10-year trajectory of β-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study

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Summary

Background **The relative contributions of β-cell function and insulin sensitivity in the pathogenesis of type 2 diabetes are not fully understood. We investigated the longitudinal change in β-cell function and insulin sensitivity in the development of diabetes and the role of genetic variants in deterioration of glucose tolerance.**

Methods **We followed up 4106 participants with normal glucose tolerance (NGT) from the Korean Genome and Epidemiology Study with oral glucose tolerance tests every 2 years for 10 years. We estimated pancreatic β-cell function with the 60 min insulinogenic index (IGI_{60}) and insulin sensitivity with the composite (Matsuda) insulin sensitivity index (ISI). We investigated the association of 66 known type 2 diabetes genetic variants with risk of prediabetes or diabetes and impaired β-cell function and insulin sensitivity.**

Findings **During 10 years of follow-up, 1093 (27%) of 4106 participants developed prediabetes and 498 (12%) participants developed diabetes. Compared with participants who remained NGT, those who progressed to diabetes had a lower IGI_{60} (unadjusted data 5·1 μU/mmol [95% CI 0·5–56·1] *vs* 7·9 μU/mmol [0·5–113·8]; p<0·0001) and lower ISI (unadjusted data 8·2 [2·6–26·0] *vs* 10·0 [3·2–31·6]; p<0·0001) at baseline. Participants who had NGT at 10 years showed a decrease in ISI (adjusted data 10·1 [9·9–10·3] *vs* 7·4 [7·3–7·6]; p<0·0001) but a compensatory increase in IGI_{60} (adjusted data 6·9 μU/mmol [6·5–7·2] *vs* 11·7 μU/mmol [11·2–12·1]; p<0·0001) compared with baseline. By contrast, participants who developed diabetes showed a decrease in ISI (adjusted data 8·4 [8·0–8·7] *vs* 3·0 [2·8–3·2]; p<0·0001) but no significant compensatory increase (p=0·95) in IGI_{60}. A genetic variant near the glucokinase gene (rs4607517) was significantly associated with progression to prediabetes or diabetes (hazard ratio 1·27, 1·16–1·38; $p=1·70\times10^{-7}$).**

Interpretation **Decreased β-cell function, which might be determined partly by genetic factors, and impaired β-cell compensation for progressive decline in insulin sensitivity are crucial factors in the deterioration of glucose tolerance.**

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Introduction

Type 2 diabetes is a common multigenic disorder with worldwide prevalence of 8·3%.[1] To fully understand its pathophysiology and develop preventive measures, efforts have been made to identify the relative contribution of impaired β-cell function and insulin sensitivity. However, which of the two is the primary defect is much debated. Several longitudinal studies have been done to investigate the trajectories of β-cell function and insulin sensitivity in the development of diabetes.[2–7] Some studies suggest that skeletal muscle insulin resistance is the most important defect and that β-cell function is augmented to offset the defect in insulin action.[2,4,6] In the Whitehall II study,[6] in which 6538 British civil servants were followed up for 13 years, those who developed diabetes had decreased baseline insulin sensitivity at 13 years before diagnosis and a steeper decline in insulin sensitivity during the past 5 years compared with those who remained non-diabetic. Results of other studies have suggested that impaired β-cell function, probably predisposed by genetic factors, is the primary underlying defect.[3,5,7] In the Insulin Resistance Atherosclerosis Study,[3] in which 1262 multiethnic participants were investigated for 5·2 years, impaired β-cell compensation was the primary determinant of incident diabetes. These conflicting results might arise from differences in ethnicity, follow-up duration, and methods for estimation of β-cell function and insulin sensitivity.[8,9] Well controlled prospective cohort studies with long duration and regular assessment of β-cell function and insulin sensitivity, preferably derived with the oral glucose tolerance test (OGTT), might provide an improved understanding of the relative contributions of β-cell function and insulin sensitivity.

Investigators of genome-wide association studies and meta-analyses have catalogued at least 77 genetic variants for type 2 diabetes.[9–11] However, few studies have been done to investigate the role of these variants in incident prediabetes or diabetes.[12–14] Whether these variants are associated with progressive deterioration of β-cell function and insulin sensitivity is unclear. Therefore, to know whether these genetic variants are associated with progressive deterioration of glucose tolerance and measures of β-cell function and insulin sensitivity is of interest.

