinsulinemia in both human and animal studies.[26,27] Insulin is an anabolic hormone that promotes fuel storage and weight gain by converting energy substrates such as glucose and FFAs into storage macromolecules. It also limits the mobilization of triglyceride from adipose tissue and inhibits the hepatic formation of very–low-density lipoprotein (VLDL) cholesterol. On the other hand, insulin promotes the catabolism of VLDL cholesterol and chylomicrons, resulting in an increase in the HDL cholesterol concentration. Hence, an insulin-resistant and hyperinsulinemic state is characterized by increased FFAs, decreased HDL cholesterol, and hypertriglyceridemia.[28,29] Increased FFAs can worsen hyperglycemia through the Randle cycle, directly induce insulin resistance by down-regulating insulin receptors and reducing glucose oxidation,[30] and impair glucose-stimulated insulin secretion and worsen hyperglycemia on a long-term basis.[1,31-33] In agreement with these physiologic findings, in this cohort of Hong Kong Chinese subjects, our quintile and correlation analyses demonstrate close associations between obesity indices (BMI and waist circumference) and increased plasma insulin, insulin resistance, increased triglyceride, and decreased HDL cholesterol. Furthermore, patients with a greater number of components of the metabolic syndrome were more obese, insulin-resistant, hyperinsulinemic, hyperglycemic, hypertensive, and dyslipidemic.

Despite the increasing prevalence of obesity[14] and the metabolic syndrome[13,15] in Hong Kong Chinese, there are few data on these relationships with catecholamines in the Chinese population. In Caucasians, some but not all studies have demonstrated close associations between obesity, catecholamine activity, insulin resistance, and hyperinsulinemia.[5,9,10,34] In par-

Table 3. Comparison of Clinical, Biochemical, and Hormonal Parameters Between Subjects Divided Into Quintiles of BMI (kg/m^2)

Parameter	Quintile 1 (16.3-20.6)	Quintile 2 (20.7-23.0)	Quintile 3 (23.1-25.2)	Quintile 4 (25.3-27.7)	Quintile 5 (27.8-38.3)	Polynomial ANOVA for the Trend	Polynomial ANCOVA for the Trend (adjusted for age and sex)
No. of subjects	115	115	116	116	115	—	—
Age (yr)	34 ± 10	39 ± 11	41 ± 9	41 ± 10	38 ± 9	NS	NS
Sex ratio (male:female)	43:57	42:58	39:61	53:47	32:68*	—	—
Weight (kg)	50.2 ± 5.8	55.7 ± 5.8	61.1 ± 6.7	69.0 ± 7.5	78.2 ± 10.5	<.001	<.001
BMI (kg/m^2)	19.1 ± 1.1	21.9 ± 0.6	24.1 ± 0.7	26.5 ± 0.8	30.9 ± 2.3	<.001	<.001
Waist circumference (cm)	67 ± 6	73 ± 6	78 ± 6	85 ± 6	93 ± 8	<.001	<.001
Waist to hip ratio	0.77 ± 0.06	0.80 ± 0.08	0.82 ± 0.06	0.86 ± 0.06	0.87 ± 0.06	<.001	<.001
Waist to height ratio	0.42 ± 0.03	0.46 ± 0.04	0.49 ± 0.03	0.53 ± 0.03	0.59 ± 0.05	<.001	<.001
Systolic blood pressure (mm Hg)	112 ± 12	120 ± 20	124 ± 19	129 ± 20	131 ± 21	<.001	<.001
Diastolic blood pressure (mm Hg)	66 ± 11	70 ± 12	74 ± 12	79 ± 14	81 ± 14	<.001	<.001
Biochemical parameters							
Fasting glucose (mmol/L)	5.5 ± 2.2	5.4 ± 2.2	5.6 ± 1.5	5.8 ± 2.3	6.8 ± 3.1	<.001	<.001
Total cholesterol (mmol/L)	4.6 ± 0.8	5.0 ± 1.2	5.1 ± 1.1	5.4 ± 1.2	5.4 ± 1.6	<.001	<.001
LDL cholesterol (mmol/L)	2.7 ± 0.8	3.1 ± 1.0	3.2 ± 0.9	3.4 ± 1.0	3.4 ± 0.8	<.001	<.001
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	<.001	<.001
Serum triglyceride (mmol/L)	0.7 ×/÷ 1.6	0.8 ×/÷ 1.7	1.1 ×/÷ 2.0	1.3 ×/÷ 2.0	1.5 ×/÷ 2.2	<.001	<.001
Plasma creatinine (μmol/L)	67 ± 15	66 ± 15	68 ± 18	73 ± 18	65 ± 16	NS	NS
24-h urinary albumin excretion (mg/d)	7.2 ×/÷ 1.9	8.4 ×/÷ 2.2	9.5 ×/÷ 2.2	15.2 ×/÷ 4.0	32.7 ×/÷ 5.2	<.001	<.001
Hormonal parameters							
Fasting insulin (pmol/L)	32.7 ×/÷ 2.1	36.7 ×/÷ 1.8	44.3 ×/÷ 1.8	52.3 ×/÷ 1.8	77.1 ×/÷ 2.0	<.001	<.001
Insulin resistance index	7.5 ×/÷ 2.3	8.5 ×/÷ 1.9	10.6 ×/÷ 1.9	12.8 ×/÷ 2.0	21.3 ×/÷ 2.4	<.001	<.001
24-h urinary norepinephrine (nmol/d)	160 ×/÷ 2	176 ×/÷ 2	182 ×/÷ 2	206 ×/÷ 2	206 ×/÷ 2	<.001	<.001
24-h urinary epinephrine (nmol/d)	72 ×/÷ 2	67 ×/÷ 2	53 ×/÷ 2	62 ×/÷ 2	41 ×/÷ 2	<.001	<.001

