

CLINICAL STUDY

Identification of factors differentially associated with isolated impaired fasting glucose and isolated post-load impaired glucose tolerance: the Hong Kong Cardiovascular Risk Factor Study

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Abstract

Background: The use of fasting and post-prandial glucose levels in the classification of hyperglycaemic states often identifies distinct subjects, but the factors determining these intermediate-isolated glucose intolerant states are yet to be clearly elucidated in Chinese subjects.

Methods: Representative subjects ($n = 2769$) were randomly recruited from the Hong Kong Chinese population and glycaemic status was determined using both fasting and 2h 75 g oral glucose tolerance test glucose levels. The relationship between the groups with isolated glucose intolerance and vascular risk factors was investigated using ANOVA and logistic regression analyses.

Results: Using either criterion, diabetes was identified in 265 (9.6%) subjects and glucose intolerance in 568 (20.5%) subjects. Of those 568, isolated impaired glucose tolerance (IGT) using the post-load criterion was identified in 49.5% and isolated impaired fasting glucose (IFG) in 30.5%. Ageing and hyperinsulinaemia were common determinants of IGT and IFG; with small hip circumference a marker of poorer early life development and being born in China rather than Hong Kong, a possible low birth weight marker was also associated with IFG. Hypertension, hypertriglyceridaemia and poor education were also associated with IGT. When we looked for factors differentially associated with these glucose intolerant states, female sex, greater hip circumference, high triglyceride levels, low fasting insulin levels, and not being born in China were independently associated with isolated IGT compared with isolated IFG.

Conclusion: Despite common antecedents to the glucose intolerant states, isolated IFG appeared to be particularly associated with early life development, and isolated IGT was more strongly associated with obesity-related determinants such as hypertriglyceridaemia.

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Introduction

Type-2 diabetes is closely associated with micro- and macrovascular disease, the major causes of morbidity and mortality in these patients, with a two- to three-fold increased risk of cardiovascular disease than those without diabetes (1–3). Glucose intolerant or prediabetic states with intermediate glucose levels have been defined. These are based on either 2h 75 g oral glucose tolerance test (OGTT) post-load glucose levels for impaired glucose tolerance (IGT) (4), or fasting glucose levels describing impaired fasting glucose (IFG) (5). Both glucose intolerant states have been shown to predict the development of diabetes (6–8). However, there is also considerable discordance between the subjects classified by these criteria (8–11). Recently, the American Diabetes

Association reduced the lower limit of IFG from 6.1 to 5.6 mmol/l, in part, to expand the proportion of subjects diagnosed with IFG to levels similar to those diagnosed with IGT using the OGTT (12), but these criteria still do not identify the same subjects.

Using the old criteria, there have been conflicting reports describing possible differences between the subjects with either IFG or IGT, with some studies reporting similar levels of cardiovascular risk factors (8, 9), and others suggesting differences between the groups (7, 8, 13, 14). The limited overlap of the IFG and IGT groups suggests the possibility that these are distinct conditions with different aetiologies (8, 15). Both these glucose intolerant states have been shown to increase vascular disease mortality, although limited comparative data tend to suggest that after adjustment for other

vascular risk factors, post-load glucose levels may be better predictors of cardiovascular disease mortality than fasting levels (8, 10), but this remains to be confirmed (14). Such associations with glucose intolerance and increased vascular risk factor levels and subsequent disease events have important health implications, yet the factors associated with the particular form of fasting or post-load glucose intolerance remain unclear. In the present study, we describe the relative prevalence of vascular risk factors associated with isolated IFG and isolated IGT, and an attempt to identify the determinants contributing to the differential development of these glucose intolerant states in a population-based study of Hong Kong Chinese.

Methods

In a cardiovascular risk factor prevalence study, 7730 Chinese, aged 25–74 years were selected for telephone interviews using randomly generated telephone numbers using random dialling. One household member, who was a Chinese Hong Kong resident aged 25–74 years was randomly selected to answer questions read by interviewers in Hong Kong from 1994 to 1996. Telephone coverage is near universal in Hong Kong households. The response rate of the telephone survey was 78%. The interviewers were trained to follow procedures of subject selection and to avoid information bias. Subjects who were pregnant, hospitalised or had serious diseases such as cancer were not included. A standardised questionnaire modified from the questionnaire used in the 1992 Singapore National Health Survey was used to collect demographic characteristics. The detailed methods of measurement had been reported elsewhere (16, 17). Data included smoking, with present smokers smoking at least 1 cigarette per week, and ex-smokers being a smoker of at least 1 cigarette per week who has quit for at least 6 months. As ex-smokers usually quit due to the result of health problems, we use an 'ever smoker' category that combines the present and ex-smoker groups for the analyses. Alcohol consumption is categorised as those who are present consumers, taking alcoholic drinks at least once per month, and others. Education levels were categorised as those with primary school or below, those who attended secondary school, and those who reached matriculation or above. Place of birth was recorded as Hong Kong or China, i.e. highlighting whether the subjects are migrants from southern China. We have found that participants born in China, a possible marker of low birth weight, are likely to have grown up under a range of poorer conditions, including limited perinatal and childhood nutrition and medical care (18). Exercise activity was dichotomised based on whether the subjects participated in more or less than 30 min of vigorous activity per week. Angina was identified using the Rose Angina questionnaire. Self-reported physician-diagnosed history of vascular disease,

