Outcomes of Screening for Diabetes in High-Risk Hong Kong Chinese Subjects

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OBJECTIVE — To examine the significance of individual risk factors on the development of diabetes in subjects who underwent screening for diabetes.

RESEARCH DESIGN AND METHODS — A total of 1,649 Chinese subjects underwent screening for diabetes. They were asymptomatic but had known risk factors for diabetes, including a positive family history of diabetes, a past history of gestational diabetes, obesity, hypertension, and/or dyslipidemia. Another 799 age-matched subjects from the community who had no risk factors for diabetes were used as the comparison group.

RESULTS — Of the 1,649 subjects who underwent screening, 241 (14.6%) had diabetes. In these subjects, 989 (60.0%) had 1 risk factor, 502 (30.4%) had 2 risk factors, 141 (8.6%) had 3 risk factors, and 17 (1.0%) had 4 or 5 risk factors for diabetes. Of the 799 control subjects, 29 (3.6%) had diabetes. Compared with the comparison group, the odds ratio (95% CI) of having diabetes after adjustment for age was 5.2 (3.5–7.7) in the 1,649 subjects with known risk factors. The odds ratio of having diabetes increased from 3.7 in subjects with 1 risk factor to 28.4 in subjects with 4 or 5 risk factors.

CONCLUSIONS — In men, age, BMI, family history of diabetes, and dyslipidemia, and in women, age, BMI, hypertension, dyslipidemia, total cholesterol, and history of gestational diabetes are associated with increased odds of developing diabetes. These risk factors have additive effects on the odds of having diabetes. Early and regular screening for diabetes and other cardiovascular risk factors is essential in these high-risk individuals.

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Diabetes is associated with significant morbidity and mortality (1,2). Optimal glycemic control has been shown to delay the onset and reduce the progression of diabetic complications in both type 1 and type 2 diabetic patients (3,4). Subjects with type 2 diabetes are often asymptomatic, and diagnosis may be delayed for many years after onset. It has been estimated that ~5.4 million adults in the U.S. have undiagnosed type 2 diabetes (5,6). In Hong Kong Chinese subjects, up to 60% of diabetic subjects identified during epidemiological studies were previously undiagnosed (7). Established risk factors for glucose intolerance include age, obesity, a positive family history of diabetes, and a history of hypertension, gestational diabetes, or dyslipidemia. The American Diabetes Association recently recommended screening for glucose intolerance in subjects with these risk factors at 3-year intervals (6). We have previously reported similar risk factors in a general Chinese population (7,8). However, their relative significance on the development of diabetes in Chinese has not been well examined. We studied 75-g oral glucose tolerance test (OGTT) results in 1,649 Chinese subjects who underwent screening for diabetes because of the presence of risk factors. We aimed to examine the significance of individual risk factors on the development of diabetes in subjects who underwent screening.

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Abbreviations: BP, blood pressure; OGTT, oral glucose tolerance test.

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

RESEARCH DESIGN AND METHODS

Subjects

Subjects with known risk factors for diabetes underwent screening at the Diabetes Center of the Prince of Wales Hospital. They were referred from the community and other Departments of the Hospital. Between 1990 and 1996, 1,649 (75-g) OGTTs were performed for this purpose. All subjects were asymptomatic but had known risk factors for diabetes, including a positive family history of diabetes, a past history of gestational diabetes, obesity, hypertension and/or dyslipidemia. For the purpose of the analysis, we defined these risk factors as follows:

- A positive family history of diabetes in parents or siblings
- Obesity defined by a BMI $\geq$27 kg/m^2
- Hypertension defined by a sitting systolic blood pressure (BP) $\geq$140 mmHg and/or sitting diastolic BP $\geq$90 mmHg
- Dyslipidemia defined by a HDL cholesterol level $<$0.9 mmol/l and/or triglyceride level $\geq$2.8 mmol/l
- Gestational diabetes diagnosed by a 3-h 50-g OGTT if 2 or more plasma glucose values equaled or exceeded the following cutoff values: fasting, 5.0 mmol/l; 1 h, 9.5 mmol/l; 2 h, 8.1 mmol/l; 3 h, 7.0 mmol/l (9,10). The 3-h 50-g OGTTs were performed at 26–28 weeks of gestation if the subjects had clinical risk factors for gestational diabetes. The latter included a previous history of having a big baby, a family history of diabetes in first-degree relatives, and/or being aged $\geq$35 years. If the subjects had one or more risk factors that might indicate early-onset or current gestational diabetes, such as a previous history of gestational diabetes, glycosuria, polyhydramnios, or fetal macrosomia, the tests were arranged immediately after the first consultation. There was no