NOTE. Data are expressed as the mean ± SD or geometric mean ×/÷ antilog SD.
* $P < .001$ by χ^2 test.

Table 4. Comparison of Clinical, Biochemical, and Hormonal Parameters Between Male Subjects Divided Into Quintiles of Waist Circumference (cm)

Parameter	Quintile 1 (61-73)	Quintile 2 (74-80)	Quintile 3 (81-86)	Quintile 4 (87-91)	Quintile 5 (92-110)	Polynomial ANOVA for the Trend
No. of subjects	48	48	47	48	48	—
Age (yr)	33 ± 10	37 ± 11	41 ± 10	43 ± 9	38 ± 9	NS
Weight (kg)	56.2 ± 6.7	61.7 ± 7.1	67.4 ± 6.3	72.3 ± 5.9	85.0 ± 19.9	<.001
BMI (kg/m^2)	20.3 ± 1.7	22.3 ± 1.9	24.9 ± 1.7	26.0 ± 1.6	30.1 ± 3.4	<.001
Waist circumference (cm)	69 ± 3	77 ± 2	83 ± 2	89 ± 2	99 ± 5	<.001
Waist to hip ratio	0.77 ± 0.04	0.84 ± 0.03	0.87 ± 0.04	0.90 ± 0.04	0.94 ± 0.04	<.001
Waist to height ratio	0.42 ± 0.03	0.46 ± 0.02	0.51 ± 0.02	0.53 ± 0.02	0.59 ± 0.04	<.001
Systolic blood pressure (mm Hg)	116 ± 12	126 ± 20	128 ± 16	136 ± 23	137 ± 19	<.001
Diastolic blood pressure (mm Hg)	69 ± 11	76 ± 15	80 ± 11	84 ± 15	87 ± 15	<.001
Biochemical parameters						
Fasting glucose (mmol/L)	5.9 ± 2.8	5.6 ± 1.7	5.5 ± 1.0	5.7 ± 1.9	7.2 ± 4.1	<.001
Total cholesterol (mmol/L)	4.6 ± 1.1	5.1 ± 1.1	5.0 ± 0.9	5.5 ± 1.1	5.7 ± 1.7	<.001
LDL cholesterol (mmol/L)	2.8 ± 1.1	3.3 ± 1.0	3.2 ± 0.8	3.5 ± 1.0	3.4 ± 0.7	<.001
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.3 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	1.0 ± 0.2	<.001
Serum triglyceride (mmol/L)	0.8 ×/÷ 1.7	1.0 ×/÷ 1.6	1.3 ×/÷ 1.7	1.5 ×/÷ 2.0	2.0 ×/÷ 2.4	<.001
Plasma creatinine (μmol/L)	78 ± 13	81 ± 17	81 ± 15	84 ± 15	80 ± 13	NS
24-h urinary albumin excretion (mg/d)	6.9 ×/÷ 2.4	10.0 ×/÷ 2.8	8.8 ×/÷ 1.9	12.9 ×/÷ 2.7	45.6 ×/÷ 5.0	<.001
Hormonal parameters						
Fasting insulin (pmol/L)	37.1 ×/÷ 2.5	37.7 ×/÷ 1.6	45.4 ×/÷ 1.6	56.3 ×/÷ 1.9	80.0 ×/÷ 1.7	<.001
Insulin resistance index	9.1 ×/÷ 2.9	8.8 ×/÷ 1.7	11.1 ×/÷ 1.7	13.4 ×/÷ 2.0	23.7 ×/÷ 2.3	<.001
24-h urinary norepinephrine (nmol/d)	166 ×/÷ 2	195 ×/÷ 2	191 ×/÷ 2	210 ×/÷ 2	264 ×/÷ 2	<.001
24-h urinary epinephrine (nmol/d)	87 ×/÷ 2	81 ×/÷ 2	61 ×/÷ 2	60 ×/÷ 2	62 ×/÷ 2	<.005