including stroke and coronary heart disease was also collected. The method of telephone interview was validated in a morbidity survey in Hong Kong (19), and the study sample of this telephone survey was shown to be comparable with the Hong Kong 1996 By-census findings in terms of gender, age, place of birth and marital status (16). The study was approved by the University of Hong Kong Ethics Committee and all subjects gave written, informed consent prior to participating in the study, which complied with the Declaration of Helsinki.

A total of 2763 subjects had physical examinations, including anthropometry and blood tests (fasting and 2h post-75 g anhydrous glucose load, OGTT) and had fasting insulin results available. The attendees and non-attendees were generally shown to match the Hong Kong population, and non-attendance bias should be small (16). For example, for place of birth, exercise, smoking status, self-reported medically diagnosed diabetes or hypertension, and general health the Cohen effect sizes were negligible (<0.1); effect sizes for job activity – a proxy for socio-economic status (0.16), and education (0.23) were slightly larger, but still acceptable. The biochemical parameters were measured in the Clinical Biochemistry Unit of Queen Mary Hospital, a teaching hospital of the Faculty of Medicine, the University of Hong Kong. The laboratory used standard methods and met international quality control standards. Blood pressure was measured in duplicate after 10 min rest, 2–3 min apart. If the readings differed by ≥ 4 mmHg then a third reading was taken. Extreme blood pressures were confirmed on a subsequent visit.

Diabetes was classified as a fasting glucose of ≥ 7.0 mmol/l or post-load glucose of ≥ 11.1 mmol/l, or as receiving hypoglycaemic medication, whereas glucose intolerance in the non-diabetic subjects was classified as fasting glucose ≥ 5.6 and <7.0 mmol/l (IFG) or post-load glucose ≥ 7.8 and <11.1 mmol/l (IGT) respectively (12, 20). Subjects were classified as having a normal glycaemic profile if their fasting plasma glucose was < 5.6 mmol/l and OGTT level was < 7.8 mmol/l. We use the term glucose intolerance as a collective term for non-diabetic subjects with IFG and/or IGT. For the indices of insulin resistance, we used the fasting insulin–glucose product, which, divided by 22.5, is numerically equivalent to the homeostasis model assessment (HOMA) (21). The fasting insulin–glucose product has been shown to correlate well with the results of the euglycaemic hyperinsulinaemic clamp in population-based studies (22), and the glucose results of the OGTT. Fasting insulin and glucose levels can also be used to estimate β -cell function ($\text{HOMA } \beta\text{-cell function} = (20 - \text{fasting insulin}) / (\text{fasting plasma glucose (FPG)} - 3.5)$) (21). Categorical classification of vascular disease risk factors was based on the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines (23): high blood pressure was defined as systolic and/or diastolic blood pressures $\geq 130/85$ mmHg or as receiving blood pressure lowering drugs; hyperglycaemia as a fasting

plasma glucose ≥ 6.1 mmol/l (110 mg/dl) or as receiving glucose lowering drugs; hypertriglyceridaemia as a fasting plasma triglycerides ≥ 1.69 mmol/l (150 mg/dl); and low high density lipoprotein (HDL)-cholesterol as a fasting HDL-cholesterol < 1.04 or 1.29 mmol (40 or 50 mg/dl) in males and females respectively. In the guidelines, central obesity is defined as a waist circumference > 88 or 102 cm in females and males respectively. However, the World Health Organisation has recognised the disproportionate contribution of obesity to the development of cardiovascular risk factors in Asians and has provisionally lowered the classification of central obesity to ≥ 80 or ≥ 90 cm in females and males respectively (24), which are the levels we used in the present analyses. Additionally, hypercholesterolaemia was defined as a total cholesterol ≥ 6.2 mmol/l or as receiving treatment to lower lipid levels (23, 25). General obesity was classified as a body mass index (BMI) ≥ 25.0 kg/m² (24).

Data from normally distributed parameters were presented as mean \pm s.d., whereas skewed data were logarithmically transformed and expressed as geometric means with 95% confidence intervals. Student's *t*-test was used to determine differences between the IFG and the IGT groups, otherwise ANOVA was used to determine differences in continuous variables between multiple groups. The χ^2 -test was used to determine differences in the prevalence rates of the categorical variables between the groups. The tertile groups of hip circumference, fasting insulin, HOMA β -cell function and BMI were produced to rank the subjects by levels of these parameters in the non-diabetic population.

