Journal of Diabetes and Its Complications xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: The MASALA study☆,☆☆,★,★★

Unjali P. Gujral [a], K.M. Venkat Narayan [a,b,c], Steven E. Kahn [d], Alka M. Kanaya [e,*]

[a] Nutrition and Health Sciences Program, Graduate Division of Biomedical and Biological Sciences, Laney Graduate School, Emory University, 1518 Clifton Road NE, Atlanta, GA 30329, USA
[b] Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[c] Department of Medicine, School of Medicine, Emory University, Atlanta, GA, USA
[d] Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA, USA
[e] Division of General Internal Medicine, University of California, San Francisco, San Francisco, CA, USA.

ARTICLE INFO

Article history:
Received 13 August 2013
Received in revised form 1 October 2013
Accepted 2 October 2013
Available online xxxx

Keywords:
Type 2 diabetes mellitus
Asian Indians
Insulin sensitivity
β-cell dysfunction
Ethnicity
Incidence
Impaired glucose tolerance
Impaired fasting glucose

ABSTRACT

Aims: We assessed the relative associations of β-cell dysfunction and insulin sensitivity with baseline glycemic status and incident glycemic progression among Asian Indians in the United States.
Methods: A 5-sample oral glucose tolerance test was obtained at baseline. Normoglycemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2DM) were defined by ADA criteria. The Matsuda Index (ISI_M) estimated insulin sensitivity, and the Disposition Index (DI_o) estimated β-cell function. Visceral fat was measured by abdominal CT. After 2.5 years, participants underwent a 2-sample oral glucose tolerance test. Standardized polytomous logistic regression was used to examine associations with prevalent and incident glycemia.
Results: Mean age was 57 ± 8 years and BMI 26.1 ± 4.6 kg/m^2. Log ISI_M and log DI_o were associated with prediabetes and T2DM after adjusting for age, sex, BMI, family history of diabetes, hypertension, and smoking. After adjusting for visceral fat, only DI_o remained associated with prediabetes (OR per SD 0.17, 95% CI: 0.70, 0.41) and T2DM (OR 0.003, 95% CI: 0.0001, 0.03). Incidence rates (per 1,000 person-years) were: normoglycemia to IGT: 82.0, 95% CI (40, 150); to IFG: 8.4, 95% CI (0, 41); to T2DM: 8.6, 95% CI (0, 42); IGT to T2DM: 55.0, 95% CI (17, 132); IFG to T2DM: 64.0, 95% CI (3, 316). The interaction between sex and the change in waist circumference (OR 1.8, per SD 95% CI: 1.22, 2.70) and the change in log HOMA-β (OR 0.37, per SD 95% CI: 0.17, 0.81) were associated with glycemic progression.
Conclusions: The association of DI_o with baseline glycemia after accounting for visceral fat as well as the association of the change in log HOMA-β with incident glycemic progression implies innate β-cell susceptibility in Asian Indians for glucose intolerance or dysglycemia.

☆ Sources of Funding: The MASALA study were supported by the NIH [grant no. K23 HL080026-01] and the American Heart Association (Western States Affiliate award #0855069F). This project was supported by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131.UP Gujral was funded by the Fulbright Nehru Scholars Program. SE Kahn was supported by the United States Department of Veterans Affairs.
☆☆ No potential conflict of interest relevant to this article was reported.
★ Parts of this study were presented at the 73rd Scientific Sessionsof the American Diabetes Association, Chicago, Illinois, 21–25 June 2013.
★★ Author Contributions: U.P.G. analyzed data, wrote the manuscript, drafted tables and figures revised the manuscript, and approved the final manuscript for submission. K.M.V.N. contributed to concept, design, analysis, and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. S.E.K contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. A.M.K. obtained the funding, collected the data, contributed to concept, design, analysis, discussion, and interpretation of the data reviewed and revised the manuscript, and approved the final manuscript for submission. U.P.G. is the guarantor of this work, has had full access to all the data in the study, and takes responsibility for the integrity of the data andthe accuracy of the data analysis.
* Corresponding author at: c/o University of California, San Francisco, Box 0320, 1545 Divisadero Street, Suite 311, San Francisco, CA 94115, USA. Tel.: +1 415 353 7919; fax: +1 415 514 8666.
E-mail address: alka.kanaya@ucsf.edu (A.M. Kanaya).