NOTE. Data are expressed as the mean ± SD or geometric mean ×/÷ antilog SD.

Table 5. Comparison of Clinical, Biochemical, and Hormonal Parameters Between Female Subjects Divided Into Quintiles of Waist Circumference (cm)

Parameter	Quintile 1 (58-67)	Quintile 2 (68-73)	Quintile 3 (74-79)	Quintile 4 (80-86)	Quintile 5 (87-108)	Polynomial ANOVA for the Trend
No. of subjects	68	68	67	67	68	—
Age (yr)	34 ± 9	39 ± 9	41 ± 8	41 ± 8	40 ± 12	NS
Weight (kg)	48.0 ± 3.7	52.7 ± 5.8	57.7 ± 5.8	65.7 ± 6.8	74.3 ± 10.0	<.001
BMI (kg/m^2)	19.9 ± 1.6	22.2 ± 1.7	24.3 ± 1.9	26.9 ± 2.4	30.9 ± 2.9	<.001
Waist circumference (cm)	64 ± 3	70 ± 1	76 ± 1	83 ± 2	94 ± 6	<.001
Waist to hip ratio	0.74 ± 0.04	0.77 ± 0.04	0.80 ± 0.07	0.82 ± 0.04	0.88 ± 0.06	<.001
Waist to height ratio	0.41 ± 0.02	0.46 ± 0.02	0.49 ± 0.02	0.53 ± 0.03	0.60 ± 0.04	<.001
Systolic blood pressure (mm Hg)	108 ± 10	116 ± 17	125 ± 23	127 ± 22	132 ± 18	<.001
Diastolic blood pressure (mm Hg)	63 ± 8	69 ± 11	74 ± 13	75 ± 12	80 ± 11	<.001
Biochemical parameters						
Fasting glucose (mmol/L)	5.0 ± 1.2	5.8 ± 2.5	5.5 ± 1.5	5.7 ± 1.7	7.2 ± 3.4	<.001
Total cholesterol (mmol/L)	4.4 ± 0.8	5.0 ± 0.9	5.3 ± 1.7	5.3 ± 1.3	5.5 ± 1.6	<.001
LDL cholesterol (mmol/L)	2.5 ± 0.7	3.1 ± 0.8	3.4 ± 1.0	3.3 ± 0.9	3.5 ± 1.1	<.001
HDL cholesterol (mmol/L)	1.6 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	<.001
Serum triglyceride (mmol/L)	0.6 ×/÷ 1.5	0.8 ×/÷ 1.6	1.1 ×/÷ 1.9	1.2 ×/÷ 2.0	1.6 ×/÷ 2.1	<.001
Plasma creatinine (μmol/L)	57 ± 8	57 ± 8	59 ± 10	58 ± 10	58 ± 12	NS
24-h urinary albumin excretion (mg/d)	6.7 ×/÷ 1.6	7.8 ×/÷ 2.0	12.2 ×/÷ 3.0	17.3 ×/÷ 4.1	28.3 ×/÷ 5.7	<.001
Hormonal parameters						
Fasting insulin (pmol/L)	33.8 ×/÷ 2.0	37.7 ×/÷ 1.8	48.0 ×/÷ 1.9	54.3 ×/÷ 1.9	77.0 ×/÷ 2.0	<.001
Insulin resistance index	7.3 ×/÷ 2.0	9.4 ×/÷ 2.0	11.4 ×/÷ 2.0	12.8 ×/÷ 2.1	22.3 ×/÷ 2.4	<.001
24-h urinary norepinephrine (nmol/d)	149 ×/÷ 2	164 ×/÷ 2	169 ×/÷ 2	186 ×/÷ 2	190 ×/÷ 2	<.001
24-h urinary epinephrine (nmol/d)	80 ×/÷ 2	53 ×/÷ 2	50 ×/÷ 2	46 ×/÷ 2	34 ×/÷ 2	<.001