Logistic regression was used to assess factors associated with the presence of glucose intolerant states (IGT and IFG) compared with normoglycaemia, and the differential presence of IGT relative to IFG. Age (25–34,

35–44, 45–54, 55–64, 65–74 years), sex, NCEP diagnosis of hypertension, NCEP low HDL-cholesterolaemia, NCEP hypertriglyceridaemia, hypercholesterolaemia (total cholesterol ≥ 6.2 mol/l), central obesity and coronary heart disease/angina, place of birth (Hong Kong/China), exercise activity (< 30 min vigorous activity per week/ ≥ 30 min vigorous activity per week), smoking (never/ever), alcohol consumption (current/non-drinker), education level (\leq primary school/secondary school/ \geq matriculation), and tertile groups of hip circumference and fasting insulin were included in the bivariate and multivariate analyses. Additionally, tertiles of the HOMA β -cell function, and general obesity were included in the bivariate analyses only, as glucose is used to define glucose intolerance and therefore any parameter containing it would be strongly associated. The inclusion of two closely related parameters may result in collinearity and therefore central rather than general obesity indices were included in the multivariate analyses. The Statistics Package for Social Sciences (SPSS for windows, version 11.0.1, 2001; SPSS, Inc., Chicago, IL, USA) was used for all the analyses.

Results

Out of 2763 Chinese subjects recruited into the study, 158 (5.7%) subjects were found to have diabetes based on the fasting glucose levels alone, with an additional 362 (12.7%) having IFG levels. When the 75 g OGTT criterion alone was used, 249 (9.0%) had diabetes and 407 (14.7%) had IGT. Using either criterion, 265 (9.6%) were diagnosed with diabetes and 568 (20.5%) with glucose intolerance. The distributions of normal, glucose intolerant and diabetic states are shown in Figure 1.

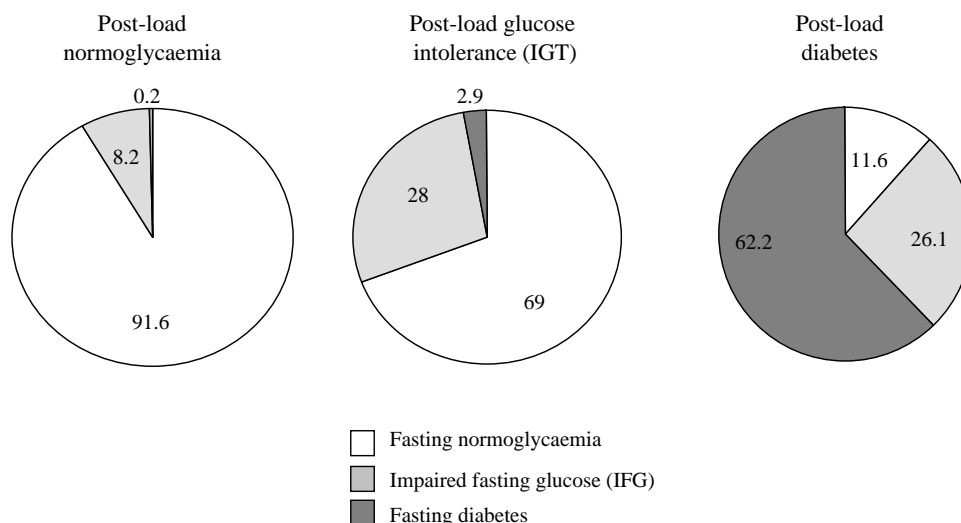


Figure 1 Pie charts describing the percentages of subjects categorised by fasting glycaemia for each of the groups with categorised post-load glycaemia. Diabetes was classified as a fasting glucose of ≥ 7.0 mmol/l or post-load glucose of ≥ 11.1 mmol/l, or as receiving hypoglycaemic medication; glucose intolerance in the non-diabetic subjects was classified as fasting glucose ≥ 5.6 and < 7.0 mmol/l (IFG) or post-load glucose ≥ 7.8 and < 11.1 mmol/l (IGT) respectively (12, 21). The subjects were classified as having a normal glycaemic profile if their fasting plasma glucose was < 5.6 mmol/l and oral glucose tolerance test level was < 7.8 mmol/l.

Although 69.9, 4.1 and 5.1% of the population were diagnosed as having normal glycaemic levels, glucose intolerance and diabetes respectively, by both fasting and post-load criteria 577 (20.8%) were differentially diagnosed. Out of 577 subjects, 5.5% of those classified as normal by the fasting glucose criterion were considered diabetic by the OGTT criterion and reciprocally 0.8% of those normal by the OGTT criterion were diabetic by the fasting glucose criterion. After excluding those identified with diabetes by either criterion, 2498 subjects remained in whom 568 (22.7%) subjects had glucose intolerance according to either criterion. Out of those 568 subjects, 114 (20.1%) had both IFG and IGT, 172 (30.5%) had isolated IFG and 281 (49.5%) had isolated IGT (Table 1). However, despite the use of different diagnostic criteria, there was still a correlation between fasting and post-load hyperglycaemia ($r=0.36$; $P<0.001$; Figure 2), even after adjustment for age and gender ($r=0.36$; $P<0.001$).

