# Plasma Insulin, Growth Hormone, Cortisol, and Central Obesity Among Young Chinese Type 2 Diabetic Patients

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**OBJECTIVE** — To examine the relationships between central obesity, insulin resistance index, plasma insulin, growth hormone (GH), and cortisol concentrations in 90 young Chinese type 2 diabetic patients (aged 33 ± 5 years) and 104 age- and sex-matched control subjects (aged 32 ± 9 years).

**RESEARCH DESIGN AND METHODS** — Young Chinese diabetic patients (aged <40 years) were recruited from the Prince of Wales Hospital. Blood pressure, height, weight, and waist and hip circumferences were determined. Venous blood was sampled for measurements of fasting plasma glucose, $HbA_{1c}$, lipids, creatinine, insulin, GH, and cortisol. A 24-h urine was assayed for urinary albumin excretion (UAE). General and central obesity was represented by BMI and waist circumference, respectively. Insulin resistance index was estimated as a product of fasting plasma insulin and glucose concentrations.

**RESULTS** — Compared with control subjects, diabetic patients were more obese, hyperglycemic, and had worse lipid profile, higher blood pressures, UAE, insulin resistance index, plasma insulin, and cortisol concentrations (all $P < 0.001$) but lower GH concentrations ($P < 0.05$). When analyzed as a whole group ($n = 194$), increasing quartiles of waist circumference were associated with increasing trends of insulin resistance index, plasma insulin, and cortisol concentrations (all $P < 0.01$) but a decreasing trend of plasma GH concentration ($P < 0.05$). Using stepwise multiple regression analysis, waist circumference was only associated with sex variable (being higher in men) in the control subjects. In the diabetic group, 51% of waist circumference was independently related to male sex and increased plasma insulin and cortisol concentrations as well as reduced plasma GH levels.

**CONCLUSIONS** — In young Chinese type 2 diabetic patients, hyperinsulinemia, hypercortisolemia, and reduced plasma GH levels were closely associated with central obesity. Based on these findings, we postulate that maladaptive hormonal responses to rapid changes in lifestyle may have led to obesity and type 2 diabetes in these young patients. Alternatively, lifestyle-related obesity may have given rise to these hormonal changes. More studies are required to delineate the nature of these relationships.

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**Abbreviations:** ANCOVA, analysis of covariance; ANOVA, analysis of variance; CV, coefficient of variation; GH, growth hormone; RIA, radioimmunoassay; TC, total cholesterol; TG, triglyceride; UAE, urinary albumin excretion; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Type 2 diabetes is often associated with aging, obesity, hyperinsulinemia, albuminuria, hypertension, and dyslipidemia (1). Although insulin resistance has been advocated as a central linking factor for this clustering of cardiovascular risk factors (1), central obesity is increasingly being recognized as a significant element of the metabolic syndrome (2). In particular, endocrine perturbations such as increased cortisol (3) and decreased growth hormone (GH) secretion (4) have been proposed for the induction of insulin resistance in association with visceral fat accumulation. These adipose tissues are characterized by enlarged fat cells that have increased lipolytic responsiveness to catecholamines or other counter-regulatory hormones (5). It has been suggested that the resultant high concentrations of free fatty acids released into the portal circulation may enhance gluconeogenesis, reduce glucose uptake by competing with glucose for oxidation (6), decrease insulin clearance (7), as well as increase insulin resistance (8). The latter may be compensated progressively by increasing insulin secretion leading to hyperinsulinemia, which itself downregulates insulin receptor (9). The combination of these events may result in a vicious cycle of increasing hyperinsulinemia, insulin resistance, stimulation of the sympathetic nervous system, hyperglycemia, dyslipidemia, and hypertension (1,10–12). When the pancreatic β-cells are unable to increase their insulin secretion to compensate for insulin resistance, glucose intolerance and diabetes may develop (12).

Diabetes is a major public health problem. Its prevalence is also increasing among nonwhite individuals, including Chinese subjects living in areas undergoing rapid lifestyle changes and increasing affluence (13). In Hong Kong, the age-adjusted prevalence of diabetes has increased from 7.7% in 1990 (14) to 8.9% in 1995 (15). Increased age and obesity and a positive family history are the major predictors for diabetes (14). Using structural equation modeling, these three factors also explained most of the variance of the various components of the metabolic syndrome in Hong Kong Chinese (16).