NOTE. Data are expressed as the mean ± SD or geometric mean ×/÷ antilog SD.

ticular, the relationship between obesity and sympathetic nervous system activation is unclear. High,[35-38] normal, or low[39,40] norepinephrine concentrations in plasma or urine have all been reported in obese subjects. Increased[41] or reduced[38,42-44] plasma or urinary epinephrine levels have also been shown.

Insulin and the Sympathoadrenal System in the Development of Obesity

Catecholamines are potent insulin-counteracting hormones that mobilize energy substrates from glycogen and triglyceride stores during emergency conditions.[45] Although norepinephrine is derived principally from the peripheral sympathetic nerves and epinephrine from the adrenal medulla, epinephrine is often taken up by the sympathetic nerve endings and co-released with norepinephrine. The co-released epinephrine binds to β-adrenoceptors on the sympathetic terminals and further augments the release of norepinephrine.[46] Epinephrine enhances hepatic glycogenolysis and gluconeogenesis. It also increases glucagon secretion and inhibits insulin secretion from the pancreas. These actions lead to increased availability of glucose, especially in stressful conditions such as hypoglycemia.[47-49] Both norepinephrine and epinephrine have potent lipolytic actions, particularly in the visceral fat depots, to release FFAs as a

Table 6. Pearson Correlation Matrix Showing Correlation Coefficients Between Age, Obesity, Lipids, Plasma Insulin, Insulin Resistance Index, and 24-Hour Urinary Catecholamine Excretion in the Whole Population

Parameter	Age	BMI	Waist	HDL Cholesterol	TG	Plasma Insulin	Insulin Resistance Index	24-Hour Urinary NE	24-Hour Urinary E
Age	|								
BMI	.10†	|							
Waist	.25‡	.76‡	|						
HDL cholesterol	NS	−.31‡	−.38‡	|					
TG	.29‡	.36‡	.46‡	.51‡	|				
Plasma insulin	NS	.37‡	.32‡	−.27‡	.33‡	|			
Insulin resistance	.12‡	.37‡	.39‡	−.30‡	.43‡	.93‡	|		
24-h urinary NE	.16‡	.23‡	.29‡	−.10*	.11‡	NS	NS	|	
24-h urinary E	NS	.22‡	−.22‡	NS	−.19‡	−.16‡	−.18‡	.29‡	|