Table 1—*Clinical characteristics of the 799 control subjects and 1,649 subjects with risk factors for diabetes stratified according to sex*

	Normal control subjects	High-risk subjects
Women		
n	391	1,208
Age (years)	36.5 ± 8.6	35.6 ± 8.2
BMI (kg/m^2)	22.1 ± 2.5	25.4 ± 4.4†
Systolic BP (mmHg)	109 ± 14	116 ± 16†
Diastolic BP (mmHg)	69 ± 9	74 ± 11†
Fasting plasma glucose (mmol/l)	4.9 ± 0.7	5.4 ± 1.5†
2-h plasma glucose (mmol/l)	5.7 ± 2.0	7.6 ± 3.5†
Glycated hemoglobin (%)	4.3 ± 1.2	5.6 ± 1.2†
Total cholesterol (mmol/l)	4.8 ± 0.9	5.3 ± 1.1†
Fasting triglyceride (mmol/l)	0.8 ± 0.4	1.4 ± 1.0†
HDL cholesterol (mmol/l)	1.6 ± 0.3	1.4 ± 0.4†
LDL cholesterol (mmol/l)	3.0 ± 0.8	3.3 ± 0.9†
Smoking	1.3 (5)	3.3 (40)*
Risk factors (*n*)	0	1.5 ± 0.7†
Diabetes	3.3 (13)	13.7 (165)†
Men		
n	408	441
Age (years)	39.5 ± 8.7	40.1 ± 9.9
BMI (kg/m^2)	22.5 ± 2.3	25.6 ± 4.2†
Systolic BP (mmHg)	121 ± 11	130 ± 17†
Diastolic BP (mmHg)	77 ± 8	82 ± 11†
Fasting plasma glucose (mmol/l)	4.9 ± 0.8	5.4 ± 1.4†
2-h plasma glucose (mmol/l)	5.6 ± 2.0	7.4 ± 3.8†
Glycated hemoglobin (%)	5.0 ± 0.7	5.4 ± 1.1†
Total cholesterol (mmol/l)	5.3 ± 1.0	5.4 ± 1.0
Fasting triglyceride (mmol/l)	1.1 ± 0.5	1.9 ± 1.2†
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.1 ± 0.3†
LDL cholesterol (mmol/l)	3.5 ± 0.9	3.4 ± 1.0
Smoking	20.1 (82)	25.6 (113)
Risk factors (n)	0	1.4 ± 0.7†
Diabetes	3.9 (16)	17.2 (76)†

Data are *n*, means ± SD, or *n* (%). *P* values comparing normal and high-risk subjects: *$P < 0.05$, †$P < 0.001$.

biochemical screening test before the 50-g OGTT was performed.

These 1,649 subjects with risk factors were then scheduled to attend our center to repeat full clinical and laboratory assessment. All subjects attended after at least 8 h of fasting. Height and weight (measured to the nearest 0.1 kg) were measured with the subject in light clothing without shoes. BMI was calculated as weight (in kilograms) divided by height squared (in meters). After sitting for at least 5 min, BP was measured in the right arm using a standard mercury sphygmomanometer. The Korotkoff sound V was taken as the diastolic BP. The mean value of 2 readings (measured 1 min apart) was used. Fasting blood was taken for measurement of glycated hemoglobin, total cholesterol, triglyceride, and HDL cholesterol. All subjects underwent a 75-g OGTT for screening of diabetes using the World Health Organization 1998 criteria, i.e., fasting plasma glucose ≥7.0 mmol/l and/or 2-h plasma glucose ≥11.1 mmol/l (11).

Another 799 age-matched subjects were recruited from the community for comparison. They came from another population-based epidemiological study for cardiovascular risk factors. These 799 subjects had none of the risk factors listed above and were recruited for the present study. By definition, they had normal BP (<140/90 mmHg), BMI <27 kg/m^2, HDL cholesterol ≥0.9 mmol/l, and triglyceride levels <2.8 mmol/l and had neither a family history of diabetes nor a past history of gestational diabetes. These control subjects were studied with a similar study protocol as subjects who had risk factors for diabetes.