1056-8727/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002

1. Introduction

The pathophysiology of type 2 diabetes is a complex process involving both decreased insulin sensitivity and impaired insulin secretion (Kasuga, 2006). Traditionally, the pathogenesis has been described as obesity driven, with progressive insulin resistance followed by a subsequent decline in β-cell function, eventually leading to overt hyperglycemia (Kasuga, 2006; Saad et al., 1991). However, decline in β-cell function has also been detected as a driving factor early in the natural history of type 2 diabetes development (Gastaldelli, Ferrannini, Miyazaki, Matsuda, & DeFronzo, 2004; Kahn, 2003). Since several genes conferring risk for type 2 diabetes are associated with β-cell dysfunction (Florez, 2008), it is possible that some ethnic groups may have an innate susceptibility for early decline in β-cell function, thereby placing them at increased risk for disease development beyond traditionally associated factors such as age, adiposity, and insulin resistance.

Asian Indians, both in India and abroad, are at a particularly increased risk for type 2 diabetes (Chiu, Cohan, Lee, & Chuang, 2010; Misra et al., 2010; Oza-Frank, Ali, Vaccarino, & Narayan, 2009; Shaw, Sicree, & Zimmet, 2010; Wild, Roglic, Green, Sicree, & King, 2004). Several studies have noted that Asian Indians are more insulin resistant than other ethnic groups at younger ages and comparative levels of body mass index (BMI) (Chiu, Austin, Manuel, Shah, & Tu, 2011; Gujral, Pradeepa, Weber, Narayan, & Mohan, 2013; Gupta, Wu, Young, & Perlman, 2011). Recent studies have also suggested that Asian Indians exhibit lower β-cell function even with mild dysglycemia, which may suggest an early etiological factor for hyperglycemia in this population (Mohan et al., 2013; Staimez et al., 2013). These studies present intriguing observations concerning the relative roles of β-cell function and insulin sensitivity in the pathophysiology of type 2 diabetes in Asian Indians in native Indian settings. However, no such studies have been conducted on Asian Indians living in a developed country environment. There is a lack of information on whether β-cell dysfunction is similarly important in Asian Indians who have migrated to developed countries where there may be additional lifestyle, environmental, and psychosocial stressors promoting obesity and insulin resistance. Furthermore, scarce data exists regarding incidence rates of type 2 diabetes in Asian Indians and the associated risk factors responsible. Therefore, in the present study, we analyzed the relative associations of β-cell function and insulin sensitivity on glycemic status and on the incidence of prediabetes and diabetes in a population-based cohort of migrant Asian Indians in the United States.

2. Subjects

2.1. Study population

The design, sampling strategy, recruitment and enrollment of the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study are as described elsewhere (Kanaya et al., 2010). In brief, a total of 150 participants from the San Francisco Bay area were enrolled between August 2006 and October 2007, with one follow up clinical visit occurring between April 2009 and January 2010. Mean follow-up time between visits was approximately 2.5 years. Eligibility criteria were designed to be similar to that of the Multi-Ethnic Study of Atherosclerosis (MESA) study (Bild et al., 2002) and required participants to be between age 45 and 84 years and self-identify as South Asian. Those individuals with pre-existing cardiovascular disease, using nitroglycerin, undergoing cancer therapy, with impaired cognitive ability, with life expectancy less than 5 years, with plans to move from the area, or living in a nursing home were excluded from the study.

3. Materials and methods

3.1. Study procedures

Participant weight was measured on a standard balance beam scale, and height was measured using a stadiometer. Waist circumference was measured using a Gullick II tape at the site of maximum circumference midway between the lower ribs and the anterior superiliac spine. Three seated blood pressure measurements were taken and mean systolic (SBP) and diastolic blood pressures (DBP) were calculated from the second and third measurements. Computed tomography was used to determine visceral and abdominal subcutaneous fat area. The correct position of the CT scan (between the L4 and the L5 vertebrae) was established by a trained radiology technician, using a lateral scout image of the spine and was conducted using standardized protocols (Kanaya et al., 2010).