Research in context

Evidence before this study

An understanding of the relative contribution of decline in β-cell function and insulin sensitivity in the pathogenesis of diabetes is important for prediction and prevention of diabetes. We did a comprehensive and focused scientific literature review by searching PubMed and MEDLINE for articles published in any language from Jan 1, 1990, to Dec 31, 2014. Our search terms included "β-cell function", "β-cell dysfunction", "cohort", "diabetes", "epidemiology", "genetic variants", "insulin resistance", "insulin secretion", "insulin sensitivity", "prediction", "prevention", "risks", "single nucleotide polymorphism", "trajectory", and "type 2 diabetes". All cross-sectional, retrospective, and prospective studies were included. Results from some studies suggested that impaired insulin sensitivity is a prerequisite for incident diabetes, whereas others suggested that decreased β-cell function is crucial in the development of diabetes, especially in Asian people. These conflicting results might be attributable to differences in ethnicity, methods used to estimate β-cell function and insulin sensitivity, and follow-up duration.

Added value of this study

We investigated the trajectories of oral glucose tolerance test-derived dynamic measures of β-cell function and insulin sensitivity for 10 years in a prospective cohort of 4106 people with normal glucose tolerance (NGT). Our study was specifically designed to investigate the environmental and genetic risk factors for diabetes. Participants who progressed to diabetes or prediabetes had decreased β-cell function at baseline compared with those who maintained NGT. Additionally, progressors to prediabetes or diabetes were not able to increase their β-cell function in compensation for the progressive decline in insulin sensitivity. A variant near the glucokinase gene (*GCK*) was associated with progressive deterioration in glucose tolerance and decreased β-cell function. This study confirms the role of impaired β-cell function in the progression of glucose intolerance in a well designed, prospective cohort, and provides novel data about genetic variants associated with decreased β-cell function.

Implications of all the available evidence

People who have limited β-cell function and cannot compensate for the declining insulin sensitivity are at high risk of developing diabetes. This information could be used to predict who will eventually develop diabetes. Since β-cell function is believed to be partly determined by genetic factors, further research into the genetics of diabetes could broaden our understanding of the pathogenesis of the disease. Possible strategies to overcome decreased β-cell function and prevent development of diabetes should be investigated, as should the effect of various anti-diabetic drugs on long-term change in β-cell function.

We did a large-scale, community-based prospective cohort study specifically designed to investigate environmental and genetic risk factors of type 2 diabetes. Additionally, some participants were genotyped with a genome-wide single nucleotide polymorphism (SNP) genotyping array. We report the 10-year follow-up results of 4106 participants with normal glucose tolerance (NGT) and their 2-yearly trajectories of β-cell function and insulin sensitivity. We also analysed the genetic predisposition associated with deterioration of glucose tolerance and measures of β-cell function and insulin sensitivity.

Methods

Participants

The Ansung–Ansan Cohort Study[15] is a prospective, community-based cohort study that has been previously described in detail. The study is part of the Korean Genome and Epidemiology Study, a Korean Government-funded epidemiological survey to investigate trends in chronic diseases. The baseline survey was undertaken in 2001–02 and follow-up examination is ongoing every 2 years. Data from 2001 to 2012 were included for analyses in this study. We enrolled participants aged 40–69 years who lived in either urban Ansan or the rural Ansung community. Among 7192 eligible residents in Ansung, 5018 were surveyed with a cluster-sampling method, stratified by age, sex, and residential district. 5020 of 124775 eligible individuals were recruited from Ansan with a random sampling method of the local telephone directory. Participants were excluded if they had diabetes or malignancy or had taken drugs that affect blood glucose, such as steroids, in the previous 3 months. 9375 participants without known diabetes were surveyed, and 635 were newly diagnosed with type 2 diabetes by 2 h 75 g OGTT. Among the remaining 8740 participants, 5675 were followed up until 2012, and 4106 people with NGT were included in the present study. 3925 (96%) participants were successfully followed up to year 10. The number of participants lost to follow-up was 184 (4%) in year 2, 334 (8%) in year 4, 423 (10%) in year 6, 288 (7%) in year 8, and 95 (2%) in year 10. OGTT was done in all 4106 participants at baseline, 2966 (72%) in year 2, 3772 (92%) in year 4, 3628 (88%) in year 6, 3732 (91%) in year 8, and 3925 (96%) in year 10. 3965 (97%) participants had at least four available OGTT results. Participants who had been diagnosed with diabetes were not required to undergo OGTT. The study protocol was approved by the ethics committee of the Korean Center for Disease Control and the institutional review board of Ajou University School of Medicine (IRB No AJIRB-CRO-07-012). All participants provided written informed consent.