**Table 1—*Clinical, biochemical, and hormonal features of young Chinese type 2 diabetic patients***

| | Whole | Male | Female |
|---|---|---|---|
| *n* | 90 | 37 | 53 |
| Age (years) | 33 ± 5 | 32 ± 6 | 33 ± 5 |
| Duration of disease (years) | 3.3 ± 3.3 | 3.6 ± 3.1 | 3.1 ± 3.5 |
| Weight (kg) | 68.2 ± 14.6 | 73.4 ± 16.9 | 64.5 ± 11.6† |
| BMI (kg/m²) | 26.3 ± 4.9 | 26.4 ± 5.6 | 26.3 ± 4.4 |
| Waist circumference (cm) | 84 ± 12 | 87 ± 13 | 82 ± 11* |
| WHR | 0.85 ± 0.07 | 0.88 ± 0.06 | 0.82 ± 0.06‡ |
| Systolic blood pressure (mmHg) | 113 ± 12 | 118 ± 11 | 110 ± 12† |
| Diastolic blood pressure (mmHg) | 72 ± 9 | 74 ± 9 | 71 ± 10 |
| General obesity | 46 (51) | 15 (41) | 31 (59) |
| Central obesity | 17 (19) | 4 (11) | 13 (25) |
| Hypertension | 5 (6) | 2 (5) | 3 (6) |
| Dyslipidemia | 21 (23) | 8 (22) | 13 (25) |
| Microalbuminuria | 18 (20) | 10 (27) | 8 (15) |
| Macroalbuminuria | 6 (7) | 1 (3) | 5 (9) |
| Biochemical parameters | | | |
| $HbA_{1c}$ (%) | 7.3 ± 1.8 | 7.6 ± 1.9 | 7.1 ± 1.8 |
| Fasting glucose (mmol/l) | 8.1 ± 3.7 | 8.7 ± 5.0 | 7.7 ± 2.3 |
| Total cholesterol (mmol/l) | 5.0 ± 1.0 | 4.9 ± 1.0 | 5.0 ± 1.1 |
| LDL cholesterol (mmol/l) | 3.0 ± 0.8 | 3.0 ± 0.6 | 3.1 ± 1.8 |
| HDL cholesterol (mmol/l) | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.2 ± 0.3 |
| Serum triglyceride (mmol/l) | 1.3 ×/÷ 7.3 | 1.3 ×/÷ 2.1 | 1.3 ×/÷ 1.8 |
| Plasma creatinine (μmol/day) | 65 ± 15 | 77 ± 11 | 57 ± 11‡ |
| 24-h UAE (mg/day) | 21.7 ×/÷ 4.8 | 21.2 ×/÷ 3.5 | 22.2 ×/÷ 5.8 |
| Hormonal parameters | | | |
| Fasting insulin (pmol/l) | 71.8 ×/÷ 1.9 | 73.1 ×/÷ 2.0 | 70.1 ×/÷ 1.9 |
| Insulin resistance index | 24.9 ×/÷ 2.3 | 27.3 ×/÷ 2.5 | 23.1 ×/÷ 2.1 |
| Plasma growth hormone (ng/ml) | 1.6 ± 1.0 | 1.5 ± 1.2 | 1.6 ± 0.9 |
| Plasma cortisol (nmol/l) | 501 ×/÷ 2 | 491 ×/÷ 2 | 512 ×/÷ 2 |

Data are means ± SD, *n* (%), or geometric means ×/÷ antilog SD. General obesity is defined by a BMI ≥27 kg/m² in men, ≥25 kg/m² in women. Central obesity is defined by a WHR >0.95 in men, >0.85 in women. Hypertension is defined by blood pressure ≥140/90 mmHg or if the patient is on antihypertensive treatment. Dyslipidemia is defined by total cholesterol >6.2 mmol/l or LDL cholesterol >4.1 mmol/l or triglyceride >2.3 mmol/l or total cholesterol/HDL cholesterol ratio >5. Microalbuminuria and macroalbuminuria are defined by urinary albumin excretion ≥30–300 and ≥300 mg/day, respectively. *$P < 0.02$, †$P < 0.01$, ‡$P < 0.001$ for comparison between men and women using $\chi^2$ or unpaired *t* tests.

Based on the 1993 Hong Kong growth survey (17), there was an average increase of 8.5 and 5.1 kg in 18-year-old Hong Kong boys and girls, respectively, compared with those surveyed 30 years ago. In addition, the prevalence of obesity has been reported to be 21 and 10% for 11-year-old boys and girls, respectively. This prevalence has increased to 34 and 13%, respectively, reported in 1998 for the same age of children and selection criterion of obesity (18). Similar findings showing increasing prevalence of childhood obesity have also been reported in other Asian children (19–21). Against this background, it is noteworthy that the crude prevalence of diabetes was <1% in those under 30 years of age in 1990 (14) and 1.5% in the 25–34 year age-group in 1995 (22). Although these prevalence rates are not directly comparable because of different sampling methods, they are in accord with the rising prevalence of diabetes within the general population. Given the rising trend of childhood obesity together with increased awareness of the condition, all these factors may contribute to the increasing number of young-onset Chinese diabetic patients.