After a 12 hour overnight fast, a 75 g oral glucose tolerance test (OGTT) was administered to all individuals at the baseline examination and to those without medication treated diabetes at the second clinical examination. At baseline, blood samples were obtained just before glucose ingestion (time 0) and then 30, 60, 90 and 120 minutes post-challenge for plasma glucose and serum insulin measurements. At the second clinical visit, approximately 2.5 years later, blood samples were obtained while fasting and at 120 minutes after the glucose challenge. Plasma glucose was measured using an automated analyzer (YSI 2300 STAT Plus, YSI Life Sciences, Yellow Sprints, OH). Serum samples were processed and stored at −80 °C for batched assays of immunoreactive insulin (RIA, Millipore, St. Charles, MO).

The assessment of life expectancy and cognitive ability was similar to that of the MESA study. Potential participants were asked whether they had been diagnosed with any diseases that may limit their life expectancy to <5 years. During eligibility assessment, participants were also asked several questions to gauge their ability to respond to simple as well as more complex questions about health status. If participants were unable to respond to these questions due to inability to remember or communicate the information, they were deemed not eligible for the study.

Hypertension was defined by the use of an anti-hypertensive medication, or if their systolic blood pressure was ≥140 mmHg or if their diastolic blood pressure was ≥90 mmHg. These are the same criteria used by the MESA study. Family history of diabetes was determined by self-report and was classified as either a parent or sibling being previously diagnosed. Smoking status was also based on self-reported answers to the baseline MASALA study questionnaire.

Diabetes was defined by the use of a glucose lowering medication or fasting plasma glucose ≥7.0 mmol/l and/or 2 hour post-challenge glucose ≥11.1 mmol/l. Prediabetes was defined by fasting plasma glucose of 5.6-6.9 mmol/l (IFG) and/or 2 hour post-challenge glucose of 7.8-11.1 mmol/l (IGT). Normal glucose tolerance was defined as those participants who had both fasting plasma glucose <5.6 mmol/l and a 2 hour post-challenge glucose <7.8 mmol/l (American Diabetes Association, 2008).

3.2. Calculations

β-Cell function was estimated at baseline by the oral disposition index (DI_o) and was calculated as $(\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30})^*(1/\text{fasting insulin})$ (Utzschneider et al., 2009). DI_o is a product of the insulin response and a surrogate measure of insulin sensitivity, and is based on the hyperbolic relationship between these two measures (Utzschneider et al., 2009). The concept of a hyperbolic relationship has also been demonstrated in humans for the first-phase response to glucose and insulin sensitivity (Kahn et al., 1993). Both the oral and intravenous approaches have been proven to be useful for examining the ability of the β-cell to compensate for differences in insulin sensitivity

Please cite this article as: Gujral, U.P., et al., The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in mig..., *Journal of Diabetes and Its Complications* (2013), http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002

Table 1
Baseline MASALA study participant characteristics by glycemic status, 2006–2007.*