Procedures

Anthropometric parameters and blood pressure were measured by standard methods. Fasting plasma glucose (FPG), insulin, total cholesterol, triglycerides, high-density

lipoprotein (HDL), and HbA_{1c} were measured in a central laboratory after a 12-h fast. Each participant underwent a 2 h 75 g OGTT at inclusion and then every 2 years. Plasma samples were taken at 0 min, 60 min, and 120 min of OGTT for measurement of plasma glucose and insulin concentrations. Plasma glucose concentrations were measured by use of the hexokinase method. Plasma insulin concentrations were measured by radioimmunoassay. HbA_{1c} concentration was measured by high-performance liquid chromatography. The definitions of NGT, prediabetes, and diabetes were based on plasma glucose results during 75 g OGTT, defined by the 1997 American Diabetes Association criteria.[16] HbA_{1c} was not used to define these categories since it was not incorporated in the diagnostic criteria at the start of the study. Smokers were divided into current smokers versus past or never smokers. Alcohol intake was divided into moderate (<420 kcal per week) versus heavy intake (≥420 kcal per week). Physical activity was classified into none versus moderate exercise (one session per week or more).

Pancreatic β-cell function was estimated by 60 min insulinogenic index (IGI_{60}) calculated with plasma insulin and glucose levels at 0 min and 60 min of OGTT and homoeostasis model assessment of β-cell function (HOMA-β).[17,18] IGI_{60} was calculated as $(insulin_{60min} - insulin_{0\,min}[\mu U/mL])/(glucose_{60\,min} - glucose_{0min}[mmol/L])$ and HOMA-β was calculated as $20 \times$(fasting insulin [μU/mL]) $\times$(fasting glucose $-3 \cdot 5$ [mmol/L]). Insulin sensitivity was measured by composite (Matsuda) insulin sensitivity index (ISI) and the homoeostasis model assessment of insulin resistance index (HOMA-IR).[18,19] The composite ISI was calculated as

$$\frac{10\,000}{\sqrt{\begin{array}{cccc}(\text{fasting} & (\text{fasting} & (\text{mean} & (\text{mean}\\ \text{glucose} \times & \text{insulin} \times & \text{glucose} \times & \text{insulin}\\ \text{[mg/dL])} & \text{[μU/mL])} & \text{[mg/dL])} & \text{[μU/mL])}\end{array}}}$$

using 0 min, 60 min, and 120 min values of OGTT, and HOMA-IR was calculated as (fasting glucose [mmol/L]) $\times$(fasting insulin [μU/mL])/$22 \cdot 5$. We estimated OGTT-derived disposition index by multiplying IGI_{60} with composite ISI to reflect β-cell function adjusting for the insulin sensitivity.

Genotyping and genetic association analysis

We extracted genomic DNA from the participants' peripheral leucocytes. The genome scan was done with an Affymetrix Genome-Wide Human SNP Array 5.0, as previously described.[20] Briefly, only unrelated participants with genotype missingness of less than 5% were included in the analysis. 3395 participants were available for genetic association analysis after quality-control filtering. Markers with significant deviations from the Hardy-Weinberg equilibrium ($p<1 \cdot 0 \times 10^{-6}$), a genotype call rate of less than $0 \cdot 95$, and minor allele frequency of less than $0 \cdot 01$ were excluded. Genotype imputation was done with Minimac software using 1000 Genomes phase 1 release as reference.[21] Of 77 confirmed diabetes variants, 66 genotyped or imputed variants were available for analysis.[10] Genotype association for combined prediabetes and diabetes or diabetes alone was tested with a Cox proportional-hazards model with reported risk allele, adjusted for baseline age, sex, and BMI. The Bonferroni-corrected significance threshold for the genetic association was $p<3 \cdot 79 \times 10^{-4}$ because 66 variants were tested for either combined prediabetes and diabetes or diabetes alone (ie, $[0 \cdot 05 \div 66] \div 2$). Genetic association with baseline IGI_{60}, composite ISI, rate of change of IGI_{60}, and composite ISI was assessed with linear regression after inverse normal transformation, with adjustment for baseline age, sex, and BMI.

For **Minimac software** see http://genome.sph.umich.edu/wiki/Minimac

Statistical analysis

Data are presented as means with SDs, n (%), or hazard ratios (HRs) with 95% CIs. We normalised variables with non-Gaussian distribution by logarithmic transformation. We compared means using Student's *t* tests or ANCOVA and, for categorical variables, we compared frequencies using χ^2 tests. We determined thresholds of IGI_{60} and composite ISI to categorise them into two groups to calculate HR for incident diabetes using a Cox proportional-hazards model by calculating the sensitivity and specificity of the receiver operating characteristic curve for the prediction of diabetes development. We determined cutoff values of IGI_{60} and composite ISI that maximise Youden Index ($J = \max_c[\text{sensitivity}(c) + \text{specificity}(c) - 1]$) for all possible cutoff values (c) because the differentiating ability of each measure is optimised if sensitivity and specificity are taken to be of equal importance.[22] We calculated population-attributable fractions (PAFs) by P[(HR−1)/HR], where P is the proportion of total cases in the population arising from the specified exposure category and HR is the model-adjusted HR.