Compared with the normoglycaemic subjects, those with glucose intolerance, irrespective of whether categorised by fasting or post-load glucose levels, generally had a more adverse vascular disease risk factor profile with significantly worse blood pressure, lipid and anthropometry (Table 1). When the anthropometric and biochemical parameters were compared

between the subjects with isolated IFG and isolated IGT, differences were observed, as expected, in fasting glucose and insulin–glucose product and post-load glucose levels. There were significantly fewer males in the IGT only group compared with the IFG group (65.9 vs 40.2%, $P<0.001$). Although there was no significant difference in waist circumference and waist-to-hip ratios between the two groups, these levels were significantly higher in males with isolated IGT compared with IFG (86.8 ± 10.2 vs 84.2 ± 9.5 cm, $P=0.049$, and 0.91 ± 0.07 vs 0.89 ± 0.07 , $P=0.038$ respectively). Furthermore, waist circumference was also greater in the females with IGT, but the difference did not reach significance (79.2 ± 9.6 vs 76.9 ± 9.7 cm, $P=0.11$). There were also significantly more centrally obese participants in the IGT group compared with the IFG group (41.3 vs 25.6%, $P=0.001$). Similarly, although mean levels of HDL-cholesterol and triglycerides were similar, there tended to be more subjects with low HDL-cholesterol levels (54.8 vs 45.3%, $P=0.051$) and hypertriglyceridaemia (29.2 vs 20.9%, $P=0.052$) in those with IGT compared with IFG.

When logistic regression was used to assess factors associated with the presence of glucose intolerance; a number of factors were identified in the bivariate

Table 1 Biochemical and anthropometric parameters in 2498 non-diabetic Chinese subjects grouped by fasting and post-load glucose levels.

Parameters	Normal (<i>n</i> =1931)	IFG only (<i>n</i> =172)	IGT only (<i>n</i> =281)	IFG and IGT (<i>n</i> =114)	<i>P</i> value for trend
Age (years)	43.1 ± 11.9	49.9 ± 12.6*	49.9 ± 13.4* ⁿ	53.2 ± 11.7* ^{n,n}	<0.001
Sex (% male)	48.8	65.9*	40.2* [†]	55.3* ^{n,†,‡}	NS
Fasting glucose (mmol/l)	4.94 (4.92–4.95)	5.90 (5.86–5.93)*	5.12 (5.09–5.16)* [†]	6.02 (5.97–6.07)* ^{n,‡}	<0.001
OGTT 2-h glucose (mmol/l)	5.45 (5.39–5.50)	5.87 (5.63–6.11)*	8.89 (8.80–8.98)* [†]	9.20 (9.04–9.36)* ^{†,‡}	<0.001
Fasting insulin (mIU/l)	4.45 (4.32–4.58)	6.17 (5.58–6.82)*	5.69 (5.23–6.18)* ⁿ	7.11 (6.26–8.07)* ^{n,‡}	<0.001
Fasting insulin–glucose product	21.9 (21.3–22.6)	36.4 (29.3–40.2)*	29.3 (26.9–31.9)* [†]	42.7 (37.6–48.6)* ^{n,‡}	<0.001
HOMA β-cell function	10.3 (10.1–10.5)	5.3 (4.9–5.7)*	7.8 (7.2–8.3)* [†]	4.6 (2.5–5.1)* ^{n,‡}	<0.001
Systolic blood pressure (mmHg)	115 ± 17	125 ± 19*	124 ± 23* ⁿ	133 ± 20* ^{n,†,‡}	<0.001
Diastolic blood pressure (mmHg)	73 ± 10	77 ± 11*	77 ± 12* ⁿ	81 ± 11* ^{n,†,‡}	<0.001
Fibrinogen (g/l)	2.50 ± 0.57	2.58 ± 0.56 ⁿ	2.63 ± 0.59* ⁿ	2.70 ± 0.62* ^{n,n}	<0.001
Total cholesterol (mmol/l)	4.96 ± 0.95	5.31 ± 0.97*	5.37 ± 0.96* ⁿ	5.44 ± 0.96* ^{n,n}	<0.001
HDL-cholesterol (mmol/l)	1.29 ± 0.33	1.23 ± 0.32 ⁿ	1.21 ± 0.31* ⁿ	1.14 ± 0.31* ^{n,n}	<0.001
Apolipoprotein A1 (mmol/l)	1.37 ± 0.27	1.40 ± 0.24 ⁿ	1.36 ± 0.27 ^{n,n}	1.39 ± 0.29* ^{n,‡}	NS
LDL-cholesterol (mmol/l)	3.16 ± 0.85	3.51 ± 0.88*	3.50 ± 0.88* ⁿ	3.56 ± 0.88* ^{n,n}	<0.001
Apolipoprotein B (mmol/l)	0.91 ± 0.29	1.04 ± 0.28*	1.05 ± 0.31* ⁿ	1.10 ± 0.25* ^{n,n}	<0.001
LDL-cholesterol-to-apolipoprotein B ratio	3.57 ± 0.66	3.40 ± 0.54*	3.45 ± 0.71* ⁿ	3.25 ± 0.55* ^{n,n}	<0.001
Triglyceride (mmol/l)	0.95 (0.93–0.97)	1.12 (1.04–1.21)*	1.27 (1.19–1.35)* ⁿ	1.45 (1.19–1.35)* ^{†,‡}	<0.001
Lipoprotein (a)	143 (131–155)	138 (107–180) ⁿ	148 (116–189) ^{n,n}	110 (83–146) ^{n,n}	NS
Body mass index (kg/m ²)	23.5 ± 3.4	24.8 ± 3.8*	25.3 ± 3.9* ⁿ	26.1 ± 3.2* ^{n,‡}	<0.001
Waist circumference (cm)	77.1 ± 9.6	81.8 ± 10.1*	82.3 ± 10.5* ⁿ	84.8 ± 8.8* ^{†,‡}	<0.001
Hip circumference (cm)	93.5 ± 6.4	93.9 ± 7.2 ⁿ	94.9 ± 6.9* ⁿ	96.2 ± 6.9* ^{†,‡}	<0.001
Waist-to-hip ratio	0.82 ± 0.08	0.87 ± 0.08*	0.87 ± 0.08* ⁿ	0.88 ± 0.07* ^{n,n}	<0.001
Prevalence of CHD/angina (%)	4.4	3.5 ⁿ	6.8 ^{n,n}	6.1 ^{n,n}	NS
Place of birth (China, %)	39.6	59.3*	48.9* [†]	55.3* ^{n,n}	<0.001
Alcohol consumption (current, %)	18.7	25.1*	15.3* [†]	21.2 ^{n,n}	NS
Smokers (daily, %)	25.4	29.5 ⁿ	20.6 ^{n,n}	29.8 ^{n,n}	NS

