The Singapore Impaired Glucose Tolerance Follow-Up Study

Does the ticking clock go backward as well as forward?

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OBJECTIVE — To *1*) document the change in glucose tolerance for subjects with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) over time, *2*) identify baseline factors associated with worsening of glucose tolerance, and *3*) determine whether cardiovascular disease (CVD) risk factors associated with IGT improved in tandem with glucose tolerance.

RESEARCH DESIGN — Subjects with IGT and NGT (matched for age, sex, and ethnic group) were identified from a cross-sectional survey conducted in 1992. Subjects with IGT (297) and NGT (298) (65.0%) were reexamined in 2000. Glucose tolerance (assessed by 75-g oral glucose tolerance test), anthropometric data, serum lipids, blood pressure, and insulin resistance were determined at baseline and at the follow-up examination.

RESULTS — For NGT subjects, 14.0% progressed to IGT and 4.3% to diabetes over 8 years. For IGT subjects, 41.4% reverted to NGT, 23.0% remained impaired glucose tolerant, and 35.1% developed diabetes. Obesity, hypertriglyceridemia, higher blood pressure, increased insulin resistance, and lower HDL cholesterol at baseline were associated with worsening of glucose tolerance in both IGT and NGT subjects. Those with IGT who reverted to NGT remained more obese and had higher blood pressure than those with NGT in both 1992 and 2000. However, serum triglyceride, HDL cholesterol, and insulin resistance values in 2000 became indistinguishable from those of subjects who maintained NGT throughout the study period.

CONCLUSIONS — Some, but not all, CVD risk factors associated with IGT and with the risk of future diabetes normalize when glucose tolerance normalizes. Continued surveillance and treatment in subjects with IGT, even after they revert to NGT, may be important in the prevention of CVD.

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Diabetes is associated with increased risk of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (1). The latter manifests primarily as cardiovascular disease (CVD) (2). Diabetes is now recognized as a CVD risk equivalent in the National Cholesterol Education Program Adult Treatment Panel III (3). Although microvascular complications have been shown to be associated with the duration of diabetes (4–6), the same cannot be said of CVD (7).

It has been suggested that the lack of association between the duration of diabetes and CVD might be related to the presence of diabetes-associated CVD risk factors (dyslipidemia, hypertension, and obesity—all features of the metabolic syndrome) before the onset of glucose intolerance. As such, the atherosclerotic process is already underway by the time glucose intolerance sets in. In support of this hypothesis, in 1990, Haffner et al. (8) reported the 8-year follow-up of 614 nondiabetic Mexican Americans and compared the baseline characteristics of those who did and did not develop diabetes. Subjects who developed diabetes exhibited an atherogenic pattern of risk factors, including dyslipidemia, obesity, and hypertension, even in the nondiabetic state at baseline. This prompted the authors to ask the question, "Does the clock for coronary heart disease start ticking before the onset of clinical diabetes?" Later studies (9–15) have confirmed that an atherogenic pattern of CVD risk factors precedes diabetes. This has become known as the "ticking clock" hypothesis.

Most studies of progression in impaired glucose tolerance (IGT) have focused on features that predict diabetes. This is clearly an important issue, especially since several trials have demonstrated that specific interventions can reduce the rate of progression from IGT to diabetes (16–19). However, it must be remembered that glucose tolerance can change in more than one direction. A significant proportion of subjects with IGT (ranging from 16.8 to 62.8% [13–14,20, 21]) revert back to normal glucose tolerance (NGT) over time.

Subjects in whom IGT reverted to NGT have been examined in only four studies. Two examined the risk of future diabetes, and the data are conflicting. One study reported an increased risk of diabetes (22) and another reported no such increased risk (23). Two other studies have reported the baseline features that predict conversion from IGT to NGT. Both found that plasma lipids, at baseline, were predictive of reversion from IGT to NGT

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Abbreviations: CVD, cardiovascular disease; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

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

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(24,25). What remains unclear is what happens to these CVD risk factors in these individuals when their glucose tolerance returns from IGT to NGT. Do the factors reverse or do they remain the same, such that these individuals continue to be at increased risk of CVD?