We did longitudinal analysis of $\log_2$-transformed fasting glucose, 2 h glucose, IGI_{60}, composite ISI, and disposition index with a linear mixed-effects model to estimate mean levels of the parameters over time within groups from baseline to up to 10 years of follow-up, using all available data.[23] The fixed effects were time, group, and group-by-time, and individual was included as a random effect. We estimated the average rate of change from baseline to 10 years from a linear contrast of the model-estimated means over time, which was included as a categorical variable.

For the retrospective analysis (appendix p 12), we set the year of diabetes onset or final follow-up as year 0 and traced β-cell function and insulin sensitivity backwards. Because some participants with prediabetes at final follow-up had several transitions between NGT and prediabetes, they were combined with non-progressors. We used a non-linear mixed-effects model to estimate the trajectories of fasting glucose, 2 h glucose, IGI_{60},

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composite ISI, and disposition index in patients with diabetes before diagnosis and in non-diabetic participants before last screening.[23] All analyses were done with SPSS (version 18.0) or R (version 3.0.3).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. JHO, SHK, KSP, and NHC had access to the raw data. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 4106 participants with NGT at baseline, 1093 (27%) progressed to prediabetes, and 498 (12%) progressed to

	Non-progressor (n=2515)	Progressor to prediabetes (n=1093)	Progressor to diabetes (n=498)	p value for comparison between non-progressors and progressors		Statistically significant post-hoc analysis comparisons (p<0·05)
				Partly adjusted*	Fully adjusted†	
Age (years)	50·6 (8·3)	51·4 (8·2)	52·8 (8·9)	<0·0001	0·0347	a, b, c
Men	1134 (45·1%)	526 (48·1%)	285 (57·2%)	<0·0001	0·0078	b, c
BMI (kg/m^2)	24·0 (2·9)	25·0 (3·0)	24·9 (3·2)	<0·0001	<0·0001	a, b
Waist circumference (cm)	80·9 (8·4)	83·3 (8·2)	84·5 (8·7)	<0·0001	<0·0001	a, b, c
Systolic blood pressure (mm Hg)	113·5 (16·2)	117·5 (17·4)	119·5 (18·1)	<0·0001	<0·0001	a, b
Diastolic blood pressure (mm Hg)	73·2 (10·7)	75·7 (11·9)	77·0 (11·3)	<0·0001	<0·0001	a, b
FPG (mmol/L)	4·5 (0·4)	4·7 (0·4)	4·8 (0·4)	<0·0001	<0·0001	a, b, c
2 h glucose (mmol/L)	5·7 (1·1)	6·1 (1·1)	6·3 (1·1)	<0·0001	<0·0001	a, b, c
HbA_{1c}	5·2 (0·3%)	5·4 (0·3%)	5·5 (0·4%)	<0·0001	<0·0001	a, b, c
Fasting insulin (pmol/L)‡	37·8 (1·8)	40·1 (1·8)	39·0 (1·9)	0·0031	0·3912	a
IGI_{60}‡	7·9 (3·9)	6·6 (3·4)	5·1 (3·4)	<0·0001	<0·0001	a, b, c
HOMA-β‡	131 (2·0)	122 (2·0)	110 (2·0)	<0·0001	0·4871	a, b, c
Composite ISI‡	10·0 (1·8)	8·6 (1·8)	8·2 (1·8)	<0·0001	<0·0001	a, b
HOMA-IR‡	1·27 (1·8)	1·38 (1·9)	1·37 (1·9)	<0·0001	0·3811	a, b
Disposition index‡	72·9 (3·5)	52·9 (2·9)	39·7 (2·7)	<0·0001	<0·0001	a, b, c
Total cholesterol (mmol/L)‡	4·79 (1·2)	4·89 (1·2)	4·96 (1·2)	<0·0001	0·7561	a, b
HDL cholesterol (mmol/L)‡	1·20 (1·3)	1·14 (1·3)	1·11 (1·3)	<0·0001	<0·0001	a, b
Triglycerides (mmol/L)‡	1·34 (1·6)	1·58 (1·6)	1·77 (1·7)	<0·0001	<0·0001	a, b, c
Hypertension	169 (6·7%)	129 (11·8%)	80 (16·1%)	<0·0001	<0·0001	a, b, c
Family history of diabetes	223 (8·9%)	139 (12·7%)	64 (12·9%)	<0·0001	0·00070	a, b

Data are unadjusted means (SD), geometric means (geometric SD), or n (%). FPG=fasting plasma glucose. IGI_{60}=insulinogenic index at 60 min. HOMA-β=homoeostasis model assessment of β-cell function. ISI=insulin sensitivity index. HOMA-IR=homoeostasis model assessment of insulin resistance. a=non-progressor *vs* progressor to prediabetes. b=non-progressor *vs* progressor to diabetes. c=progressor to prediabetes *vs* progressor to diabetes. *p values are adjusted for baseline age and sex. †p values are adjusted for baseline age, sex, FPG, and HbA_{1c}. ‡Variable was log-transformed before statistical analysis and shown as geometric mean (geometric SD).