Abbreviations: TG, triglyceride; NE, norepinephrine; E, epinephrine.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

source of energy, especially in a caloric deficit situation.[42,50,51]

Using urinary norepinephrine and epinephrine to reflect adrenosympathetic activities,[8] we have apparently resolved the previously conflicting reports on urinary catecholamine excretion in obese patients. In accordance with other studies in Caucasians,[26,27,52,53] we found close associations between obesity (BMI and waist circumference), increased urinary norepinephrine, and decreased urinary epinephrine excretion. These findings suggest that there can be dissociations between the sympathetic nervous system and adrenal medullary responses, as shown with other reflex responses.[54] Young et al suggested that the two branches of the sympathoadrenal system may operate in reciprocal fashion under certain situations such as thermogenesis and insulin secretion. Despite their divergent associations with obesity, we found a positive association between urinary norepinephrine and epinephrine excretion, as well as a negative relationship between epinephrine excretion and triglyceride levels, suggesting complex counterrelationships between norepinephrine and epinephrine in relation to obesity. It has been proposed that food intake stimulates insulin secretion, which enhances glucose uptake and metabolism by hypothalamic cells. This in turn leads to an increase of the central sympathetic activity to promote energy production.[4,55] Hence, diminished adrenomedullary activity, which limits adipose tissue triglyceride mobilization for energy consumption, may predispose to obesity.[7] Prospective or intervention studies are needed to elucidate these relationships.

Westernization, Hormone Abnormalities, and Obesity

Our present findings and others[26-28,34,56-58] lend support to the complex interactions between insulin and the sympathoadrenal system in the development of obesity and the metabolic syndrome (Fig 1). We hypothesize that these hormonal changes associated with obesity may represent a maladaptation from a hunter-gatherer to a sedentary westernized life-style with food abundance and greatly reduced physical activity. The "thrifty genotype hypothesis" states that the evolution of a genotype that facilitates efficient energy storage might confer a survival advantage in times of fluctuating food supply but predisposes to the development of obesity and type 2 diabetes mellitus in the presence of food abundance.[59] Hence, some individuals may develop a hyperinsulinemic response in anticipation of food intake to facilitate the uptake of energy substrates. This is accompanied by activation of the sympathetic nervous system with increased norepinephrine release,[4,55] which plays a central role in the "fight and flight" concepts of Cannon.[60] However, in affluent societies, especially in the presence of physical inactivity, these energy substrates are not used effectively, resulting in obesity. As in most biologic systems with dual regulatory mechanisms, this may lead to a paradoxic decrease in epinephrine output to attenuate the increase in blood glucose and lipids.[61] All of these events can lead to increased FFA production, reduced glucose utilization or storage, and progressive β-cell failure in susceptible individuals, resulting in diabetes mellitus.[1,31-33] These can then contribute independently or in combination to the worsening of lipid profiles, leading to dyslipidemia.[28,56] Norepinephrine and, to some extent, insulin can increase blood pressure, especially in subjects who do not have effective systems to buffer these hypertensive effects.[3]