To answer this question, we conducted the Singapore Impaired Glucose Tolerance Follow-Up Study. The aims of the study were to *1*) document the change in glucose tolerance for subjects with NGT and IGT over time, *2*) identify baseline risk factors associated with worsening of glucose tolerance over time, and *3*) determine whether the other associated CVD risk factors also improved among those in whom glucose tolerance returned to normal.

RESEARCH DESIGN AND METHODS

— This was a prospective cohort study comprising subjects with IGT and NGT who were examined in 1992 and 2000. In 1992, a representative cross-sectional sample of the entire Singapore population, comprising 3,568 subjects aged 18–69 years, was examined in a health survey to determine the prevalence of risk factors for major noncommunicable diseases in Singapore. The methodology and population characteristics have been described previously (26). With the exception of 121 subjects who were on oral hypoglycemic agents or insulin for the treatment of diabetes and 11 subjects with venepuncture failure, all subjects (96.3%) were subjected to a 75-g oral glucose tolerance test. The glucose tolerance status was thus determined for 3,557 (99.7%) of the 3,568 subjects who participated in the survey.

A total of 469 subjects with IGT were identified in 1992. In the year 2000, all subjects with IGT and 468 subjects with NGT (matched for age, sex, and ethnicity) were invited to the follow-up study. The discrepancy of one subject arose due to the unavailability of sufficient Chinese women with NGT aged 65–69 years. Among the 937 NGT and IGT subjects selected, 1 died, 1 was mentally ill, and 20 could not be traced. Of the remaining 915 subjects, 595 participated in the study, giving a response rate of 65.0%. Using the baseline data from 1992, we compared the participants with the nonparticipants (Table 1). There were no statistically significant differences for age, sex, race, fasting glucose level, diastolic blood pressure, BMI, waist-to-hip ratio, serum lipid concentrations, or family history of diabetes between participants and nonparticipants. However, the nonparticipants received fewer years of formal education and were more likely to be single or divorced. Furthermore, they had higher systolic blood pressure and 2-h postload glucose than the participants.

Table 1—*Comparison between respondents and nonrespondents, the Singapore Impaired Glucose Tolerance Follow-Up Study*

	Respondents	Nonrespondents	*P*
Age (years)*	44.1 ± 11.62	43.8 ± 14.36	0.81
Waist (cm)	80.99 ± 10.98	79.59 ± 10.66	0.19
BMI (kg/m^2)	25.22 ± 4.43	24.66 ± 4.52	0.20
Waist-to-hip ratio	0.82 ± 0.08	0.82 ± 0.07	0.38
SBP (mmHg)	124.74 ± 17.59	128.74 ± 22.02	0.04
DBP (mmHg)	74.18 ± 11.36	74.33 ± 12.65	0.90
Fasting glucose (mmol/l)	5.75 ± 0.55	5.75 ± 0.58	0.98
2-h postchallenge glucose (mmol/l)	8.86 ± 0.85	9.08 ± 0.91	0.01
Cholesterol (mmol/l)	5.55 ± 1.02	5.74 ± 1.17	0.09
LDL cholesterol (mmol/l)	3.58 ± 0.96	3.76 ± 1.10	0.09
HDL cholesterol (mmol/l)	1.20 ± 0.30	1.23 ± 0.31	0.32
Triglyceride (mmol/l)	1.93 ± 1.66	1.77 ± 1.74	0.33
ApoB (mg/dl)	1.41 ± 0.35	1.44 ± 0.38	0.32
Insulin resistance	2.62 ± 1.72	2.85 ± 2.43	0.24
Ethnic group (%)			
Chinese	70.2	74.8	0.58
Malay	16.4	13.5	
Indian	13.4	11.6	
Sex (%)			
Male	47.2	43.2	0.43
Female	52.8	56.8	
Years of formal education (%)			
≤10 years	83.9	89.7	0.01
>10 years	16.1	10.3	
Marital status (%)			
Single/divorced/widowed	19.1	30.3	0.02
Married	80.9	69.7	
Smoking (%)			
Yes	24.4	24.5	1.00
No	75.6	75.5	
Family history of diabetes (%)			
Yes	28.4	22.6	0.37
No	71.6	77.4	

Data are means ± SD or %. Estimated means ± SD were calculated by ANCOVA and adjusted for age and sex. ApoB, apolipoprotein B-100; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Unadjusted.