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HOMA, homeostatic model assessment; HDL, high density lipoprotein; LDL, low density lipoprotein; CHD, coronary heart disease; OGTT, oral glucose tolerance test; $P<0.05$ compared with the *normoglycaemic, [†]IFG, and [‡]IGT groups; *n*, non-significant.

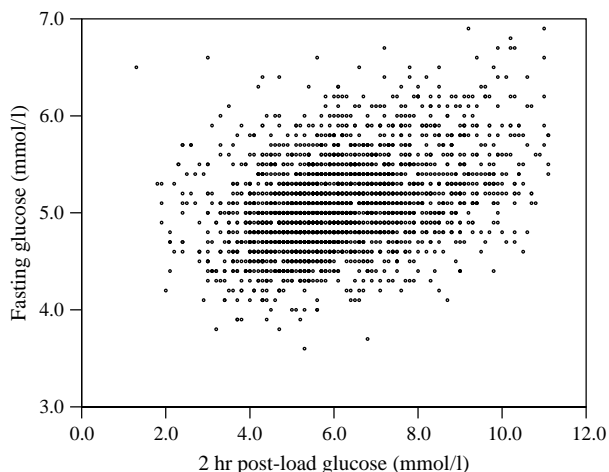


Figure 2 Scatter plot of fasting and 2h post-load glucose levels in the non-diabetic Chinese participants.

analyses compared with normoglycaemic group (Table 2). Ageing, hypertension, dyslipidaemia, hyperinsulinaemia and decreased β -cell function were associated with the glucose intolerant states compared with the normoglycaemic group (Table 2). As expected, increased adiposity indices, particularly central obesity, were associated with increased prevalence of the glucose intolerant states (Table 2). Although there appears to be a positive association with hip circumference and glucose intolerance (Table 2), after adjustment for general adiposity (BMI), there was a clear significant inverse relationship with both IFG (odds ratio 0.61 (0.47–0.80), $P < 0.001$, across each tertile) and IGT (odds ratio 0.72 (0.58–0.89), $P = 0.002$, across each tertile).

A number of these factors remained independently associated with glucose intolerance when multivariate analyses were performed (Table 3). IFG was associated with ageing, male gender, hypertension, decreasing hip circumference, hyperinsulinaemia, and being born in China when compared with the normoglycaemics, whereas, ageing, hypertension, hypertriglyceridaemia, and decreased education were associated with increased prevalence of IGT (Table 3).

When comparing those with IFG and IGT only, female sex was strongly associated with IGT status relative to the IFG group increasing the odds ratio by over 400%. Similarly, those with hypertriglyceridaemia had an excess risk of 157%, whereas the excess risk in the highest hip circumference tertile compared with the lowest was 133%. In contrast, being born in China compared with Hong Kong, and having higher insulin levels were associated with having IFG status, with risk of having IGT decreased by 50% if born in China, and 74% for the highest insulin tertile group compared with the lowest.