In keeping with these findings, we have previously reported that 17% of diabetic patients attending a hospital-based clinic had been diagnosed before the age of 35 years (23). As in other non-Caucasian groups (24,25), autoimmune type 1 diabetes remains relatively uncommon in Chinese, even among patients with acute (26,27) or early onset of disease (28). Type 2 diabetes being the predominant form of disease (23), more than 50% of these young patients were obese and had features that resembled the metabolic syndrome (28). In agreement with other workers (29), we have also reported the close associations between visceral fat accumulation, as quantified by magnetic resonance imaging, and various cardiovascular risk factors in Chinese type 2 diabetic patients (30). All these findings point to the important role of obesity in the development of diabetes in Chinese, including the young patients.

Given the possible effects of GH, cortisol, and insulin on the deposition of visceral fats and the metabolic consequences, we examined the relationships between these hormonal parameters, obesity, and biochemical abnormalities in a subgroup of Chinese type 2 diabetic patients with young onset of disease (28).

## RESEARCH DESIGN AND METHODS

### Subjects

A total of 153 young Chinese diabetic patients with age of onset of disease ≤35 years and age <40 years who had no past history of cardiovascular diseases, were recruited from the Prince of Wales Hospital Diabetes Clinic in 1995 (28). A fasting plasma glucose ≥7.8 mmol/l and/or 2-h post-glucose loading or random plasma glucose ≥11.1 mmol/l were used for the diagnosis of diabetes (31). Seventeen patients (11%) were considered to have autoimmune type 1 diabetes as indicated by the presence of antibodies to GAD >18 U (32). One patient had renal impairment (plasma creatinine ≥150 μmol/l), 21 (14%) had diabetic retinopathy, and 51 (33%) were treated with insulin. Because exogenous insulin treatment might lead to a falsely high plasma insulin concentration that was used in the calculation of the insulin resistance index, insulin-treated patients were excluded from the present analysis. Also, the effects of diabetic complications and renal impairment on various hormonal parameters remain uncertain. Hence, together with the type 1 diabetic and insulin-treated patients, patients with complications were also excluded. The remaining 90 type 2 diabetic patients had been included in the present analysis.

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients gave informed written consent. No medication was taken on the morning of the study day. Height, weight, and waist (min-

imum circumference between the umbilicus and xiphoid process) and hip (maximum circumference around the buttock and symphysis pubis) circumferences were measured. BMI was calculated as weight (kg) divided by height squared ($m^2$) as an index of general obesity. Waist circumference and waist-to-hip ratio (WHR) were used as indices of central obesity. Retinopathy was assessed by diabetologists after dilatation of the pupils. Blood pressure was taken as the mean of two readings separated by a 1-min interval and measured by a Dinamap 8100 automated blood pressure monitor (Critikon, Tampa, FL) after at least a 5-min sitting. Fasting venous blood was assayed for plasma glucose, $HbA_{1c}$, total cholesterol (TC), HDL cholesterol, LDL cholesterol, triglyceride (TG), renal function, insulin, GH, and cortisol. A 24-h urine was collected for the measurement of urinary albumin excretion (UAE).

A total of 104 unpaid Chinese healthy volunteers, either hospital staff or friends, were recruited from the Clinical Pharmacology Study Unit at the Prince of Wales Hospital. All subjects had a plasma creatinine <150 μmol/l, blood pressure <120/80 mmHg (33), fasting plasma glucose <6.1 mmol/l, TC <5.2 mmol/l, LDL cholesterol <3.4 mmol/l, and TG <2.0 mmol/l. All women had an HDL cholesterol >1.2 mmol/l and men >1.0 mmol/l (34).

**Table 2—*Comparison of clinical, biochemical, and hormonal parameters between control subjects and young Chinese type 2 diabetic patients***