Characteristics	NGT	Prediabetes	T2DM	P-value
n (%)	58 (38.7)	51 (34.0)	41 (27.3)	
Male sex (%)	31.0	54.9	70.7	<0.01
Never smoker (%)	87.9	82.4	78.1	0.43
Family history of diabetes (%)	51.7	56.9	58.5	0.77
Current hypertension (%)	17.2	45.1	73.2	<0.01
Age (years)	56.5 ± 7.5	57.8 ± 9.3	57.5 ± 7.3	0.70
Years lived in the United States	23.6 ± 10.9	24.1 ± 11.1	23.8 ± 12.7	0.98
BMI (kg/m^2)	24.6 ± 3.5	27.1 ± 5.4	27.2 ± 4.5	0.01
Waist circumference (cm)	91.2 ± 10.7	97.1 ± 13.2	102.0 ± 11.0	<0.001
Visceral fat area (cm^2)	107.4 ± 45.3	136.5 ± 52.8	166.8 ± 58.4	<0.001
Subcutaneous fat area (cm^2)	233.3 ± 88.8	265.6 ± 138.4	261.3 ± 106.7	0.27
Systolic blood pressure (mmHg)	116.6 ± 15.9	126.8 ± 16.2	132.6 ± 14.4	<.001
Diastolic blood pressure (mmHg)	69.0 ± 9.0	73.8 ± 12.0	76.0 ± 11.4	0.005
Fasting glucose (mmol/l)	4.8 ± 0.4	5.3 ± 0.6	7.3 ± 1.6	<0.001
2 h glucose (mmol/l)	6.0 ± 1.0	8.6 ± 1.3	15.7 ± 3.4	<0.001
Measures of insulin sensitivity				
Log ISI_M (μIU/ml*mg/ml)	2.3 ± 0.5	1.9 ± 0.6	1.7 ± 0.6	<0.001
Log HOMA-IR (μIU/ml*mmol/l)	0.7 ± 0.5	0.9 ± 0.7	1.5 ± 0.7	<0.001
Measures of β-cell function				
Disposition Index (pmol/mmol)*pmol	3.4 ± 3.3	1.8 ± 2.0	0.4 ± 0.3	<0.001
Log HOMA-β (μIU/ml/mmol/l)	5.0 ± 0.4	4.8 ± 0.7	4.4 ± 0.8	<0.001

* Values represent mean ± SD or %.

(Bergman, Finegood, & Kahn, 2002). Insulin sensitivity at baseline was also estimated using the Matsuda Index (ISI_M) calculated as 10,000/√(fasting glucose*fasting insulin)*(mean OGTT glucose concentration*mean OGTT insulin concentration) (Matsuda & DeFronzo, 1999). ISI_M was chosen as a measure of insulin sensitivity as it represents a composite of both hepatic and muscular tissue insulin sensitivity and correlates well with the euglycemic insulin clamp as a measure of insulin sensitivity (Matsuda & DeFronzo, 1999). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (WHO Expert Committee on Physical Status, 1995).

At the follow up examination, 30-minute post-challenge glucose and insulin concentrations were not measured, therefore DI_o could not be calculated. Instead HOMA-β was used to measure β-cell function in longitudinal analysis and was calculated as [20*I_0(μIU/ml)/G_0 (mmol/l)- 3.5], and HOMA-IR was used to measure insulin resistance and calculated as [I_0(μIU/ml) * G_0 (mmol/l)/22.5] (Matthews et al., 1985). Person years were calculated as the sum of years each person at risk contributed to the study between baseline and follow up. The time between the baseline and follow-up visits of those with incident cases was divided in half to arrive at total person years for all those at risk.

3.3. Statistical analysis

Baseline characteristics of study participants were compared by glucose tolerance category using chi-squared test or ANOVA as appropriate. Non-normally distributed variables were log transformed. Standardized polytomous logistic regression was used to compare the odds of prediabetes or type 2 diabetes to normal glucose tolerance. Initially, unadjusted regression models were created to compare the individual associations of DI_o and ISI_M with prevalent glycemic status. Multivariable models were created to adjust for covariates including age, sex, smoking status, family history of diabetes, hypertension, and visceral adipose tissue area. In order to assess multi-linearity in the models, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables. If it was determined that strong relationships existed between variables that would yield the model unreliable, one of those variables was removed from the final model (Kleinbaum & Klein, 2002). Backwards stepwise elimination was used to remove variables with a $P > 0.05$ from the model to retain only the most relevant covariates.

For the longitudinal analyses, baseline and second visit characteristics were compared using chi-squared or paired t-tests as appropriate. We used standardized logistic regression models to examine the covariates associated with glycemic conversion. Since both HOMA-IR and HOMA-β are functions of fasting glucose (Matthews et al., 1985), assessing the associations of these variables with incident glycemic status from increased fasting glucose would result in fasting glucose being used as both an outcome and an association variable. We therefore restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-h post-challenge glucose measures, thereby eliminating the use of fasting glucose as both a predictor and an outcome variable. Bivariable models were used to assess preliminary associations, and multivariable models were used to adjust for possible confounders. Again, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables to assess multi-linearity in the models. Backwards stepwise elimination was used to remove variables with a $P > 0.05$. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC).