All subjects gave informed consent, and the study was approved by the Ethical Committee of the Chinese University of Hong Kong.

Analytical methods

Plasma glucose was measured by a glucose oxidase method (Diagnostic Chemicals reagent kit). Glycated hemoglobin was measured by an automated ion-exchange chromatographic method (Bio-Rad, Hercules, CA). Total cholesterol and triglyceride were measured in plasma enzymatically with commercial reagents (Dimension; Dupont Instruments, DE). HDL cholesterol was measured by the same enzymatic assay after precipitation of HDL by the heparin/manganese method. LDL cholesterol was calculated using Friedewald's equation (12).

Statistical analysis

Statistical analysis was performed using SPSS software (version 8.0) on an IBM compatible computer. All results are expressed as means ± SD. The χ^2 test and Student's *t* test were used for between-group comparisons. Odds ratios and 95% CIs of diabetes likelihood in subjects with risk factors compared with control subjects were calculated by logistic regression after adjustment for age. Multiple logistic regression analysis (stepwise forward) using age, BMI, hypertension, total cholesterol, LDL cholesterol, dyslipidemia (triglyceride ≥2.8 mmol/l and/or HDL cholesterol <0.9 mmol/l; 1 = yes, 0 = no), family history of diabetes (1 = yes, 0 = no), and past history of gestational diabetes (1 = yes, 0 = no) as independent variables was performed to estimate the independent effects of these variables on the risk of having diabetes. A *P* value <0.05 (2-tailed) was considered to be significant.

RESULTS — Of the 1,649 subjects who underwent screening, 441 (26.7%) were men and 1,208 (73.3%) were women. Their mean age was 38.0 ± 8.8 years (median 38.0, range 18–75). Of the 799 age-matched subjects in the comparison group, 408 (51.1%) were men and 391 (48.9%) were women. Their mean age was 36.8 ± 8.9 years (median 35.0, range 17–81). Table 1 summarizes the clinical characteristics of the high-risk subjects and control subjects. The percentages of diabetes in the high-risk subjects and control subjects were 14.6% (*n* = 241) and 3.6%

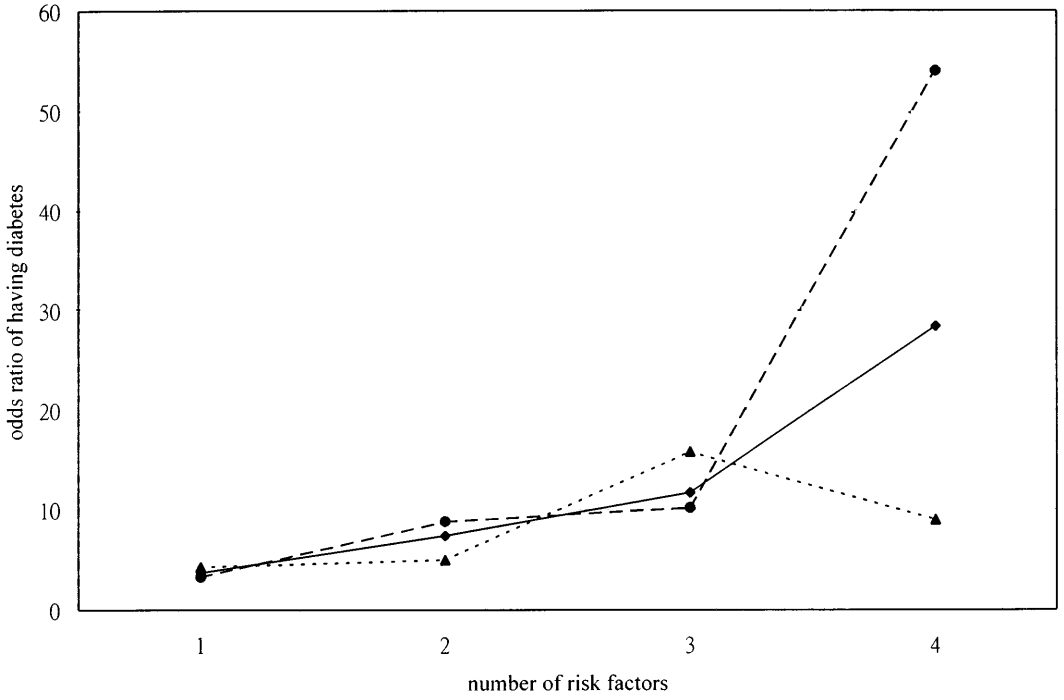

Figure 1—*Odds ratio of having diabetes in the 1,649 subjects with different numbers of risk factors compared with the 799 normal control subjects after adjustment for age.* —◆—, *Total subjects (*n = *1,649);* – –●– –, *women (*n = *1,208);* - - ▲ - -, *men (*n = *441).*