Table 1: **Baseline characteristics of study participants divided into three groups by glycaemic status at the end of 10-year follow-up: non-progressors, progressors to prediabetes, and progressors to diabetes**

	High IGI_{60}/high ISI (n=658)	High IGI_{60}/low ISI (n=717)	Low IGI_{60}/high ISI (n=2206)	Low IGI_{60}/low ISI (n=489)
Incident diabetes	23 (3·5%)	84 (11·7%)	269 (12·2%)	120 (24·5%)
Model A	1·00	3·41 (2·15–5·41; p<0·0001)	3·68 (2·40–5·63; p<0·0001)	7·89 (5·05–12·32; p<0·0001)
Model B	1·00	3·50 (2·20–5·55; p<0·0001)	3·58 (2·34–5·48; p<0·0001)	8·04 (5·15–12·57; p<0·0001)
Model C	1·00	3·31 (2·08–5·27; p<0·0001)	3·44 (2·24–5·26; p<0·0001)	7·74 (4·95–12·13; p<0·0001)
Model D	1·00	2·62 (1·64–4·18; p<0·0001)	3·35 (2·18–5·13; p<0·0001)	6·08 (3·87–9·55; p<0·0001)
PAF*	..	10·5% (6·6–12·9)	38·0% (29·4–43·7)	20·2% (17·9–21·7)

Data are n (%) or HR (95% CI). The cutoff for dichotomising 60 min insulinogenic index (IGI_{60}) into high versus low was 10·5 and composite insulin sensitivity index (ISI) into high versus low was 6·9. Model A=unadjusted. Model B=adjusted for age, sex, and region (urban *vs* rural). Model C=model B plus adjustments for smoking, sporting activity (once per week or more), alcohol intake (≥420 kcal per week), and family history of diabetes. Model D=model C plus adjustments for systolic blood pressure, waist circumference, alanine aminotransferase, total cholesterol, high-density lipoprotein cholesterol, and triglyceride. *Population-attributable fraction (PAF) was calculated using multivariable-adjusted hazard ratio (HR; model D). For example, the PAF of individuals with high-IGI_{60}/low-ISI was calculated as (84/496) × (2·62 – 1·00) / 2·62 × 100 = 10·5%.

Table 2: **Incidence, HR, and PAF of diabetes development during 10-year follow-up in four groups categorised by baseline IGI_{60} and composite ISI**

type 2 diabetes during the 10-year follow-up. The mean follow-up duration was 9·3 years (SD 1·6). After adjustment for baseline age, sex, fasting glucose, and HbA_{1c}, progressors to prediabetes or diabetes had higher BMI, waist circumference, blood pressure, and triglycerides than did non-progressors (p<0·0001; table 1). Progressors had significantly higher baseline fasting glucose, 2 h glucose, and HbA_{1C} than did non-progressors (p<0·0001) and lower unadjusted baseline IGI_{60} of 5·1 μU/mmol (95% CI 0·5–56·1) compared with 7·9 μU/mmol (0·5–113·8; 35·4%; p<0·0001) than did non-progressors. Progressors also had lower composite ISI (unajusted data 8·2 [95% CI 2·6–26·0] *vs* 10·0 [3·2–31·6]; 18·0%; p<0·0001) than did non-progressors, suggesting that insulin secretory defects might at least coexist with decreased insulin sensitivity during the course of diabetes development.

We investigated the relative contribution of baseline β-cell function and insulin sensitivity on incident diabetes (table 2). We categorised participants into four groups (high IGI_{60}/high ISI, high IGI_{60}/low ISI, low IGI_{60}/high ISI, and low IGI_{60}/low ISI) by the baseline IGI_{60} and composite ISI cutoff values of 10·5 μU/mmol for IGI_{60} and 6·9 for ISI. We assessed the HR of incident diabetes for each group using the Cox proportional-hazards model. The HR of incident diabetes compared with the reference (high IGI_{60}/high ISI) group was highest (HR 6·08, 95% CI 3·87–9·55; p<0·0001) in participants who had both decreased β-cell function and decreased insulin sensitivity (low IGI_{60}/low ISI). The HR was 2·62 (1·64–4·18; p<0·0001) for participants with only decreased insulin sensitivity (high IGI_{60}/low ISI), and 3·35 (95% CI 2·18–5·13; p<0·0001) for those with only decreased β-cell function (low IGI_{60}/high ISI). The PAF was 38·0% (29·4–43·7) for low IGI_{60}/high ISI, and 10·5% (6·6–12·9) for high IGI_{60}/low ISI. Impairment of β-cell function has a more profound effect on incident diabetes than does decreased insulin sensitivity.