4. Results

4.1. Baseline visit

Of the 150 participants in the MASALA study, at baseline 58 (39%) had normal glucose tolerance, 51 (34%) had prediabetes, and 41 (27%) had type 2 diabetes. Of those with prediabetes at baseline, 8 (16%) had isolated IFG, 35 (69%) had isolated IGT, and 8 (16%) had both IFG and IGT. These results differ slightly from those published previously because earlier MASALA studies did not use 2-hour glucose levels in their classifications of glycemic status in order to remain consistent with classifications used by the MESA study (Kanaya et al., 2010). Additionally, 63 participants (42%) had hypertension at baseline, 48 of whom were using anti-hypertensive medication. Table 1 describes participant characteristics by glycemic status. Those with diabetes were more likely to be male, have a history of hypertension, higher levels of systolic and diastolic blood

Please cite this article as: Gujral, U.P., et al., The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in mig..., *Journal of Diabetes and Its Complications* (2013), http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002

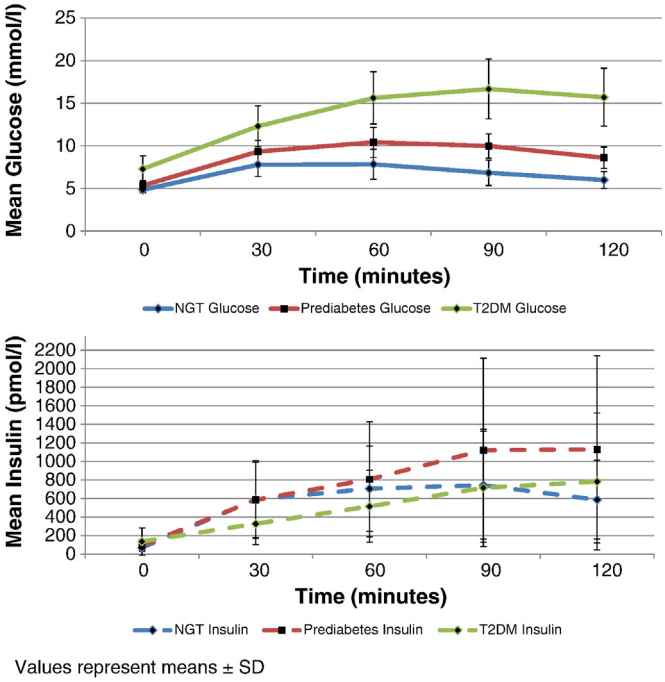

Fig. 1. Change in mean glucose and insulin over time by glycemic status. Values represent means ± SD.

pressure, a larger body habitus based on BMI, more central adiposity assessed by waist circumference and visceral fat area, were more insulin resistant based on log HOMA-IR and log ISI_M and had poorer β-cell function based on DI_o than those with normal glucose tolerance. With regard to mean log ISI_M, there was a significant difference between normal glycemia and prediabetes, while the mean log ISI_M between prediabetes and type 2 diabetes was not significantly different. Furthermore, while there was a difference in BMI between those with type 2 diabetes and normal glucose tolerance, there was little difference between those with prediabetes and type 2 diabetes. Waist circumference and visceral fat area were both greater in a graded fashion from normal glucose tolerance to type 2 diabetes mellitus.

Fig. 1 shows mean glucose and insulin responses during the OGTT by glycemic status. Consistent with higher fasting and 2-hour glucose levels in those with pre-diabetes and diabetes, the values at the intermediate time points (30, 60 and 90 minutes) were greater in those with abnormal glucose tolerance compared to those with normal glucose tolerance. Mean insulin also differed amongst groups. Those with type 2 diabetes had the highest mean insulin at fasting, but the lowest mean insulin at 30, 60, and 90 minutes post-challenge. Those with normal glucose tolerance and prediabetes had similar mean insulin levels until 30 minutes post challenge. After this time point, mean insulin was significantly higher in those with prediabetes than those with normal glucose tolerance.