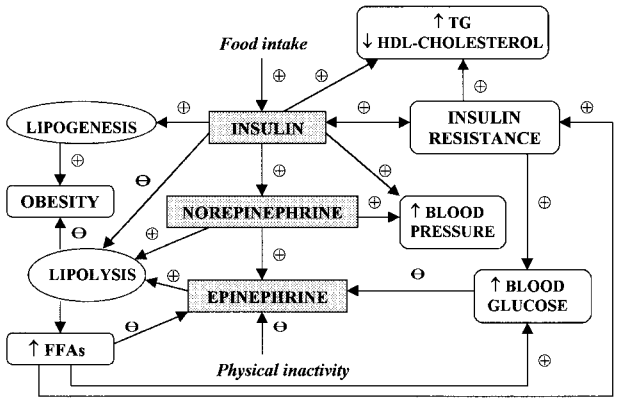

Fig 1. A hypothetic model depicting the interactions between insulin, insulin resistance, norepinephrine, epinephrine, and obesity. Increased food intake is associated with hyperinsulinemia and activation of the sympathetic nervous system. Hyperinsulinemia promotes energy storage, obesity, and dyslipidemia. Increased lipolytic activity due to catecholamines results in increased FFAs, which together with increased insulin can lead to insulin resistance and hyperglycemia due to fuel competition. Both sympathetic nervous system activation and hyperinsulinemia can contribute to the development of hypertension. The high blood glucose and reduced physical activity may reduce epinephrine output from the adrenal medulla to attenuate the metabolic disturbances. TG, triglyceride.

Table 7. Interrelationships Between Age, Sex, Obesity, Plasma Insulin, and HDL Cholesterol, Serum Triglyceride, and 24-Hour Urinary Norepinephrine and Epinephrine Excretion in Chinese Subjects With a Varying Number of Components of the Metabolic Syndrome Using Stepwise Multiple Regression Analysis

	Dependent Variables	
	BMI	Waist Circumference
	R^2 = .34, F = 38.8‡	R^2 = .45, F = 56.2‡
Independent variables		
Age	NS	NS
Sex (male = 0, female = 1)	β = 0.12*	β = −0.19‡
Plasma HDL cholesterol	β = −0.18†	β = −0.16‡
Serum triglyceride	β = 0.17‡	β = 0.23‡
Plasma insulin	β = 0.25‡	β = 0.19‡
24-h urinary NE excretion	β = 0.26‡	β = 0.28‡
24-h urinary E excretion	β = −0.19‡	β = −0.26‡

Abbreviation: β, standard regression coefficient.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.

ACKNOWLEDGMENT

We thank Stanley Ho, the senior technician in the Department of Medicine and Therapeutics, for invaluable advice on the laboratory work. We also thank the following research nurses, Maggie S.W. Lau, Cherry K.P. Chiu, Evelyn Y.M. Chow, Karen S.Y. Wong, and Elce H.S. Au Yeung, for their dedication and nursing skills in the recruitment of subjects.