Discussion

Out of the 568 (20.5%) subjects with glucose intolerance, 30.5% were found to have isolated IFG and 49.5% to have isolated IGT, but only 20.1% were similarly classified by both IFG and IGT criteria. Therefore, approximately 80% of those with glucose intolerance were differentially categorised by the two criteria. Even with the new criteria for FPG, which utilises the lower cut-off point of 5.6 mmol/l, the proportion of subjects with glucose intolerance by the fasting criterion was smaller than when described using the post-load glucose levels (30.5 vs 49.5%), particularly if the overlapping subjects were excluded. Similar observations have been reported in Western and other Asian populations (8, 26, 27).

Of the subjects with isolated glucose intolerance, those with isolated IGT were predominantly female, with about 26% more females than in the isolated IFG group, in which males predominated. In the analyses, female sex was therefore strongly associated with having isolated IGT. The higher prevalence of females in the isolated IGT group has been reported in a number of studies in Asia and Europe (8, 26, 27). It has been proposed that due to the smaller build of females, the same dose of glucose load has a proportionally larger effect than in the males. In this Hong Kong Chinese population, the males are about 8% taller (165.0 vs 153.3 cm, $P < 0.001$) and 18% stronger (66.3 ± 10.5 vs 56.2 ± 9.1 kg, $P < 0.001$) than females, which may account, in part, the observed differences in the prevalence of isolated IGT between the males and females.

We found that smaller hip circumference after adjustment for adiposity was associated with glucose intolerance, and in particular, with isolated IFG. It has been proposed that a relatively small hip circumference may reflect, at least in part, a relatively small leg muscle mass (28). Skeletal muscle is the major site of glucose disposal and a relatively smaller muscle mass may predispose individuals to the deleterious effects of insulin resistance (29). Similar relationships between relatively small hip circumferences and diabetes have been reported (28, 30–33). These relationships may be determined by adaptive programming to overcome the adverse intrauterine milieu associated with early life growth retardation termed 'thrifty phenotype', and/or rapid lifestyle changes in genetically susceptible populations termed 'thrifty genotype' effects (34, 35). Hip circumference has been reported to be a marker of early development, with a small hip circumference associated with low birth weight (36). Poor foetal development, proxied by low birth weight has been shown to be associated with an increased risk of glucose intolerance (34, 35). Low birth weight, from either inadequate maternal nutrition or abnormal placental function, results in foetal nutritional deprivation inducing possible secondary metabolic adaptations and

Table 2 Crude odds ratios (95% confidence intervals) for univariate determinants of glucose intolerance groups relative to reference groups using logistic regression analyses. An odds ratio > 1 suggests the parameter increases risk of having glucose intolerance relative to the reference group.

Parameters (%)	Categories	IFG only versus normoglycaemia ^a	P value	IGT only versus normoglycaemia ^a	P value	IGT versus IFG ^a	P value
Age	25–34	1		1		1	
	35–44	1.87 (1.08–3.23)	0.025	1.56 (1.05–2.33)	0.029	0.84 (0.43–1.62)	NS
	45–54	3.29 (1.90–5.72)	<0.001	1.89 (1.22–2.92)	0.004	0.57 (0.29–1.13)	NS
	55–64	3.36 (1.86–6.07)	<0.001	2.80 (1.80–4.35)	<0.001	0.83 (0.41–1.69)	NS
	65–74	6.20 (3.40–11.32)	<0.001	5.55 (3.54–8.70)	<0.001	0.90 (0.44–1.81)	NS
Sex	Male	1		1		1	
	Female	0.49 (0.35–0.67)	<0.001	1.42 (1.10–1.83)	0.007	2.92 (1.97–4.34)	<0.001
Hypertension	No	1		1		1	
	Yes	2.69 (1.94–3.72)	<0.001	2.58 (1.98–3.37)	<0.001	0.96 (0.65–1.42)	NS
Hypercholesterolaemia	No	1		1		1	
	Yes	2.61 (1.71–3.98)	<0.001	2.26 (1.58–3.24)	<0.001	0.87 (0.53–1.43)	NS
Low HDL-cholesterol	No	1		1		1	
	Yes	1.39 (1.02–1.91)	0.038	2.04 (1.58–2.62)	<0.001	1.46 (1.00–2.14)	0.051
Hypertriglyceridaemia	No	1		1		1	
	Yes	1.82 (1.23–2.69)	0.003	2.83 (2.12–3.78)	<0.001	1.56 (0.99–2.44)	0.053
Central obesity	No	1		1		1	
	Yes	1.59 (1.11–2.28)	0.012	3.25 (2.50–4.24)	<0.001	2.05 (1.35–3.10)	0.001
General obesity	No	1		1		1	
	Yes	1.94 (1.41–2.66)	<0.001	2.71 (2.10–3.49)	<0.001	1.40 (0.96–2.05)	0.085
Hip circumference	Low	1		1		1	
	Medium	1.19 (0.82–1.72)	NS	1.17 (0.85–1.61)	NS	0.99 (0.62–1.57)	NS
	High	1.04 (0.70–1.55)	NS	1.60 (1.18–2.18)	0.003	1.53 (0.95–2.47)	0.078
Fasting insulin	Low	1		1		1	
	Medium	2.17 (1.33–3.53)	0.002	1.45 (1.01–2.09)	0.046	0.67 (0.37–1.21)	NS
	High	4.20 (2.65–6.66)	<0.001	2.48 (1.75–3.51)	<0.001	0.59 (0.34–1.03)	0.061
HOMA β-cell function	Low	1		1		1	
	Medium	1.57 (1.01–2.45)	0.044	1.36 (0.94–1.97)	NS	0.86 (0.50–1.50)	NS
	High	2.06 (1.34–3.17)	0.001	2.10 (1.48–2.29)	<0.001	1.02 (0.60–1.73)	NS
History of CHD/angina	No	1		1		1	
	Yes	0.80 (0.34–1.85)	NS	1.58 (0.95–2.65)	0.081	1.99 (0.78–5.09)	NS
Education	≤ Primary school	1		1		1	
	Secondary school	0.57 (0.41–0.80)	0.001	0.53 (0.40–0.70)	<0.001	0.93 (0.62–1.40)	NS
	≥ Matriculation	0.41 (0.25–0.67)	<0.001	0.46 (0.31–0.67)	<0.001	1.12 (0.62–2.03)	NS
Exercise activity	< 30 mins	1		1		1	
	≥ 30 mins	0.74 (0.53–1.02)	0.062	0.90 (0.70–1.17)	NS	1.23 (0.83–1.82)	NS
Alcohol consumption	Non-drinker	1		1		1	
	Present	1.05 (0.76–1.45)	NS	0.78 (0.60–1.02)	0.068	0.74 (0.50–1.10)	NS
Daily smokers	Never	1		1		1	
	Ever	1.24 (0.88–1.75)	NS	0.77 (0.56–1.04)	0.087	0.62 (0.40–0.96)	0.030
Place of birth	Hong Kong	1		1		1	
	China	2.23 (1.62–3.06)	<0.001	1.46 (1.14–1.88)	0.003	0.66 (0.45–0.97)	0.032