Table 2 shows the relative associations of Log ISI_M and DI_o with glycemic status both bivariately and after multivariate adjustment. Bivariately, log ISI_M and DI_o were each associated with glycemic status. For every standardized unit increase in ISI_M the odds of prediabetes was 57% lower and the odds of type 2 diabetes was 70% lower compared to having normal glucose tolerance. For every one standardized unit increase in DI_o the odds of prediabetes was 85% lower and the odds of type 2 diabetes 98% lower compared to normal glucose tolerance. When both log ISI_M and DI_o were included in the model, after controlling for age, sex, BMI, family history of diabetes, hypertension, and smoking status, both factors, along with hypertension, remained significantly associated with prediabetes and type 2 diabetes. However, the association of ISI_M with both prediabetes and type 2 diabetes was no longer significant once visceral fat was included in the model, while the association of DI_o and glycemic status remained robust.

4.2. Follow-up visit

Approximately 2.5 years after the baseline visit, 132 (88%) of participants returned for the second clinical examination. Of the 18 participants who did not follow-up, 2 had died, 4 had moved away from the study area, 3 had developed serious illnesses, 6 were unable to schedule an appointment for logistical reasons, and 3 refused continued study participation. There were no significant differences in the baseline characteristics of those who remained in the study and those who withdrew. At the second examination, 24 (18%) of the 132 participants were being treated with glucose lowering medication; 17 of which were on glucose lowering medication both at baseline and at the second examination and 7 of which were newly on glucose lowering medication at follow up. Oral glucose tolerance tests were not performed on these participants. Table 3 describes participant characteristics at baseline and second clinical examination of those at risk for developing T2DM at the second clinical exam. Only mean log HOMA-IR and mean Log HOMA-β were significantly different between visits.

Table 2
Factors associated with baseline prediabetes and/or type 2 diabetes.

Model	Prediabetes		Type 2 diabetes		P
	OR	95% CI	OR	95% CI	
Log ISI_M					
Log ISI_M	0.43	(0.26, 0.70)	0.30	(0.17, 0.51)	<0.001
Log DI_0					
Log DI_o	0.15	(0.06, 0.36)	0.02	(0.01, 0.02)	<0.001
MV-adjusted Model 1*					
Log ISI_M	0.51	(0.27, 0.95)	0.35	(0.15, 0.87)	0.05
Log DI_o	0.22	(0.09, 0.58)	0.003	(0.001, 0.03)	<0.0001
Hypertension	4.30	(1.49, 12.41)	5.54	(1.08, 28.54)	0.02
MV-adjusted Model 2**					
Log DI_o	0.17	(0.70, 0.41)	0.003	(0.001, 0.03)	<0.0001
Visceral fat area	1.01	(1.00, 1.02)	1.02	(1.00, 1.04)	0.02
Hypertension	3.9	(1.4, 11.3)	4.3	(0.88, 22.15)	0.04

* Multivariate model adjusted for sex, age, BMI, family history of diabetes, smoking status, and hypertension.
** In addition to variables in Model 1, also adjusted for visceral fat area.

Table 3
Baseline and second clinical exam characteristics among those at risk for developing diabetes.*

Characteristics	Baseline	Second visit	P-value
n (%)	97	97	
Male sex (%)	42.3	42.3	1.0
Current hypertension (%)	30.9	29.9	0.88
Age (years)	57 ± 8	59 ± 8	0.02
BMI (kg/m^2)			
Male	25.8 ± 4.2	26.0 ± 4.2	0.91
Female	25.7 ± 4.8	26.1 ± 4.9	0.66
Waist circumference (cm)			
Male	96.4 ± 9.5	95.7 ± 9.5	0.74
Female	91.6 ± 12.5	89.2 ± 12.7	0.32
Systolic blood pressure (mmHg)	122 ± 17	124 ± 14	0.25
Diastolic blood pressure (mmHg)	71 ± 11	72 ± 11	0.53
Fasting glucose (mmol/l)	5.1 ± 0.6	5.1 ± 0.7	0.96
2 hr glucose (mmol/l)	7.2 ± 1.7	7.5 ± 2.3	0.29
Log HOMA-IR (μIU/ml*mmol/l)	0.8 ± 0.6	1.2 ± 0.5	<0.001
Log HOMA-β (μIU/ml/mmol/l)	4.9 ± 0.6	5.3 ± 0.5	<0.001

* We have excluded those with prevalent diabetes at baseline from both columns; values represent mean ± SD or %.