Diabetes and IGT were diagnosed on the basis of the 1998 World Health Organization criteria (27). Diabetes was diagnosed if the subject's fasting plasma glucose was ≥7.0 mol/l or the 2-h postchallenge glucose value during the oral glucose tolerance test was ≥11.1 mmol/l, or if the subject reported that a physician had

Table 2—*Change in glucose tolerance for subjects with NGT and IGT from 1992 to 2000, the Singapore Impaired Glucose Tolerance Follow-Up Study*

	NGT	IGT	Diabetes	*P*
NGT	227 (81.7)	39 (14.0)	12 (4.3)	<0.001
IGT	122 (41.4)	67 (23.0)	102 (35.1)	

Data are *n* (%). This table excludes 26 of the initial 595 subjects. Eight subjects were excluded because of incomplete data for fasting or 2-h postload glucose. A further 18 subjects with impaired fasting glycemia but not IGT at baseline or on follow-up were also excluded.

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Table 3—*Baseline (1992) characteristics based on change of glucose status between 1992 and 2000*

Baseline CVD risk factors, 1992	NGT-NGT	NGT-IGT	NGT-diabetes	IGT-NGT	IGT-IGT	IGT-diabetes	*P* NGT-NGT vs. IGT-NGT	*P* Overall
n	227	39	12	122	67	102		
Waist (cm)	74.6 ± 0.6	78.7 ± 1.4	83.8 ± 2.4	78.7 ± 0.8	80.2 ± 1.1	84.1 ± 0.9	<0.001	<0.001
Waist-to-hip ratio	0.79 ± 0.01	0.82 ± 0.01	0.83 ± 0.01	0.81 ± 0.01	0.82 ± 0.01	0.84 ± 0.01	<0.001	<0.001
BMI (kg/m^2)	22.5 ± 0.3	24.7 ± 0.6	26.2 ± 1.1	24.4 ± 0.4	24.7 ± 0.5	26.4 ± 0.4	<0.001	<0.001
SBP (mmHg)	117 ± 1	123 ± 3	122 ± 4	122 ± 1	125 ± 2	127 ± 2	0.001	<0.001
DBP (mmHg)	68 ± 1	73 ± 2	74 ± 3	72 ± 1	75 ± 1	76 ± 1	<0.001	<0.001
Total cholesterol (mmol/l)	5.47 ± 0.06	5.70 ± 0.15	5.46 ± 0.26	5.35 ± 0.09	5.70 ± 0.12	5.61 ± 0.10	0.296	0.153
Triglyceride (mmol/l)	1.25 ± 0.05	1.58 ± 0.11	1.95 ± 0.19	1.47 ± 0.07	1.65 ± 0.09	1.86 ± 0.08	0.008	<0.001
LDL cholesterol (mmol/l)	3.63 ± 0.06	3.85 ± 0.14	3.47 ± 0.25	3.48 ± 0.09	3.70 ± 0.12	3.61 ± 0.10	0.156	0.320
HDL cholesterol (mmol/l)	1.27 ± 0.02	1.13 ± 0.04	1.11 ± 0.08	1.20 ± 0.03	1.25 ± 0.04	1.15 ± 0.03	0.032	0.001
ApoB	1.32 ± 0.02	1.50 ± 0.05	1.43 ± 0.09	1.33 ± 0.03	1.46 ± 0.04	1.46 ± 0.03	0.974	<0.001
LDL:apoB ratio	2.77 ± 0.03	2.60 ± 0.06	2.47 ± 0.10	2.62 ± 0.04	2.54 ± 0.05	2.49 ± 0.04	0.002	<0.001
Insulin resistance	1.50 ± 0.09	1.91 ± 0.19	3.48 ± 0.31	2.27 ± 0.12	2.36 ± 0.15	2.96 ± 0.13	<0.001	<0.001