| | Normal control subjects | Young type 2 diabetic patients | Unpaired *t* test | ANCOVA (adjustment for BMI and waist) |
|---|---|---|---|---|
| *n* | 104 | 90 | — | — |
| Age (years) | 32 ± 9 | 33 ± 5 | NS | NS |
| Sex (M/F) | 39/61 | 41/59 | NS | NS |
| Weight (kg) | 54.2 ± 7.9 | 68.2 ± 14.6 | <0.001 | NS |
| BMI ($kg/m^2$) | 20.8 ± 2.2 | 26.3 ± 4.9 | <0.001 | — |
| Waist circumference (cm) | 68 ± 6 | 84 ± 12 | <0.001 | — |
| WHR | 0.76 ± 0.05 | 0.85 ± 0.07 | <0.001 | — |
| Systolic blood pressure (mmHg) | 109 ± 7 | 113 ± 12 | <0.001 | NS |
| Diastolic blood pressure (mmHg) | 61 ± 7 | 72 ± 9 | <0.001 | <0.001 |
| Biochemical parameters | | | | |
| $HbA_{1c}$ (%) | 5.3 ± 0.6 | 7.3 ± 1.8 | <0.001 | <0.001 |
| Fasting glucose (mmol/l) | 4.8 ± 0.4 | 8.1 ± 3.7 | <0.001 | <0.001 |
| Total cholesterol (mmol/l) | 4.2 ± 0.5 | 5.0 ± 1.0 | <0.001 | <0.05 |
| LDL cholesterol (mmol/l) | 2.4 ± 0.5 | 3.0 ± 0.8 | <0.001 | <0.05 |
| HDL cholesterol (mmol/l) | 1.5 ± 0.3 | 1.2 ± 0.3 | <0.001 | NS |
| Serum triglyceride (mmol/l) | 0.6 ×/÷ 1.5 | 1.3 ×/÷ 1.3 | <0.001 | <0.005 |
| Plasma creatinine (μmol/day) | 67 ± 16 | 65 ± 15 | NS | NS |
| 24-h UAE (mg/day) | 6.9 ×/÷ 1.9 | 21.7 ×/÷ 4.8 | <0.001 | NS |
| Hormonal parameters | | | | |
| Fasting insulin (pmol/l) | 32.3 ×/÷ 1.8 | 71.8 ×/÷ 1.9 | <0.001 | <0.001 |
| Insulin resistance index | 6.9 ×/÷ 1.8 | 24.9 ×/÷ 2.3 | <0.001 | <0.001 |
| Plasma growth hormone (ng/ml) | 2.6 ± 3.1 | 1.6 ± 1.0 | <0.05 | NS |
| Plasma cortisol (nmol/l) | 312 ×/÷ 2 | 501 ×/÷ 2 | <0.001 | <0.001 |

Data are means ± SD or geometric means ×/÷ antilog SD.

### Biochemical measurements

Plasma insulin was assayed by the DAKO Insulin ELISA (DAKO Diagnostics, Glostrup, Denmark). The intra-assay coefficients of variation (CVs) were 6.8 and 2.2% at 10.9 ± 0.7 and 31.5 ± 0.7 pmol/l. The inter-assay CVs were 4.4 and 6.4% at 11.2 ± 0.5 and 27.3 ± 1.8 pmol/l, respectively. Plasma-free GH and cortisol were measured by the commercially available Double Antibody Human Growth Hormone radioimmunoassay (RIA) (Diagnostic Products, Los Angeles, CA) and the Coat-a-Count Cortisol RIA (Diagnostic Products), respectively. The intra- and interassay CVs of both assays were <8%. Measurements of $HbA_{1c}$, plasma glucose, lipids, renal function, and urinary albumin were performed by routine assays in the Department of Chemical Pathology at the Prince of Wales Hospital, as previously described (28).

### Definitions

General obesity was defined as a BMI >27 $kg/m^2$ in men or >25 $kg/m^2$ in women (35). Central obesity was defined as a WHR >0.95 in men or >0.85 in women (36). Subjects were considered to be hypertensive if they were on antihypertensive drugs or had a blood pressure ≥140/90 mmHg (33). Subjects who had TC >6.2 mmol/l, LDL cholesterol >4.1 mmol/l, TG >2.3 mmol/l, or TC–to–HDL cholesterol ratio >5 were considered to have dyslipidemia (34,37,38). Normo-, micro-, and macroalbuminuria were defined as a 24-h UAE <30, 30–300, and ≥300 mg/day, respectively (39). Insulin resistance index was calculated as a fasting plasma insulin (pmol/l) and glucose (mmol/l) product divided by 22.5. This is numerically the same as that derived from the homeostasis model assessment equation: insulin resistance = fasting serum insulin/(22.5 $e^{-\ln \text{fasting plasma glucose}}$) (40).

### Statistical analysis

Plasma insulin, cortisol, serum TG, and UAE were logarithmically transformed because of skewed distributions. All data are expressed as means ± SD or geometric means ×/÷ antilog SD as appropriate. $\chi^2$ and unpaired *t* tests were used for between-group comparisons. Quartile analysis was performed by dividing the study population into four groups according to their waist circumferences. Analysis of variance (ANOVA) with polynomial approach was used to determine the significance of trends across the quartiles. Analysis of covariance (ANCOVA) was used to compare the variables between groups after controlling for the confounding factors. Stepwise multiple regression analysis was used to examine the independent relationships among different variables. Significance was taken as a *P* value <0.05 (two-tailed). All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 6.0).