(*n* = 29), respectively. Among the 1,649 high-risk subjects, the prevalence of diabetes increased from 10.9, 19.0, 26.4% to 52.8% for subjects aged <40, 40–49, 50–59, and ≥60 years, respectively (*P* value for trend: <0.001). Compared with the comparison group, the odds ratio (95% CI) of having diabetes after adjustment for age in the subjects with known risk factors was 5.2 (3.5–7.7) ($P < 0.001$) [women: 5.1 (2.8–9.1); men: 5.1 (2.9–9.0)].

Of the 1,649 subjects who underwent screening for diabetes because of the presence of risk factors, 989 (60.0%; 691 women, 298 men) had 1 risk factor, 502 (30.4%; 393 women, 109 men) had 2 risk factors, 141 (8.6%; 110 women, 31 men) had 3 risk factors, and 17 (1.0%; 14 women, 3 men) had 4 or 5 risk factors for diabetes. There were 678 (41.1%) subjects with a family history of diabetes, 195 (11.8%) with hypertension, 324 (19.6%) with dyslipidemia, 533 (32.3%) with obesity, and 755 (62.5% of women) with a history of gestational diabetes. The mean number of risk factors was 1.5 ± 0.7. This result remained constant among subjects aged <40 years (1.5 ± 0.7), 40–49 years (1.5 ± 0.7), 50–59 years (1.5 ± 0.6), and ≥60 years (1.5 ± 0.8) (NS). Figure 1 shows the relationship between the odds ratio of having diabetes and the number of risk factors. The odds ratio (95% CI) of having diabetes after adjustment for age increased from 3.7 (2.4–5.7) in subjects with 1 risk factor to 7.4 (4.7–11.8) in subjects with 2 risk factors, 11.7 (6.4–21.1) in subjects with 3 risk factors, and 28.4 (8.8–91.1) in subjects with 4 or 5 risk factors. The progressive additive effect of risk factors on diabetes is obvious in women. However, the odds ratio reached a peak for those men who had 3 risk factors.

The effects of the individual risk factors on having diabetes were examined by analyzing those 989 subjects with only one of these risk factors. They were compared with the comparison group with no risk factors. The respective odds ratio of each risk factor are shown in Table 2. Multiple logistic regression analysis on all subjects with or without risk factors (*n* = 2,448) showed that age, BMI, family history of diabetes, and dyslipidemia had significant independent effects on having diabetes in men, whereas age, BMI, hypertension, dyslipidemia, total cholesterol, and history of gestational diabetes had significant independent effects on having diabetes in women (Table 3).

Table 2—*Odds ratios (95% CIs) of having diabetes in the 989 Chinese subjects with only one of the risk factors compared with the 799 control subjects after adjustment for age*

	Odds ratio for having diabetes	
	Women	Men
n	691	298
Family history of diabetes	0.63 (0.31–1.31)	2.87* (1.47–5.60)
History of gestational diabetes	1.85* (1.07–3.19)	—
Hypertension	2.65† (1.01–7.09)	0.65 (0.23–1.79)
Dyslipidemia	1.44 (0.47–4.45)	3.37* (1.74–6.53)
Obesity	2.29* (1.30–4.05)	2.15 (0.87–5.31)

Hypertension equals systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg; obesity equals BMI ≥27 kg/m^2; dyslipidemia equals HDL cholesterol level <0.9 mmol/l and/or fasting triglyceride level ≥2.8 mmol/l. *$P < 0.001$; †$P < 0.05$.