Data are means ± SE. Groups are named on the basis of baseline glucose tolerance (1992) followed by glucose tolerance on follow-up examination (2000). Analysis utilized ANCOVA adjusted for age and sex. Pairwise comparison between groups was carried out using the least square difference method. This table excludes 26 of the initial 595 subjects. Eight subjects were excluded because of incomplete data for fasting or 2-h postload glucose. A further 18 subjects with impaired fasting glycemia but not IGT at baseline or on follow-up were also excluded. ApoB, apolipoprotein B-100; DBP, diastolic blood pressure; SBP, systolic blood pressure.

diagnosed diabetes during the follow-up period with laboratory confirmation. IGT was diagnosed if the 2-h postload glucose was ≥7.8 mmol/l and <11.1 mmol/l. Eight subjects had incomplete data for fasting glucose or 2-h postload glucose on the follow-up examination due to venepuncture failure and were excluded. The study population included a small number of individuals (14 at baseline and 4 at the follow-up examination) with impaired fasting glycemia (6.0 < fasting plasma glucose < 7.0 mmol/l and 2-h postload glucose ≤7.8 mmol/l). In view of previous evidence that these subjects may differ from those with IGT in terms of progression to diabetes and due to the small number of subjects in this group, these 18 subjects were also excluded, leaving 569 subjects for analysis in Tables 2–4.

Clinical and biochemical assessments

Identical survey methodology was used for both the baseline (1992) and follow-up (2000) examinations. Information regarding demographic indexes (age, ethnic group, marital status, and sex), medical history of diabetes or hypertension, and lifestyle factors (including exercise frequency and smoking habits) were collected using interviewer-administered questionnaires. Smokers were defined as those who smoked daily. Regular exercise was defined as exercise for at least 20 min on three or more occasions per week.

For the follow-up examination, the interviewers comprised investigators and nurses who had prior experience with the

Table 4—*Follow-up (2000) characteristics based on change of glucose status between 1992 and 2000*

CVD risk factors, 2000	NGT-NGT	NGT-IGT	NGT-diabetes	IGT-NGT	IGT-IGT	IGT-diabetes	*P* NGT-NGT vs. IGT-NGT	*P* Overall
n	227	39	12	122	67	102		
Waist (cm)	80.8 ± 0.6	86.0 ± 1.5	91.4 ± 2.6	83.4 ± 0.9	86.3 ± 1.2	89.0 ± 1.0	0.019	<0.001
Waist-to-hip ratio	0.85 ± 0.01	0.87 ± 0.01	0.89 ± 0.04	0.86 ± 0.01	0.87 ± 0.01	0.89 ± 0.01	0.193	<0.001
BMI (kg/m^2)	23.5 ± 0.3	25.9 ± 0.7	26.8 ± 1.2	24.7 ± 0.4	25.9 ± 0.6	27.3 ± 0.5	0.015	<0.001
SBP (mmHg)	127 ± 1	136 ± 3	130 ± 5	133 ± 2	137 ± 2	139 ± 2	0.006	<0.001
DBP (mmHg)	77 ± 1	82 ± 2	80 ± 3	80 ± 1	85 ± 1	84 ± 1	0.059	<0.001
Total cholesterol (mmol/l)	5.58 ± 0.07	5.83 ± 0.16	5.54 ± 0.27	5.50 ± 0.10	5.90 ± 0.13	5.85 ± 0.11	0.529	0.036
Triglyceride (mmol/l)	1.35 ± 0.06	1.75 ± 0.13	1.93 ± 0.23	1.38 ± 0.08	1.61 ± 0.11	1.87 ± 0.09	0.797	0.01
LDL cholesterol (mmol/l)	3.51 ± 0.06	3.77 ± 0.15	3.46 ± 0.25	3.45 ± 0.09	3.71 ± 0.12	3.73 ± 0.10	0.565	0.197
HDL cholesterol (mmol/l)	1.44 ± 0.02	1.25 ± 0.05	1.25 ± 0.09	1.42 ± 0.03	1.44 ± 0.04	1.34 ± 0.04	0.761	0.004
Insulin resistance	1.65 ± 0.11	2.72 ± 0.26	4.75 ± 0.45	1.90 ± 0.16	2.67 ± 0.21	4.56 ± 0.18	0.192	<0.001