## RESULTS

### Clinical characteristics

The mean age of these 90 type 2 diabetic patients was 33 ± 5 years (range 17–40) with duration of disease ranging from newly diagnosed (0 years) to 15 years (3.3 ± 3.3 years). The men were heavier, were more centrally obese, and had a higher sys-

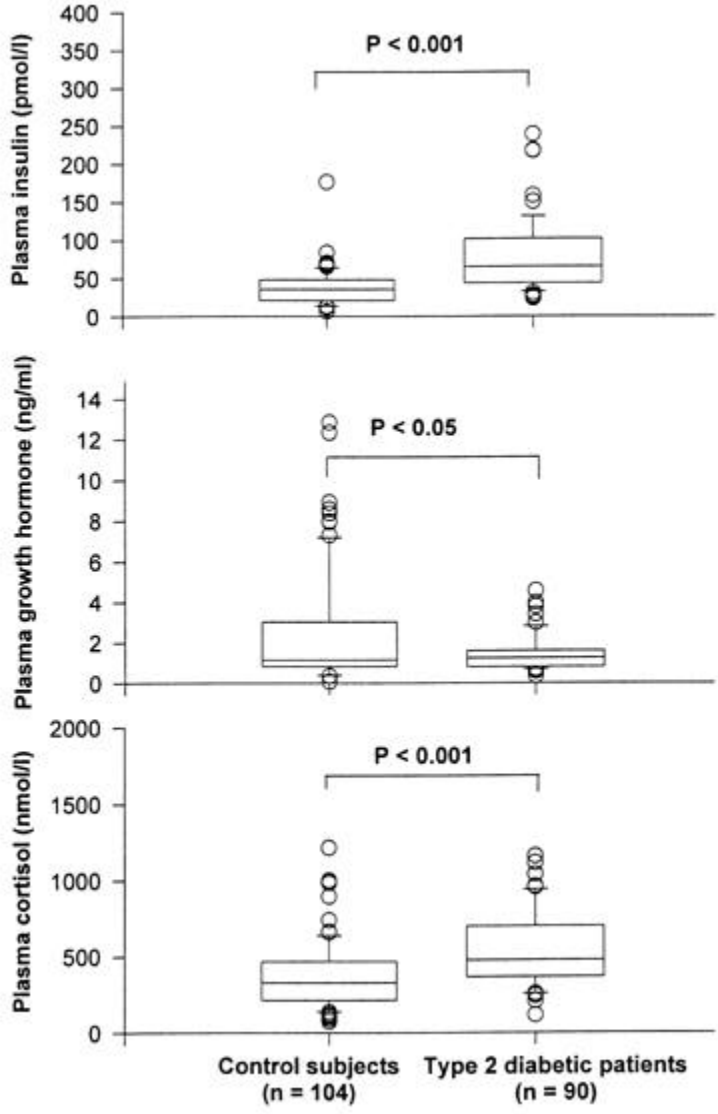


**Figure 1**—*Comparisons of plasma insulin, growth hormone, and cortisol concentrations between 104 control subjects and 90 type 2 diabetic patients. The lower and upper margins of the box represent the 25th and 75th percentiles, with the extended arms representing the 10th and 90th percentiles, respectively. The median is shown as the horizontal line within the box. Outlying points are shown individually.*

tolic blood pressure than women (all $P <$ 0.05). Nearly 50% of these young patients (46/90) had general obesity and >20% had central obesity. Of these patients, 6% (5/90), 23% (21/90), and 27% (24/90) had hypertension, dyslipidemia, and increased albuminuria, respectively. The hormonal profiles were similar between the two sex cohorts (Table 1).

### Comparisons between young type 2 diabetic patients and control subjects

The young diabetic patients were more obese and insulin-resistant; had higher blood pressure, $HbA_{1c}$, fasting plasma glucose concentrations, and 24-h UAE; and had worse lipid profile than the age- and sex-matched control subjects (Table 2). These young diabetic patients also had lower plasma GH ($P < 0.05$) but higher plasma cortisol and insulin concentrations than the control subjects (all $P < 0.001$, Fig. 1).

When analyzed as a group ($n$ = 194), waist circumference was correlated with plasma insulin ($r$ = 0.60, $P < 0.001$), insulin resistance index ($r$ = 0.70, $P <$ 0.001), plasma GH ($r = -0.24$, $P < 0.02$), and cortisol ($r$ = 0.38, $P < 0.001$) concentrations. After adjustment for obesity (BMI and waist circumference) using ANCOVA (Table 2), the differences in plasma GH between the diabetic patients and control subjects disappeared. However, the diabetic patients remained to be more insulin-resistant and had higher plasma insulin and cortisol concentrations than the control subjects (all $P < 0.001$).