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL, high density lipoprotein; HOMA, homeostatic model assessment; CHD, coronary heart disease.
^aReference group.

Table 3 Odds ratios (95% confidence intervals) of independent determinants of glucose intolerance groups relative to reference groups adjusted using logistic regression analyses. Only significant values are shown. An odds ratio > 1 suggests the parameter increases risk of having glucose intolerance relative to reference group.

Parameters (%)	Categories	IFG only versus normoglycaemia ^a	P value	IGT only versus normoglycaemia ^a	P value	IGT versus IFG ^a	P value
Age	25–34	1		1			
	35–44	1.80 (0.96–3.38)	0.067	4.01 (1.35–11.91)	0.013		
	45–54	2.46 (1.24–4.86)	0.010	6.05 (1.97–18.57)	0.002		
	55–64	1.94 (0.88–4.28)	0.098	8.39 (2.55–27.57)	<0.001		
	65–74	3.14 (1.33–7.42)	0.009	10.23 (2.89–36.28)	<0.001		
Sex	Male	1		1		1	
	Female	0.33 (0.21–0.51)	<0.001			5.12 (2.73–9.59)	<0.001
Hypertension	No	1					
	Yes	1.46 (1.94–3.72)	<0.001	2.03 (1.26–3.29)	0.004		
Hypertriglyceridaemia	No			1		1	
	Yes			2.52 (1.51–4.20)	<0.001	2.57 (1.36–4.88)	0.004
Hip circumference	Low	1				1	
	Medium	0.94 (0.60–1.47)	NS			1.22 (0.65–2.26)	NS
	High	0.56 (0.32–0.98)	0.040			2.33 (1.18–4.81)	0.022
Fasting insulin	Low	1				1	
	Medium	2.44 (1.46–4.09)	0.001			0.47 (0.23–0.94)	0.033
	High	5.38 (3.16–9.18)	<0.001			0.26 (0.09–0.42)	<0.001
Education	≤ Primary school			1			
	Secondary school			0.59 (0.34–1.00)	0.048		
	≥ Matriculation			0.53 (0.25–1.12)	NS		
Place of birth	Hong Kong	1				1	
	China	1.57 (1.05–2.37)	0.030			0.50 (0.29–0.86)	0.012

IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

^aReference group.

epigenetic modifications (34, 35). This has been proposed to promote impaired pancreatic development and insulin resistance predisposing to diabetes in later life (35). An additional hypothesis infers that these adaptive changes may provide intrauterine benefits but contribute to disease risk in later life (34, 37). Low birth weight infants have been shown to have inappropriate basal insulin secretion and hepatic insulin resistance to the inhibition of gluconeogenesis (37), as described in groups with IFG (8, 15). Additional supporting evidence that developmental issues may promote glucose intolerance, particularly isolated IFG, comes from the independent association with being born, at that time, into poorer circumstances in China, with widespread perinatal and childhood food shortages and inadequate medical care. Being born in China may thus represent a surrogate marker of low birth weight, levels of which were not recorded in the present study, but likely results in the subsequent inadequacies in glucose homeostasis as described earlier. We have previously shown that migration from China to Hong Kong during the first 20 years of life compared with those born in Hong Kong is associated with increased risk of diabetes, hypertension and vascular disease (18). Therefore, low birth weight likely contributes to skeletal muscle insulin resistance and pancreatic insufficiency, which would promote both forms of glucose intolerance.