Data are means ± SE. Groups are named on the basis of baseline glucose tolerance (1992) followed by glucose tolerance on follow-up examination (2000). Analysis utilized ANCOVA adjusted for age and sex. Pairwise comparison between groups was carried out using the least square difference method. This table excludes 26 of the initial 595 subjects. Eight subjects were excluded because of incomplete data for fasting or 2-h postload glucose. A further 18 subjects with impaired fasting glycemia but not IGT at baseline or on follow-up were also excluded. ApoB, apolipoprotein B-100; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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1992 Singapore National Health Survey. Interviewers were blinded for the baseline glucose tolerance status of the subjects during the interviews. The interview questionnaire was prepared in English and subsequently sent to the Ministry of Information and the Arts for translation to Chinese, Malay, and Tamil. Data entry was repeatedly checked by random case selection and outlier reviews.

Blood pressure and anthropometric data (weight, height, waist circumference, and hip circumference) were measured for all individuals. Blood lipids (total cholesterol, triglyceride, and HDL cholesterol), glucose, and insulin were assayed after a 10-h fast.

Laboratory methods

Details of the assays used in 1992 have been previously reported (26). In the year 2000, serum lipids and plasma glucose were analyzed by enzymatic methods on the Cobas Integra automated analyzer (Roche Diagnostics, Basel, Switzerland) within 4 h of specimen collection. Serum insulin was measured by immunoassay on the Abbott Axsym analyzer (Abbott Laboratories) within 6 h of collection. LDL cholesterol was derived from the Friedewald equation. Insulin resistance was derived mathematically using the homeostasis model assessment (28).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.0 for Windows (SPSS, Chicago, IL). Comparisons between continuous variables were carried out using ANCOVA using general linear models. χ^2 tests were used for the categorical variables. Highly skewed variables (HDL cholesterol, insulin, insulin resistance, and triglycerides) were log transformed to improve the normality of distribution before performing statistical tests.

Ethical considerations

The study protocol was approved by the institutional review board and the ethics committee of the Alexandra Hospital. Informed consent was obtained from all participants. Patients' privacy and right of refusal to participate without giving reasons were fully respected. All information and data collected were deemed confidential. All patients received a hardcopy of their own biochemical results, and follow-up advice was given where medical treatment was required.

Table 5—*Comparison between NGT and IGT groups at baseline.*

	NGT	IGT	*P* (IGT vs. NGT)
n	298	297	
Age (years)*	43.7 ± 0.7	43.8 ± 0.7	0.925
Waist (cm)	75.8 ± 0.5	81.2 ± 0.5	<0.001
BMI (kg/m^2)	23.1 ± 0.2	25.2 ± 0.2	<0.001
Waist-to-hip ratio	0.80 ± 0.003	0.83 ± 0.003	<0.001
SBP (mmHg)	118 ± 1	125 ± 1	<0.001
DBP (mmHg)	69 ± 1	74 ± 1	<0.001
Fasting glucose (mmol/l)	5.4 ± 0.3	5.7 ± 0.3	<0.001
2-h postchallenge glucose (mmol/l)	5.9 ± 0.5	8.9 ± 0.5	<0.001
Total cholesterol (mmol/l)	5.51 ± 0.06	5.54 ± 0.06	0.657
Triglycerides (mmol/l)	1.42 ± 0.08	1.95 ± 0.08	<0.001
HDL cholesterol (mmol/l)	1.24 ± 0.02	1.19 ± 0.02	0.026
LDL cholesterol (mmol/l)	3.65 ± 0.05	3.659 ± 0.05	0.452
ApoB (mg/dl)	1.36 ± 0.02	1.41 ± 0.02	0.064
LDL:apoB ratio	2.73 ± 0.02	2.56 ± 0.02	<0.001
Fasting insulin (IU/l)	6.9 ± 0.3	10.0 ± 0.3	<0.001
Insulin resistance	1.67 ± 0.08	2.58 ± 0.08	<0.001

Data are means ± SE. This table includes all subjects who attended the follow-up examination (n = 595). Estimated means ± SE are calculated by ANCOVA and adjusted for age and sex. ApoB, apolipoprotein B-100; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Unadjusted.