### Relationships between central obesity, plasma insulin, GH, and cortisol concentrations

Table 3 summarizes the clinical and biochemical characteristics of all subjects divided into quartiles by their waist circumferences. Increasing quartiles of waist circumference were associated with increasing BMI, plasma glucose, blood pressure, and UAE and worse lipid profile (all $P <$ 0.01). Plasma GH concentrations declined ($P < 0.05$) while insulin resistance index, plasma insulin, and cortisol concentrations ($P < 0.01$) increased progressively with increasing waist circumference quartiles.

Table 4 shows the relationships between waist circumference, age, sex, plasma insulin, GH, and cortisol concentrations using stepwise multiple regression analysis. In the control subjects, sex (being higher in men) was the only independent factor for waist circumference. In the diabetic group, 51% of the variability of waist circumference was related to male sex, increased insulin and cortisol concentrations, as well as reduced GH levels.

**CONCLUSIONS** — In Caucasians, autoimmune type 1 diabetes is the predominant form of diabetes in patients with young onset of disease (41), which, however, remains relatively uncommon in Asian populations (25). In this cohort of Chinese diabetic patients with young onset of disease (28), we have excluded the 10% (17/153) of patients with autoimmune type 1 disease as suggested by the presence of antibodies to GAD. The remaining young type 2 diabetic patients have been previously reported to be more obese and have an older age of diagnosis, higher blood pressure, and worse lipid profiles than the type 1 patients (32).

In the present analysis, we further excluded patients who had renal impairment, insulin treatment, or retinopathy. In these remaining type 2 diabetic patients, 51% had general obesity and 19% had central obesity. The mean BMI of our young diabetic men and women was only 26.4 and 26.3 kg/m$^2$, respectively. These figures are much lower than the respective BMI of 29.5 and 33.1 kg/m$^2$ in Caucasian diabetic patients (42). Similarly, the mean waist cir-

**Table 3—*Comparison of clinical, biochemical, and hormonal parameters between subjects divided into quartiles of waist circumference***

| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---|---|---|---|---|
| Range of waist circumference (cm) | 58–67 | 68–74 | 75–84 | 85–123 |
| *n* | 49 | 48 | 48 | 49 |
| Age (years) | 33 ± 9 | 35 ± 7 | 32 ± 7 | 32 ± 6 |
| Male sex (%) | 21 | 39 | 51 | 50* |
| Duration of disease (years) | 5.0 ± 1.6 | 2.6 ± 2.1 | 2.8 ± 2.9 | 3.7 ± 3.7 |
| Weight (kg) | 48.4 ± 4.9 | 56.7 ± 4.2 | 63.3 ± 6.5 | 80.5 ± 12.3‡ |
| BMI (kg/m$^2$) | 19.8 ± 1.4 | 22.0 ± 1.7 | 24.4 ± 2.0 | 30.5 ± 3.9‡ |
| Waist circumference (cm) | 63 ± 3 | 71 ± 2 | 79 ± 3 | 94 ± 9‡ |
| WHR | 0.74 ± 0.04 | 0.78 ± 0.04 | 0.83 ± 0.04 | 0.89 ± 0.06‡ |
| Systolic blood pressure (mmHg) | 107 ± 8 | 109 ± 7 | 111 ± 11 | 118 ± 12‡ |
| Diastolic blood pressure (mmHg) | 62 ± 7 | 65 ± 8 | 68 ± 9 | 74 ± 10‡ |
| Biochemical parameters | | | | |
| $HbA_{1c}$ (%) | 6.1 ± 2.1 | 6.5 ± 2.1 | 7.1 ± 1.5 | 7.3 ± 1.8† |
| Fasting glucose (mmol/l) | 4.9 ± 0.6 | 6.1 ± 2.2 | 6.9 ± 2.4 | 8.8 ± 4.7‡ |
| Total cholesterol (mmol/l) | 4.2 ± 0.6 | 4.5 ± 0.7 | 4.9 ± 1.0 | 5.1 ± 1.1‡ |
| LDL cholesterol (mmol/l) | 2.4 ± 0.6 | 2.7 ± 0.7 | 3.0 ± 0.7 | 3.1 ± 0.9‡ |
| HDL cholesterol (mmol/l) | 1.6 ± 0.3 | 1.4 ± 0.3 | 1.2 ± 0.2 | 1.1 ± 0.3‡ |
| Serum triglyceride (mmol/l) | 0.5 ×/÷ 1.4 | 0.7 ×/÷ 1.5 | 1.2 ×/÷ 1.7 | 1.8 ×/÷ 2.0‡ |
| Plasma creatinine (μmol/l) | 62 ± 14 | 66 ± 16 | 68 ± 15 | 69 ± 17* |
| 24-h UAE (mg/day) | 6.2 ×/÷ 1.6 | 8.7 ×/÷ 2.3 | 20.1 ×/÷ 5.1 | 27.9 ×/÷ 5.2‡ |
| Hormonal parameters | | | | |
| Fasting insulin (pmol/l) | 30.3 ×/÷ 1.8 | 34.5 ×/÷ 1.6 | 63.3 ×/÷ 1.9 | 93.6 ×/÷ 1.7‡ |
| Insulin resistance index | 6.4 ×/÷ 1.8 | 8.8 ×/÷ 1.8 | 17.4 ×/÷ 2.1 | 33.6 ×/÷ 2.3‡ |
| Plasma growth hormone (ng/ml) | 2.1 ± 1.2 | 1.9 ± 1.3 | 1.4 ± 0.9 | 1.5 ± 1.0* |
| Plasma cortisol (nmol/l) | 316 ×/÷ 2 | 329 ×/÷ 2 | 396 ×/÷ 2 | 511 ×/÷ 2† |