Please cite this article as: Gujral, U.P., et al., The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in mig..., *Journal of Diabetes and Its Complications* (2013), http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002

Between baseline and the second examination, 11 (8%) of the 132 participants converted from normal glycemia to prediabetes, 1 (0.75%) converted from normal glycemia to type 2 diabetes, and 6 (5%) converted from prediabetes to type 2 diabetes. Of those with normal glucose tolerance who converted to prediabetes, the incidence rate of impaired glucose tolerance was 82 per 1,000 person-years; 95% CI (40, 150) while the incidence rate of conversion to impaired fasting glucose was 8 per 1,000 person-years; 95% CI (0, 41). Based on both fasting and 2-hr OGTT values at follow-up, of those with prediabetes at baseline, the incidence rate from IGT to type 2 diabetes was 55 per 1,000 person years, 95% CI (17, 132). The incidence rate of conversion from IFG to type 2 diabetes was 64 per 1,000 person years, 95% CI (3, 316), and the incidence rate of diabetes for those who had both IFG and IGT was 66 per 1,000 person years, 95% CI (33, 324).

Between baseline and visit 2, mean standardized log HOMA-IR increased by 0.92 ± 1.00 μIU/ml*mmol/l. However, mean standardized log HOMA-β also increased by 0.70 ± 1.00 μIU/ml*mmol/l. In examining the covariates associated with glycemic progression, either from NGT to IGT, from NGT to type 2 diabetes, or from IGT to type 2 diabetes, in bivariate analysis the change in log HOMA-β (OR 0.44 per SD, 95% CI: 0.21, 0.90) and the interaction between sex and change in waist circumference (OR 1.58 per SD, 95% CI: 1.13, 2.22) were associated with glycemic conversion. In multivariable models which included baseline values for HOMA-IR and HOMA-β, the change in HOMA-β (OR 0.37 per SD, 95% CI: 0.17, 0.81) between the first and second exam and the interaction between sex and change in waist circumference (OR 1.81 per SD, 95% CI: 1.22, 2.70) were significantly associated with any glycemic status conversion, while no measures of baseline insulin sensitivity, baseline β-cell function, or change in insulin sensitivity were associated either in bivariate or multivariable models.

5. Discussion

We found that at baseline, the association between DI_o, a measure of β-cell function relative to insulin sensitivity, was more strongly associated with both prediabetes and type 2 diabetes than ISI_M, a measure of whole body insulin sensitivity, in our cohort of Asian Indians in the United States. This association remained strong even after adjustment for well known risk factors such as age, BMI, family history and visceral adiposity. Additionally, there may be more rapid progression from normal to impaired glucose tolerance and from impaired glucose tolerance to type 2 diabetes among Asian Indians than previously reported in other ethnic groups (Bonora et al., 2004; Valdes, Botas, Delgado, Alvarez, & Cadorniga, 2007) Changes in β-cell function over time were associated with glycemic progression in our cohort. Together, these findings suggest a possible independent effect of impaired β-cell function in the pathogenesis of type 2 diabetes in Asian Indians which could be the result of an innate susceptibility.

Recent studies conducted in India have also found early reductions in β-cell function as a possible primary etiological factor for diabetes development in Asian Indians (Mohan et al., 2013; Staimez et al., 2013). A cross-sectional study conducted on 1,264 individuals without known diabetes from Chennai, India noted that after adjusting for age, sex, BMI, waist circumference and family history, compared to normal glycemia, the odds of impaired fasting glucose or impaired glucose tolerance were more significant for DI_o than for HOMA-IR. These results suggest that reductions in β-cell function are apparent in Asian Indians even in early stages of dysglycemia, irrespective of factors known to impact disease development (Staimez et al., 2013). Another cross-sectional study from Chennai, India, compared Asian Indians with normal glucose tolerance and prediabetes with individuals in whom the onset of diabetes occurred before the age of 25 years (Mohan et al., 2013). Results of this study showed independent associations with both DI_o and Matsuda Index and type 2 diabetes and prediabetes. However, after adjusting for BMI, waist circumference, and age, DI_o remained significant for both stages of glycemia, while the Matsuda Index did not (Mohan et al., 2013). These findings of strong associations with β- cell dysfunction and hyperglycemia in Asian Indians even at very young ages suggest that the pathogenesis of type 2 diabetes in Asian Indians in India is primarily a function of declining β-cell function rather than the development of insulin resistance.