FPG, and especially 2 h glucose, increased in progressors to diabetes during follow-up (appendix p 10). To understand the trajectories of β-cell function and insulin sensitivity in the development of diabetes, we analysed the biennial changes in IGI_{60} and composite ISI (figure). We excluded data points with negative IGI_{60} and disposition index (2548 [12%] of 22011 available data points). However, 3540 (86%) participants had at least

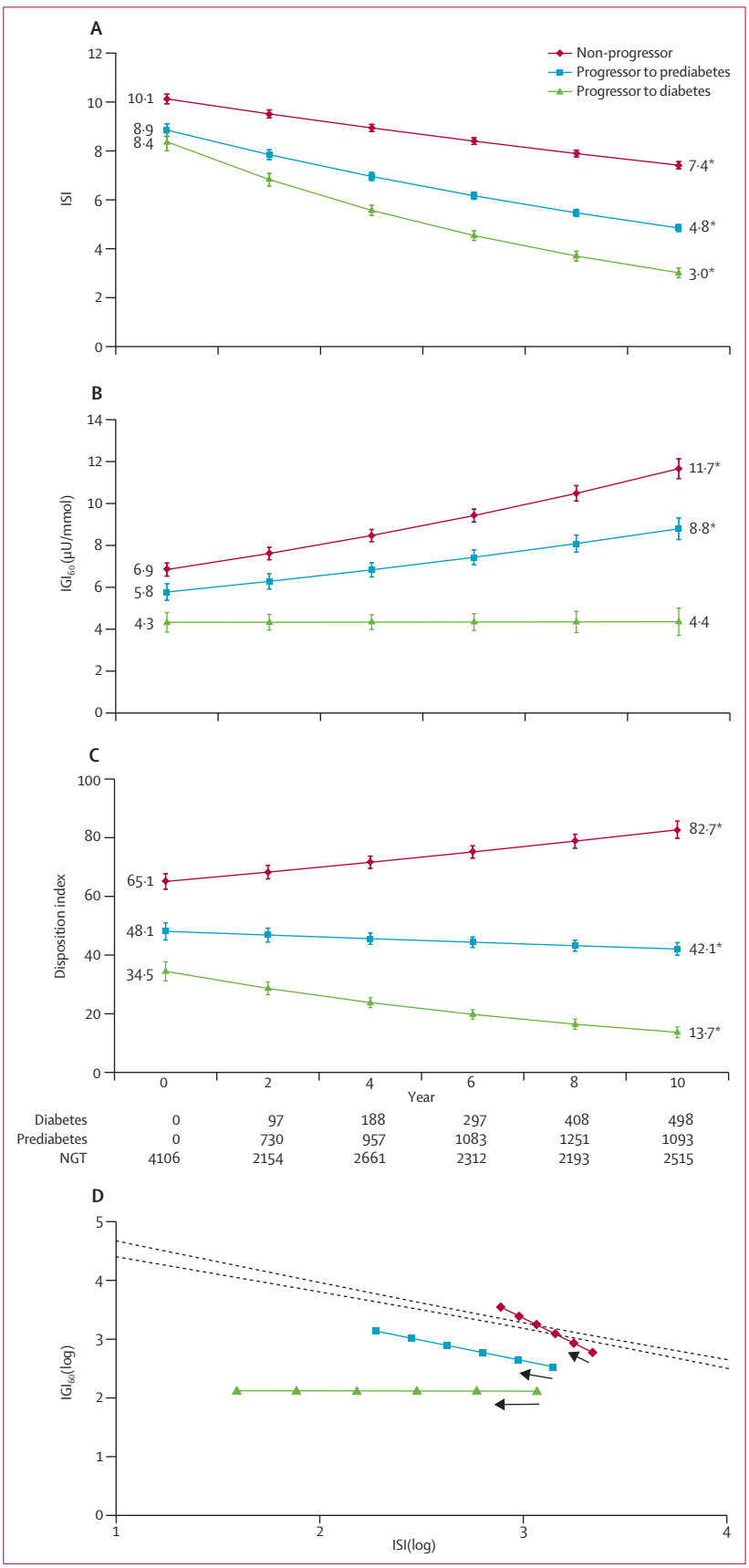

***Figure*: Trajectories of IGI_{60} and composite ISI during 10 years of follow-up**
The time series change in composite insulin sensitivity index (ISI; A), 60 min insulinogenic index (IGI_{60}; B), and disposition index (C), adjusted for baseline age and sex, are plotted from baseline to year 10 at 2-year intervals. Numbers below part C show the number of participants who had normal glucose tolerance (NGT), progressed to prediabetes, or diabetes in the specified year. Error bars represent 95% CIs. Vector plot of log_2-transformed composite ISI and IGI_{60} (D) shows that progressors to diabetes underwent a substantial decrease in insulin sensitivity, which was not compensated for by an adequate increase in β-cell function. The dashed lines show the 95% confidence limit of the linear regression line between composite ISI and IGI_{60} based on the regression of log(IGI_{60}) on log(ISI) with all 4106 participants with NGT at baseline. *p<0·01 for 10 versus 0 years.