RESULTS — Table 5 shows the baseline characteristics of NGT and IGT subjects who were included in this analysis. IGT subjects showed increased levels of several CVD risk factors, including obesity, blood pressure, hypertriglyceridemia, low HDL cholesterol concentration, and a low LDL cholesterol:apolipoprotein B ratio.

Table 2 shows the change in glucose tolerance among those with NGT and IGT over the 8-year follow-up period. Overall, 35.1% of subjects with IGT progressed to diabetes compared with 4.3% of those with NGT ($P < 0.001$). The rate of progression to diabetes was eight times higher in those with IGT at baseline (4.4% per year) than in those with NGT at baseline (0.53% per year). More than one-third of subjects with IGT reverted to NGT over the 8-year follow-up.

We subsequently divided the study population into six groups according to the change in glucose tolerance during the follow-up period. The six groups were named according to their glucose tolerance at baseline, followed by the glucose tolerance at the follow-up examination. Thus, those who had NGT at baseline and IGT at follow-up were grouped together under NGT-IGT. The same risk factors that were associated with IGT at baseline (Table 5) were also seen in those in whom glucose tolerance deteriorated over the 8 years of the study (NGT-IGT, NGT-diabetes, and IGT-diabetes) (Table 3). This pattern of CVD risk factors was seen before the development of diabetes (Table 3). When we compared the baseline levels of these same CVD risk factors between those with IGT at baseline who reverted to NGT (IGT-NGT) and those with NGT at baseline who remained NGT (NGT-NGT), we found that they were significantly different. The former subjects were significantly more obese, had higher serum triglyceride concentration, higher blood pressure, greater insulin resistance, and lower HDL cholesterol concentration.

Table 4 shows the anthropometric and biochemical characteristics for the same six groups as measured in the year 2000. Compared with the differences seen at the baseline examination, the differences in the CVD risk factors between the IGT-NGT and NGT-NGT groups decreased during the follow-up period. At follow-up (2000), the former group remained significantly more obese (although the difference in waist-to-hip ratio was not significant). They also had higher systolic blood pressure than that of the NGT-NGT group. However, differences in serum triglyceride concentration, serum HDL cholesterol concentration, fasting insulin, and insulin resistance were no longer detectable.

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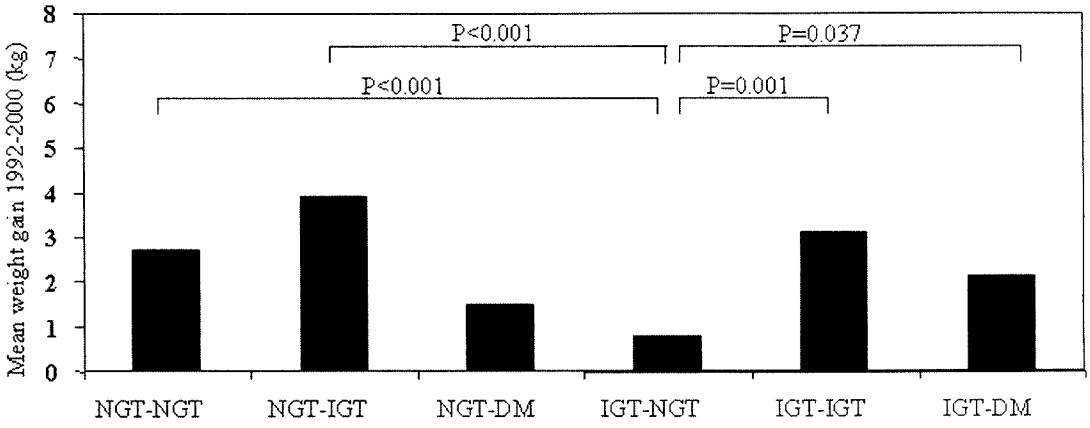