Data are means ± SD or geometric means ×/÷ antilog SD. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ for the trend using polynomial analysis of variance.

cumference was 87 and 82 cm in our young Chinese diabetic men and women, respectively, compared with 100 and 98 cm in Caucasian diabetic patients (42). Similar findings have also been reported in our general population. Based on two large-scale population-based studies performed in 1990 (14,43) and 1995 (22), the mean BMI was only 23–24 kg/m$^2$ for both men and women. The mean waist circumferences were 81–83 cm for men and 75 cm for women in both studies. These figures are again much lower than the respective mean BMI of 26.0 and 26.3 kg/m$^2$ and waist circumference of 93 and 82 cm in Caucasian men and women (44). Based on these figures, we conclude that young Chinese diabetic patients had similar BMI and waist circumference as nondiabetic Caucasian subjects. However, they were markedly more obese than the control subjects, and the close relationships between body weight and distribution of obesity and cardiovascular risks remain in these relatively lean populations.

In comparison with the control subjects, these young type 2 diabetic patients were also more hyperinsulinemic, insulin-resistant, and dyslipidemic, and had higher blood pressure and increased albuminuria. These features resemble closely those of the metabolic syndrome associated with late-onset type 2 diabetes in Caucasians (1). In this respect, it is noteworthy that the mean age of these patients was only 33 years and the mean disease duration was 3 years, with some patients having the disease for as long as 15 years. Hence, unlike in Caucasian subjects, type 2 diabetes and the associated features of metabolic syndrome may have a much earlier presentation and occur at a lower degree of adiposity in Chinese subjects.

These young type 2 diabetic patients also had lower GH and higher cortisol concentrations than the control subjects.

**Table 4—*Standardized regression coefficients (β) for the relationships between waist circumference, age, sex, plasma insulin, growth hormone, and cortisol using stepwise multiple regression analyses in the separate control and diabetic groups***

| | Control subjects | Type 2 diabetic patients |
|---|---|---|
| *n* | 104 | 90 |
| Dependent variable: waist circumference | | |
| $R^2$ | 0.40 | 0.51 |
| *F* test | 29.2‡ | 9.8‡ |
| Independent variables | | |
| Age | NS | NS |
| Sex (male = 0, female = 1) | −0.67‡ | −0.27* |
| Plasma insulin | NS | 0.47‡ |
| Plasma growth hormone | NS | −0.41† |
| Plasma cortisol | NS | 0.33† |

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

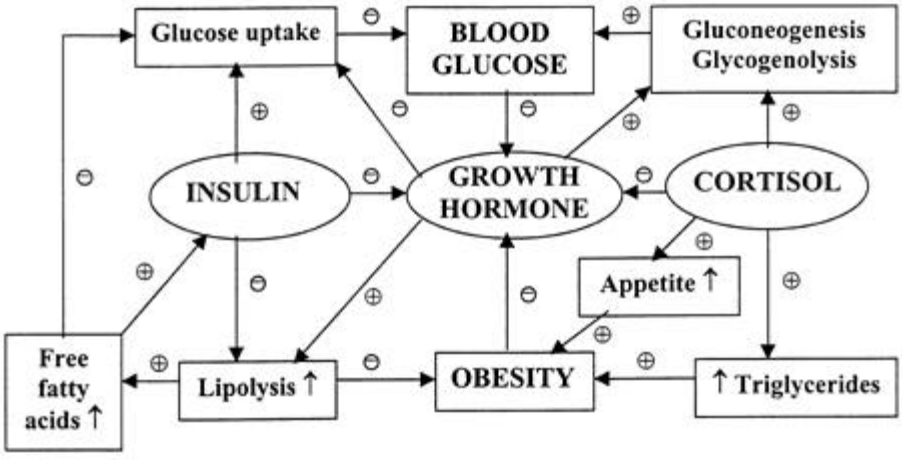


**Figure 2—***A hypothetical model describing the regulation of glucose and lipid metabolism by insulin, growth hormone, and cortisol. Growth hormone enhances lipolysis and increases peripheral glucose production. Its secretion is inhibited by obesity, insulin, and cortisol. Cortisol increases obesity by stimulating appetite. It also increases triglyceride synthesis and peripheral glucose production. Insulin inhibits lipolysis and peripheral glucose production as well as increases peripheral glucose uptake.*