Although the bivariate analyses highlight significant similarities in the factors associated with the presence of glucose intolerance, such as ageing, early life growth

markers, increased adiposity and other vascular disease risk factors, comparison of these factors between the isolated IFG and the IGT groups allows the description of their relative independent associations. The early developmental issues appear more important for the isolated IFG group as the potential surrogates of birth weight and childhood development, i.e. being born in China and smaller BMI-adjusted hip circumference, and fasting hyperinsulinaemia were more strongly associated with the isolated IFG group compared with the isolated IGT group.

Conversely, therefore, relative to isolated IFG, isolated IGT was associated with larger hip circumference, and being born in Hong Kong. Although the proportion of females, who generally have narrower waists than their male counterparts, was greater and thus an independent predictor of IGT, waist circumference between the two glucose intolerant groups was similar. This difference in gender prevalence possibly attenuated the apparent contribution of central obesity to IGT, although there was an increased proportion of centrally obese subjects in the IGT group, and waist circumference tended to be bigger in those with IGT when gender-specific analyses were performed. Similarly, hypertriglyceridaemia, which is closely associated with central obesity (38), was independently associated with the presence of IGT, and may have incorporated a proportion of the model's variance that would have otherwise been attributed to central obesity. Central adiposity is closely associated with insulin resistance (39), as in the present study, and

subsequent development of hyperglycaemia (40, 41). Centrally deposited fat is metabolically more active and less sensitive to the regulatory effects of insulin and catecholamines (42, 43). Increased free fatty acid production is associated with increases in triglyceride, seen to a greater extent in the present study in patients with isolated IGT compared to those with IFG, and reduces insulin clearance, and increases gluconeogenesis and insulin resistance (42, 43).

Insulin resistance in subjects with IFG has been reported to be the result of insulin resistance in both skeletal muscle, and in particular the liver, which prevents suppression of hepatic gluconeogenesis, whereas in the IGT group, skeletal insulin resistance is the predominant form (15). In the present study, each of the glucose intolerant groups was significantly more insulin-resistant, with poorer β -cell function than the normoglycaemic group. However, in contrast to other studies (8, 15), those subjects with isolated IFG were found to have significantly more adverse levels of insulin resistance than the isolated IGT group. The insulin-glucose product is a measure of insulin resistance that has been shown to correlate well with the results of the euglycaemic hyperinsulinaemic clamp, which measures whole body glucose disposal, in the population-based studies (22). However, the index may not be able to differentiate effectively insulin resistance in the fasting and post-prandial state given that, by definition, the components of the index are based on fasting levels. As insulin levels were similar between the two glucose intolerant groups, the observed difference in insulin resistance is likely to be driven by fasting glucose levels that are, by definition, greater in the IFG group than in the IGT group. Using post-load insulin resistance markers, it would be expected that IGT would appear more resistant to the actions of insulin. Overall, those with combined glucose intolerance or diabetes had a greater degree of insulin resistance than either of the two groups with isolated glucose intolerance.

When interpreting statistical findings derived from regression equations, it is important to remember that they are designed to explain the largest proportion of variance in the model, rather than identifying biologically relevant parameters involved in disease pathogenesis. For instance, in the present study, central obesity was not identified as an independent predictor of the glucose intolerance states, despite waist circumference being significantly greater in those groups. In the bivariate analyses, after age, waist circumference (central obesity) showed the strongest association with IGT. However, waist circumference is closely associated with a range of vascular risk factors (38), including hypertension, hypertriglyceridaemia, and in particular, age, all of which were independent predictors of IGT. It is likely that these parameters incorporated a significant proportion of the variance that would otherwise have been attributed to the central obesity index. For instance, age *per se* is unlikely to directly cause glucose

intolerance, yet was incorporated as an independent variable as it acts as a composite variable for risk factors with which it is closely correlated. Conversely, exclusion of a parameter, such as waist circumference, clearly does not preclude it from directly contributing to the pathogenesis of these disorders, merely the variance attributed to the parameter is accounted for by the other variables.

In summary, there were many common antecedents to glucose-intolerant states in this population, such as ageing and hyperinsulinaemia. Those with isolated IFG appear to be particularly associated with early life events, with small hip circumference and being born in China being independently associated. In contrast, isolated IGT appeared more strongly associated with vascular risk factors, including hypertriglyceridaemia, which are closely associated with central adiposity. Avoiding the development of obesity, and subsequently the associated vascular risk factors, may have important consequences in preventing the development of glucose intolerance and in particular isolated IGT, as well as other vascular disease risk factors, and may be particularly important for those with poor early life development.

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