four IGI_{60} and disposition index data points, and 3912 (95%) participants had at least three IGI_{60} and disposition index data. Insulin sensitivity, assessed by composite ISI decreased significantly (p<0·0001) from baseline to year 10 in all three groups, by 26·7% (adjusted data 10·1 [95% CI 9·9–10·3] *vs* 7·4 [7·3–7·6]) in non-progressors, by 44·9% (adjusted data 8·9 [8·6–9·1] *vs* 4·8 [4·4–5·0]) in progressors to prediabetes, and by 64·3% (adjusted data 8·4 [8·0–8·7] *vs* 3·0 [2·8–3·2]) in progressors to diabetes, together with the increase in waist circumference (appendix p 11). The rate of decrease in composite ISI was significantly higher in progressors to diabetes than in non-progressors (figure A, appendix p 2). IGI_{60} increased significantly (p<0·0001) compared with baseline only in non-progressors (69·6%; adjusted data 6·9 [95% CI 6·5–7·2] *vs* 11·7 [11·2–12·1]; p<0.0001) and progressors to prediabetes (51·7%; adjusted data 5·8 [5·4–6·2] *vs* 8·8 [8·3–9·3]; p<0·0001). However, we identified no significant change in IGI_{60} in progressors to diabetes (p=0·95). Non-progressors had the highest rate of change in IGI_{60}, compensating for mild decrease in insulin sensitivity (figure B). The disposition index, which reflects β-cell function, taking into account the effect of insulin sensitivity, also showed significant deterioration in progressors to diabetes during follow-up (figure C, appendix p 2). The vector plot of β-cell function and insulin sensitivity (figure D) shows that progressors to diabetes had decreased β-cell function and insulin sensitivity at baseline and had progressive impairment in insulin sensitivity, which was not offset by a concomitant increase in β-cell function. The results of the retrospective analysis (appendix p 12) also showed that decreased β-cell function is unable to compensate for impaired insulin sensitivity and is a major factor in the development of diabetes.

Finally, we investigated genetic risk factors associated with progression to prediabetes or diabetes and deterioration of β-cell function and insulin sensitivity. For the subset of 3395 participants available for genetic association analysis, genotype information was available for 66 confirmed type-2-diabetes-associated SNPs. 2046 participants who maintained NGT at final follow-up were compared with those who progressed (1349) to either prediabetes (918) or diabetes (431), by use of the Cox proportional-hazards model (appendix pp 3–4). Eight variants in or near *UBE2E2*, ST6GAL1, *TMEM154*, *GCK*, *ANK1*, *KCNJ11*, *MTNR1B*, and *C2CD4A* were nominally (p<0·05) associated with progression from NGT to prediabetes or diabetes. Only rs4607517 G→A variant near the glucokinase gene (*GCK*) was significantly associated with incident progression to prediabetes or diabetes after Bonferroni correction (HR 1·27, 95% CI 1·16–1·38; $p=1·70\times10^{-7}$, Bonferroni corrected $p=2·2\times10^{-5}$). This variant was also nominally associated with progression to diabetes (p=0·025; appendix p 3) and higher fasting glucose (β=0·039, 0·016–0·061; p=0·00083) at baseline (appendix p 5). The variant was nominally associated with decreased baseline IGI_{60} (β= –0·08, 95% CI –0·15 to –0·01; p=0·027) and disposition index (β= –0·07, –0·14–0·00; p=0·039; appendix pp 6–7). Furthermore, the variant was nominally associated with progressive decline in disposition index, as estimated by the rate of change with the linear mixed-effects model (β= –0·10, 95% CI –0·17 to –0·03; p=0·0041; appendix pp 8–9).

Discussion

To the best of our knowledge, our study is one of the largest to investigate trajectories of β-cell function and insulin sensitivity for as long as 10 years in a prospective cohort specifically designed to study environmental and genetic risk factors for diabetes. Progressors to diabetes had 35·4% lower IGI_{60} at baseline than did non-progressors. Impairment in β-cell function was more predictive of incident diabetes than was insulin sensitivity. At trajectory analysis, the decrease in insulin sensitivity was not offset by increased β-cell function among progressors to diabetes.