When analyzed as a whole group, there were close associations between central obesity, reduced plasma GH, and insulin resistance index, as well as elevated plasma insulin and cortisol levels. These hormonal patterns are similar to that described in subjects with Cushing's syndrome and GH deficiency due to hypopituitarism. Both of these conditions are characterized by massive visceral fat accumulation (4,45–47). Other workers (48) have also reported reduced basal GH concentrations in type 2 diabetic patients. The secretion of GH and cortisol follows a well-defined circadian rhythm. GH secretion is periodic and occurs in a pulsatile fashion (49), whereas plasma cortisol has a peak in the early day (50). Hence, ideally, mean 24-h hormone concentrations, based on measurements taken at different intervals, should be used. However, such an assessment is labor intensive, expensive, and difficult to perform in a large sample size like that in the present study. Despite the inherent limitations of a single blood measurement, we were able to demonstrate the intimate relationships between GH, cortisol, and central obesity in these young type 2 diabetic patients. One would therefore expect stronger associations if multiple measurements had been involved.

In experimental studies, insulin resistance increases when a nondiabetic individual consumes excessive calories and gains weight. This is followed by increased insulin secretion to offset the insulin resistance (51). In animal studies, chronic overfeeding is also associated with hypersecretion of insulin (45). Apart from reflecting energy balance, the deposition of adipose tissue and intermediary metabolism are under complex hormonal regulation. In glucoregulation, insulin lowers blood glucose by stimulating peripheral glucose uptake as well as inhibiting gluconeogenesis and glycogenolysis. On the other hand, both GH and cortisol inhibit peripheral glucose utilization and enhance peripheral glucose production (6,52). In lipid metabolism, lipolysis is inhibited by insulin but stimulated by GH. The latter also enhances fat oxidation (53) and reduces fat deposition in the upper body adipocytes (54). Cortisol has potent effects on lipid metabolism. It stimulates hepatic triglyceride synthesis (55), increases the number of adipocytes in the visceral depots (56), and stimulates appetite and hence obesity (57). It also induces insulin resistance probably by antagonizing the antilipolytic effect of insulin (58) or increasing triglyceride production (59). On the other hand, GH secretion may be attenuated by obesity (60), the presence of excess fuels including glucose and lipid intermediates (61), hyperinsulinemia (62), and hypercortisolemia (63). Figure 2 summarizes the hypothetical model depicting the complex regulations of glucose and lipid metabolism by insulin, GH, and cortisol.

It has been hypothesized that periods of food deprivation and partial starvation may facilitate the development of a neurohormonal system characterized by hyperinsulinemia and hypercortisolemia, which aim to conserve energy (64). By contrast, caloric restriction, weight loss, or increased physical exercise have been shown to reduce plasma insulin concentrations (65), improve insulin resistance (66), and increase GH levels (67). In our young type 2 diabetic patients, 51% of the waist circumference, which was a good marker for central adiposity (68), was associated with male sex, increased plasma insulin, decreased plasma GH, and increased plasma cortisol.

Although there have been a number of reports on cardiovascular risk factors, hormonal derangement, and central obesity in type 2 diabetes, most of these data related to late-onset type 2 diabetes in Caucasians. In this article, we have presented novel and comprehensive data on all these aspects in Chinese type 2 diabetic patients with young-onset of disease. Until recently, autoimmune type 1 diabetes was presumed to be the main form of disease in young people. Our work and others' work (23,27,28) have now refuted this notion. This article provides additional evidence about the importance of obesity in young Chinese type 2 diabetic patients. Our hormonal data have also generated a new hypothesis to be tested regarding the pathogenesis of this highly prevalent disease in developing countries. Given the rising trend of childhood obesity and that 25% of the world's population is Chinese, our findings provide important epidemiological information.

In this cross-sectional study, we observed intimate relationships between GH, cortisol, insulin, and adiposity in young Chinese type 2 diabetic patients. Based on the rising trend of childhood obesity in Hong Kong Chinese (17,18), together with findings from other workers (69–71), we postulate that maladaptive hormonal responses to rapid changes in lifestyle characterized by overnutrition and physical inactivity may have led to obesity and type 2 diabetes in these young patients. On the other hand, it is also plausible that lifestyle-related obesity may have given rise to these hormonal patterns. Further studies, both clinical and experimental, are required to test these hypotheses.

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