Table 3—*Multiple logistic regression analysis using age, BMI, family history of diabetes, hypertension, total cholesterol, LDL cholesterol, dyslipidemia, and past history of gestational diabetes (in women only) as independent variables accounting for the risk of having diabetes (*n = *2,448)*

	Multiple logistic regression analysis*			
Independent variables	β	SEM	*P*	Odds ratio (95% CI)
Women (*n* = 1,599)				
Age (years)	0.063	0.011	<0.001	1.06 (1.04–1.09)
BMI (kg/m^2)	0.104	0.020	<0.001	1.11 (1.07–1.15)
Hypertension (yes, no)	0.803	0.287	0.004	1.30 (1.11–1.52)
Total cholesterol (mmol/l)	0.260	0.080	0.001	2.48 (1.56–3.95)
Dyslipidemia (yes, no)	0.909	0.237	<0.001	2.29 (1.31–4.03)
Gestational diabetes (yes, no)	0.703	0.206	<0.001	2.02 (1.35–3.03)
Men (*n* = 849)				
Age (years)	0.090	0.013	<0.001	1.09 (1.07–1.12)
BMI (kg/m^2)	0.093	0.034	0.006	1.10 (1.03–1.17)
Family history of diabetes (yes, no)	0.866	0.268	0.001	2.27 (1.34–3.85)
Dyslipidemia (yes, no)	0.819	0.269	0.002	2.38 (1.40–4.02)

*For women, family history of diabetes and LDL cholesterol did not enter the model; for men, hypertension, total cholesterol, and LDL cholesterol did not enter the model. Hypertension equals sitting BP ≥140/90 mmHg; dyslipidemia equals fasting triglyceride level ≥2.8 mmol/l and/or HDL cholesterol level <0.9 mmol/l.

CONCLUSIONS — Most of the epidemiological studies in the U.S. have shown that as many as 50% of type 2 diabetic patients were not diagnosed previously (5,6). Similar figures (30–50%) were reported in studies from Europe (13), Taiwan (14), and Singapore (15). In Hong Kong, only 38% of diabetic subjects had been previously diagnosed (7). There are now epidemiological and interventional studies showing that hyperglycemia is an independent risk factor for mortality, cardiovascular morbidity, and diabetic complications (3,16,17). In view of the insidious onset of hyperglycemia in type 2 diabetes, early diagnosis by screening may help to reduce the risk of development and progression of cardiovascular events and diabetic complications (3,4,18).

Type 2 diabetes is frequently associated with dyslipidemia, obesity, hypertension, and old age (19–22). Subjects with a positive family history of diabetes (23,24) and a past history of gestational diabetes (25,26) also have increased risk or odds of developing diabetes. In this analysis, subjects with one or more risk factors had overall 5.2-fold increased odds of having diabetes compared with subjects with no risk factors. There was also an additive relationship between the number of risk factors and the relative odds of diabetes, especially in women. Odds increased from 3.7-fold in subjects with 1 risk factor to 28-fold in those with ≥4 risk factors.

It is noteworthy that among subjects with risk factors for diabetes, 40% had more than 1 risk factor. Given the effect of age on glucose intolerance and obesity, the incidence of diabetes in this high-risk group is expected to increase further with time. Prospective studies examining the additive effects of these risk factors on mortality and cardiovascular morbidity as well as diabetic complications are obviously needed in Chinese subjects. Nevertheless, there is now strong evidence from other studies, such as the Framingham Study and the Multiple Risk Factors Intervention Trial, confirming these associations (27–29).

In conclusion, age, BMI, family history of diabetes, and dyslipidemia in men and age, BMI, hypertension, dyslipidemia, total cholesterol, and history of gestational diabetes in women are associated with increased odds of developing diabetes in Hong Kong Chinese subjects. These risk factors are associated with age and have additive effects on the odds of having diabetes. Early and regular screening for diabetes and other cardiovascular risk factors is essential in these high-risk individuals.