REFERENCES

1. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991
2. Felig P: Disorders of carbohydrate metabolism, in Bondy PK, Rosenberg LE (eds): Metabolic Control and Disease (ed 8). Philadelphia, PA, Saunders, 1980, pp 277-301
3. Landsberg L, Troisi R, Parker D: Obesity, blood pressure and the sympathetic nervous system. Ann Epidemiol 1:295-303, 1991
4. Landsberg L, Young JB: The influence of diet on the sympathetic nervous system, in Muller EE, MacLeod RM, Frohman LA (eds): Neuroendocrine Perspectives. Amsterdam, The Netherlands, Elsevier Science, 1985, pp 191-218
5. Smith U, Lager I: Insulin-antagonistic effects of counterregulatory hormones: Clinical and mechanistic aspects. Diabetes Metab Rev 5:511-525, 1989
6. Cryer PE: Glucose counterregulation: Prevention and correction of hypoglycemia in humans. Am J Physiol 264:E149-E155, 1993
7. Lafontan M, Berlan M: Fat cell adrenergic receptors in the control of white and brown fat cell function. J Lipid Res 34:1057-1092, 1993
8. Young JB, Rosa RM, Landsberg L: Dissociation of sympathetic nervous system and adrenal medullary responses. Am J Physiol 247: E35-E40, 1984
9. Troisi RJ, Weiss ST, Parker DR, et al: Relation of obesity and diet to sympathetic nervous system activity. Hypertension 17:669-677, 1991
10. Ward KD, Sparrow D, Landsberg L, et al: The relationship of epinephrine excretion to serum lipid levels: The Normative Aging Study. Metabolism 43:509-513, 1994
11. Chan JCN, Cockram CS: Diabetes in the Chinese population and its implications for health care. Diabetes Care 20:1785-1790, 1997
12. Janus ED: Epidemiology of cardiovascular risk factors in Hong Kong. Clin Exp Pharmacol Physiol 24:987-988, 1997
13. 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
14. Ko GTC, Chan JCN, Woo J, et al: Simple anthropometric indexes and cardiovascular risk factors in Chinese. Int J Obes 21:995-1001, 1997
15. Anderson PJ, Chan JCN, Chan YL, et al: Visceral fat and cardiovascular risk factors in Chinese NIDDM patients. Diabetes Care 20:1854-1858, 1997
16. Lee ZSK, Critchley JAJH: Simultaneous measurement of catecholamines and kallikrein in urine using boric acid preservative. Clin Chim Acta 276:89-102, 1998
17. Chan JCN, Tomlinson B, Nicholls MG, et al: Albuminuria, insulin resistance and dyslipidaemia in Chinese patients with non–insulin-dependent diabetes (NIDDM). Diabet Med 13:150-155, 1996
18. World Health Organization: Diabetes mellitus. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 727: 1985
19. National Institutes of Health: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD, National Institutes of Health, 1997
20. The Prince of Wales Hospital: Pathology Handbook (ed 3). Hong Kong, Hong Kong Government Press, 1997
21. Wong SP, Cockram CS, Janus ED, et al: Guide to plasma lipids and lipoproteins for Hong Kong doctors. J H K Cardiol 4:81-89, 1996
22. Assmann G, Schulte H: Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerosis coronary artery disease (the PROCAM experience). Am J Cardiol 70:733-737, 1992
23. International Obesity Task Force: The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Health Communications Australia, on behalf of the Steering Committee, World Health Organization, Western Pacific region, 2000
24. Rowe DJF, Dawnay A, Warts GF: Microalbuminuria in diabetes mellitus: Review and recommendations for the measurement of albumin in urine. Ann Clin Biochem 27:297-312, 1990
25. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419, 1985
26. Yki-Jarvinen H, Taskinen MR, Koivisto VA, et al: Response of adipose tissue lipoprotein lipase activity and serum lipoproteins to acute hyperinsulinemia in man. Diabetologia 27:374-369, 1984
27. Baynes C, Henderson AD, Anyaoku V, et al: The role of insulin insensitivity and hepatic lipase in the dyslipidemia of type 2 diabetes. Diabet Med 8:560-566, 1991
28. Orchard TJ, Becker DJ, Bates M, et al: Plasma insulin and lipoprotein concentrations: An atherogenic association? Am J Epidemiol 118:326-337, 1983
29. Laakso M, Sarlund H, Mykkanen L: Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. Arteriosclerosis 10:223-231, 1990
30. Olefsky JM: The insulin receptor: Its role in insulin resistance of obesity and diabetes. Diabetes 25:1154-1162, 1976
31. Reaven GM: The fourth musketeer—From Alexander Dumas to Claude Bernard. Diabetes 38:3-13, 1995
32. Unger RH: Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Diabetes 44:863-870, 1996
33. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. Diabetes Care 13:610-630, 1990
34. Landsberg L, Young JB: Insulin-mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. Int J Obes 9:63-68, 1985
35. Kjeldsen SE, Eide I, Aakesson I, et al: Influence of body weight on plasma catecholamine patterns in middle-aged, normotensive men. Scand J Clin Lab Invest 43:339-342, 1983
36. Tuck ML: Obesity, the sympathetic nervous system, and essential hypertension. Hypertension 19:167-177, 1992 (suppl 1)
37. Tataranni PA, Young JB, Bogardus C, et al: A low sympathoadrenal activity is associated with body weight gain and development of central adiposity in Pima Indian men. Obes Res 5:341-347, 1997
38. Young JB, Troisi RJ, Weiss ST, et al: Relationship of catecholamine excretion to body size, obesity, and nutrient intake in middle-age and elderly men. Am J Clin Nutr 56:827-834, 1992
39. Schutz Y, Bessard T, Jequier E: Diet-induced thermogenesis measured over a whole day in obese and nonobese women. Am J Clin Nutr 40:542-552, 1984
40. Schwartz RS, Jaeger LF, Veith RC: The importance of body composition to the increase in plasma norepinephrine appearance rate in elderly men. J Gerontol 42:540-551, 1987
41. Connacher AA, Bennet WM, Jung RT, et al: Effect of adrenaline infusion on fatty acid and glucose turnover in lean and obese human subjects in post-absorptive and fed states. Clin Sci (Colch) 81:635-644, 1991
42. Peterson HR, Rothschild M, Weinberg CR, et al: Body fat and the activity of the autonomic nervous system. N Engl J Med 318:1077-1083, 1988
43. Leonetti DL, Bergstrom RW, Shuman WP, et al: Urinary catecholamines, plasma insulin and environmental factors in relation to body fat distribution. Int J Obes 15:345-357, 1991
44. Jensen MD, Haymond HW, Rizza RA, et al: Influence of body fat distribution on free fatty acid metabolism in obesity. J Clin Invest 83:1167-1173, 1989