Figure 1—*Weight gain (mean in kilograms) from 1992–2000 according to the change in glucose tolerance (adjusted for age and sex) in the Singapore Impaired Glucose Tolerance Follow-Up Study. The category (x) axis represents the baseline glucose tolerance in 1992 followed by the follow-up glucose tolerance in 2000. DM, diabetes.*

Figure 1 shows the weight gained over 8 years for each group. In general, all groups showed an increase in weight over 8 years. However, the group that reverted from IGT to NGT showed the least weight gain. The difference between this group and all other groups was statistically significant, with the exception of those that developed diabetes from baseline NGT. However, this group was also the smallest ($n = 12$). It appeared that those who developed diabetes gained less weight than those who did not. However, this did not reach statistical significance.

CONCLUSIONS — Several aspects of our data serve to confirm the findings of previous studies. First, IGT is associated with an atherogenic pattern of CVD risk factors (Table 5). These factors include obesity, hypertriglyceridemia, low HDL cholesterol levels, and hypertension (29–32). Second, IGT is associated with increased risk of future diabetes (33–36) (Table 2). The rate of progression from IGT to diabetes in this study was 4.3% per year. Because the majority of our population comprises ethnic Chinese, we compared this rate against two previous studies carried out in ethnic Chinese. We found that the rate of conversion was significantly lower in our study compared with those carried out in Taiwan (8.8% per year) (14) and China (11.2% per year) (18). In a study conducted on the Micronesian island of Nauru, the progression rate was 4% per year (37), which is very similar to ours. Third, as with previous studies, we have shown that a significant proportion of IGT subjects return to NGT over time (13,14,20,21). The proportion of IGT subjects who revert to NGT is comparable with that observed in Pima Indians (20). Finally, we have shown that the same atherogenic pattern of CVD risk factors seen in those with IGT is present before the onset of glucose intolerance (Table 3). We have therefore validated the ticking clock hypothesis. In fact, irrespective of baseline glucose tolerance (IGT or NGT), subjects who developed diabetes were found to have similar baseline measures of these risk factors (Table 3).

Our data demonstrate that when glucose tolerance improves from IGT to NGT, dyslipidemia and insulin resistance also improve. Two groups had NGT at the second examination (NGT-NGT and IGT-NGT, in Tables 3 and 4). These two groups had serum triglyceride concentrations, serum HDL cholesterol concentrations, and insulin resistance levels that were significantly different at baseline. In these same subjects, these parameters became indistinguishable in 2000. However, not all CVD risk factors were reversed. IGT-NGT subjects remained significantly more obese and had higher blood pressure than NGT-NGT subjects, even after the glucose tolerance of the former group returned to normal. To our knowledge, this reversibility of CVD risk factors in tandem with glucose tolerance has not been previously reported.

We were especially interested in the role of weight gain and weight loss. In our study, all groups gained weight, irrespective of the change in glucose tolerance (Fig. 1). However, the group that had IGT at baseline and reverted to NGT in 2000 gained the least weight. Previous studies have shown that a program of lifestyle changes that result in weight loss is associated with a decreased risk of progression from IGT to diabetes (16,17). Our data suggests that weight loss may not be essential. Instead, it would appear that preventing age-related weight gain could be sufficient to improve glucose tolerance and reverse some of the associated CVD risk factors.

Our study has shown that several features of the metabolic syndrome (namely dyslipidemia and glucose intolerance) are reversible and change in tandem with improvement in glucose tolerance. However, despite the normalization of some CVD risk factors, others (obesity and blood pressure) remain significantly elevated. Previous studies have shown that subjects with IGT (even if they revert to NGT) may be at increased risk of future diabetes (22) and warrant continued surveillance. Our data suggest that such surveillance, and possibly intervention, may be important for the prevention of CVD as well as diabetes. We have also shown that the reversal of IGT to NGT was seen in those who were best able to avoid weight gain with age. Unfortunately, our study provides no information regarding the means through which these subjects were able to avoid weight gain. There was no difference in the frequency of exercise between this group and other groups (data not shown). We do not have data on the dietary patterns of this group. The elucidation of these factors is of considerable importance for the prevention of diabetes

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and CVD and should be considered for future research in this field.

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