Our finding confirms previous reports that emphasised the role of β-cell dysfunction in the development of diabetes, especially in Asian people. In a study of 3059 Japanese participants who were followed up by medical check-ups,[7] impaired β-cell function had a greater effect on the development of diabetes than did insulin resistance. Asian patients with diabetes have been suggested to have lower BMI at onset of diabetes and decreased β-cell function compared with European and American patients.[24] A subgroup analysis of non-diabetic participants from the Whitehall II study showed that people with south Asian descent had more pronounced impairment of β-cell function than did white patients, associated with an age-related increase in fasting glucose.[25]

One of the strengths of our study is that we used estimates of β-cell function and insulin sensitivity incorporating several measures of glucose and insulin derived from OGTT. We mainly used IGI_{60} and composite ISI, both of which are physiological, do not need intravenous glucose infusion, and provide more information about the dynamic response of glucose and insulin than do measures from basal steady state.

In the retrospective analysis (appendix p 12), we combined NGT and prediabetes because participants in both groups had several transitions between NGT and prediabetes. Progressors to diabetes had significantly lower β-cell function than did non-progressors at baseline and were unable to compensate for the decrease in insulin sensitivity. Progressors to diabetes showed a pronounced decrease in insulin sensitivity soon before development of diabetes, suggesting that environmental factors, including increased calorie intake and decreased physical activity, also have important roles.[26]

Because β-cell function is more likely to be affected by genetic factors and ethnic differences seem to exist, we investigated genetic risk factors associated with progressive deterioration of glucose tolerance. When prediabetes and diabetes were combined, eight of 66 genetic variants showed nominal significance for

association with progression, seven of which (excluding the one in *ANK1*) had directional consistency for association with that reported from large-scale meta-analyses.[10] Among these seven genes, five (*UBE2E2*, *ST6GAL1*, *GCK*, *KCNJ11*, and *C2CD4A*) are expressed in human or rat islets, according to the Beta Cell Gene Atlas.[27] One interesting finding is that a variant (rs4607517) near *GCK* was significantly associated with progression of glucose intolerance even after Bonferroni correction. This variant was also associated with decreased baseline IGI_{60} and progressive deterioration of disposition index. Glucokinase plays an important part in insulin secretion because it senses the glucose concentration in pancreatic β cells. A pathogenic mutation in the *GCK* gene causes monogenic diabetes of the young type 2. This variant has been associated with fasting glucose concentration and β-cell function,[28] and with transition from NGT to impaired fasting glucose state.[29] From these findings, genetic predisposition can be reasonably inferred to determine β-cell function and, at least in part, resultant glucose intolerance.

Our study has several limitations. First, we only included participants with NGT at baseline. Excluding people with prediabetes enabled us to have a uniform population and minimise confounding. However, we were not able to assess how this at-risk population evolved during follow-up. Second, the mean baseline age was 51·1 years (SD 8·4), so people with early-onset diabetes, pronounced β-cell dysfunction, or impairment in insulin sensitivity might not have been captured in this cohort. Participants are less genetically predisposed to diabetes than the general Korean population, as shown by the absence of association for variants in *CDKAL1* and *CDKN2A/2B*, which are well known for their association with diabetes in Koreans.[30] Third, we used IGI_{60} as the index of β-cell function because 30 min glucose and insulin values were not available. However, IGI_{60} correlates well with IGI_{30} and is an acceptable measure of early insulin secretion.[17] Fourth, we did log_2-transformation of variables in epidemiological analysis in which clinical interpretation with original value was important, whereas we did inverse normal transformation in the genetic analysis. When IGI_{60} was log_2-transformed, negative values were regarded as missing, which might have introduced potential bias in our study. However, application of inverse normal transformation and inclusion of the negative IGI_{60} in epidemiological analysis similarly showed that progressors to diabetes do not have a compensatory increase in IGI_{60} during 10 years of follow-up (data not shown).

In conclusion, our study showed that progressors to diabetes had more pronounced impairment in baseline β-cell function than non-progressors and could not increase β-cell function in response to progressive decline in insulin sensitivity. Investigation of genetic risk factors showed that several variants implicated in β-cell function, including one near *GCK*, have what is probably a weak role in progressive deterioration in glucose tolerance. Clinically, our findings suggest that identification of people at risk of developing diabetes would be possible through assessment of β-cell function, insulin resistance, and genetic risk variants, even in people with a normoglycaemic status. Further research on the mechanism of impaired β-cell function is needed to develop preventive measures that could preserve β-cell function in this group.

Contributors

KSP and NHC designed and supervised the study. JHO, SHK, KSP, and NHC wrote the report. JHO and SHK did data analysis and prepared figures and tables. JHO, SHK, YMC, SL, HCJ, KSP, and NHC interpreted data, did literature searches, and edited the report.

Declaration of interests

We declare no competing interests.

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