45. Selye H: The Stress of Life (ed 2). New York, NY, McGraw-Hill, 1976

46. Majewski H, Tung LH, Rand MH: Hypertension through adrenaline activation of prejunctional beta-adrenoreceptors. Clin Exp Pharmacol Physiol 8:463-468, 1981

47. Muller-Hess R, Geser CA, Pittet P, et al: Interactions of insulin and epinephrine in human metabolism: Their influence on carbohydrate and lipid oxidation rate. Diabetes Metab 1:151-157, 1975

48. Astrup A, Andersen T, Henriksen O, et al: Impaired glucose-induced thermogenesis in skeletal muscle in obesity. The role of the sympathoadrenal system. Int J Obes 11:51-66, 1987

49. Porte D, Robertson RP: Control of insulin secretion by catecholamines, stress and the sympathetic nervous system. Fed Proc 32:1792-1796, 1973

50. Peiris AN, Mueller RA, Smith GA, et al: Splanchnic insulin metabolism in obesity: Influence of body fat distribution. J Clin Invest 78:1648-1657, 1986

51. Flechtner-Mors M, Ditschuneit HH, Yip I, et al: Sympathetic modulation of lipolysis in the subcutaneous adipose tissue: Effects of gender and energy restriction. J Lab Clin Med 134:33-41, 1999

52. Sims EAH, Danford E, Horton ES, et al: Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res 29:457-496, 1973

53. Bray GA, York DA: Hypothalamic and genetic obesity in experimental animals: An autonomic and endocrine hypothesis. Physiol Rev 59:719-809, 1979

54. Critchley JAJH, Ellis P, Ungar A: The reflex releases of adrenaline and noradrenaline from the adrenal glands of cats and dogs. J Physiol (Lond) 298:71-78, 1980

55. Young JB, Landsberg L: Stimulation of the sympathetic nervous system during sucrose feeding. Nature 269:615-617, 1977

56. Larsson B, Svardsudd K, Welin L, et al: Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow up of participants in the Study of Men Born in 1913. BMJ 288:1401-1404, 1984

57. Rowe JW, Young JB, Minaker KL, et al: Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. Diabetes 30:219-225, 1981

58. Reaven GM, Greenfield MS: Diabetic hypertriglyceridemia: Evidence for three clinical syndromes. Diabetes 20:66-75, 1981 (suppl 2)

59. Neel JV: Diabetes mellitus: A “thrifty” genotype rendered detrimental by “progress”? Am J Hum Genet 14:353-362, 1962

60. Cannon WB, McIver MA, Bliss SW: A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia. Am J Physiol 69: 46-66, 1924

61. Kjær M, Farrel PA, Christensen NJ, et al: Increased epinephrine response and inaccurate glucoregulation in exercising athletes. J Appl Physiol 61:1693-1700, 1986