References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factors Intervention Trial (MRFIT). *Diabetes Care* 16: 434–444, 1993
2. Jarrett R, McCartney P, Keen H: The Bedford Survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 22:79–84, 1982
3. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in IDDM. *N Engl J Med* 329: 977–986, 1993
4. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic macrovascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28: 103–107, 1995
5. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and IGT and plasma glucose levels in the US population aged 20–74 yr. *Diabetes* 36:523–534, 1987
6. American Diabetes Association: Screening for type 2 diabetes (Position Statement). *Diabetes Care* 21 (Suppl. 1):S20–S22, 1998
7. Cockram CS, Woo J, Lau E, Chan JC, Chan AY, Lau J, Swaminathan R, Donnan SP: The prevalence of diabetes mellitus and impaired glucose tolerance among Hong Kong Chinese adults of working age. *Diabetes Res Clin Pract* 21:67–73, 1993
8. Lau E, Woo J, Cockram CS, Chan A, Lam CW, Swaminathan R, Donnan SP: Serum lipid profile and its association with some cardiovascular risk factors in an urban Chinese population. *Pathology* 25:344–50, 1993
9. Abell DA, Beischer NA: Evaluation of the 3-hour OGTT in detection of significant hyperglycemia and hypoglycemia in pregnancy. *Diabetes* 24:874–880, 1975
10. Lau TK, Li YC: A perinatal audit of stillbirths in a teaching hospital in Hong Kong. *Aust N Z J Obstet Gynaecol* 28:190–192, 1988
11. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 15: 539–553, 1998
12. Friedewald WT, Levy RI, Fredrickason DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
13. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ: Prevalence and determinants of glucose tolerance in a Dutch Caucasian population: the Hoorn Study. *Diabetes Care* 18:1270–1273, 1995
14. Chou P, Chen HH, Hsiao KJ: Community-

based epidemiological study on diabetes in Pu-Li, Taiwan. *Diabetes Care* 15:81–89, 1992
15. Thai AC, Yeo PPB, Lun KC: Changing prevalence of diabetes mellitus in Singapore over a ten year period. In *Epidemiology of Diabetes Mellitus. Proceedings of the International Symposium on Epidemiology of Diabetes Mellitus.* Vannasaeng S and Vichayanrat A, Eds. Bangkok, Thailand, Crystal House, 1986, p. 63–67
16. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry Study. *Diabetes Care* 20:163–169, 1997
17. Chan JCN, Swaminathan R, Cheung CK, Critchely JA, Cheung MY, Cockram CS: Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. *Diabetes Care* 18: 1013–1016, 1995
18. Eastman RC, Cowie CC, Harris MI: Undiagnosed diabetes or impaired glucose tolerance and cardiovascular risk. *Diabetes Care* 20:127–128, 1997
19. Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, Wai HP, Li JK, So WY, Cockram CS: Simple anthropometric indexes and cardiovascular risk factors in Chinese. *Int J Obes* 21:995–1001, 1997
20. Ferrannini E, DeFronzo RA: The association of hypertension, diabetes and obesity: a review. *J Nephrol* 1:3–15, 1989
21. Chan JCN, Cheung CK, Swaminathan R, Nicholls MC, Cockram CS: Obesity, albuminuria and hypertension among Hong Kong Chinese with NIDDM. *Postgrad Med J* 69:204–210, 1993
22. Ko GT, Chan JC, Woo J, Lau EM, Yeung VT, Chow CC, Wai HP, Li JK, So WY, Cockram CS: The effect of age on cardiovascular risk factors in Chinese women. *Int J Cardiol* 61: 221–227, 1997
23. Mykkanen L, Kuusisto J, Pyorala K, Laakso M: Cardiovascular disease risk factors as predictors of type 2 diabetes mellitus in elderly subjects. *Diabetologia* 36:553–559, 1993
24. Haas T, Svacina S, Pav J, Hovorka R, Sucharda P, Sonka J: Risk calculation of type 2 diabetes. *Comput Methods Programs Biomed* 41:297–303, 1994
25. Henry OA, Beischer NA: Long-term implications of gestational diabetes for the mother. *Bailliere's Clin Obstet Gynecol* 5: 461–483, 1991
26. O'Sullivan JB: Diabetes mellitus after GDM. *Diabetes* 29:131–135, 1991
27. Seidell JC, Verschuren WM, van Leer EM, Kromhout D: Overweight, underweight, and mortality: a prospective study of 48,287 men and women. *Arch Intern Med* 156:958–963, 1996
28. Isles CG, Hole DJ, Gillis CR, Hawthorne VM, Lever AF: Plasma cholesterol, coronary heart disease and cancer in the Renfrew and Paisley Survey. *Br Med J* 298:920–924, 1989
29. Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K: Central obesity and coronary heart disease in men. *Lancet* 1:821–824, 1987