Our current study adds additional evidence that there is a strong association between β-cell dysfunction and both prediabetes and type 2 diabetes in Asian Indians and goes further to indicate that declines in β-cell function may be an underlying factor in type 2 diabetes development in this ethnic group regardless of the environmental setting. This is supported by the mean differences in insulin sensitivity (measured by log ISI_M) and β-cell function (measured by DI_o) between glycemic groups in our population, the associations with ISI_M and DI_o and glycemic status in polytomous standardized regression, and the association of HOMA-β with glycemic progression. While mean insulin sensitivity at baseline was only significantly different between normal glycemia and prediabetes, mean β-cell function was significantly different amongst all pairwise comparisons, thereby suggesting an early decline in β-cell function which continues to deteriorate as glucose tolerance declines. Furthermore, in bivariate standardized polytomous regression models, both insulin sensitivity and β-cell function were independently associated with both prediabetes and type 2 diabetes. However, in multivariable analyses the association with insulin sensitivity was considerably attenuated. Furthermore, after adjusting for visceral fat area associations with insulin sensitivity for both prediabetes and type 2 diabetes were no longer significant. This was not the case with β-cell function as DI_o remained significantly associated with both prediabetes and diabetes in multivariable models even after the adjustment of other well known risk factors. Additionally, changes in HOMA-β were associated with glycemic progression at follow up while changes in HOMA-IR were not. Our results, taken in aggregate with similar studies from India, indicate a possible innate susceptibility to β-cell dysfunction in Asian Indians that is independent of age, BMI, and abdominal obesity. These results point to early declines in β-cell function as an important contributing factor to type 2 diabetes development in this ethnic group that exists regardless of a developed or developing country setting.

While other studies have examined the relative associations of both β-cell function and insulin sensitivity across the entire spectrum of glycemia in native Asian Indians, our study is the first to do so in a cohort residing in the United States, thereby indicating that early reductions in β-cell function are apparent despite environmental, behavioral, or migratory factors and exist in both developing and developed country environments. However, the primarily cross-sectional nature of our study makes it impossible to determine when precisely during the natural history of type 2 diabetes pathogenesis the initial decline in β-cell function begins to occur. Additionally, the small sample size and short duration of follow up in our study resulted in unstable incidence rates with wide confidence intervals. A study from Chennai, India followed participants for a period of 8 years and determined that the incidence of type 2 diabetes was very high (20.2 per 1,000 person years) among Asian Indians living in an urban Indian setting (Mohan, Deepa, Anjana, Lanthorn, & Deepa, 2008). While this study provides valuable insight as to the rapid rate of conversion from normal glycemic or hyperglycemic states to overt type 2 diabetes in this population, it was conducted solely on Asian Indians living in urban South India and did not include other ethnic groups for comparison. Therefore, additional large longitudinal studies, including several ethnic groups, and with a long duration of follow-up are needed in order to accurately assess rates of glycemic conversion in Asian Indians compared to other ethnicities. Additional limitations to our study include the exclusion of

Please cite this article as: Gujral, U.P., et al., The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in mig..., *Journal of Diabetes and Its Complications* (2013), http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002

participants under the age of 45 and also those with pre-existing cardiovascular disease. Lastly, 30-minute post-challenge glucose and insulin were not measured at follow up. Therefore, we could not evaluate change in log ISI_M and DI_o as measures of insulin sensitivity and β-cell function during follow up, and instead relied on HOMA-IR and HOMA-β as measures of insulin sensitivity and β-cell function respectively. Since the calculations for HOMA-IR and HOMA-β involve fasting glucose, we restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-hr post-challenge glucose measures, thereby eliminating any potential bias caused by the use of fasting glucose as both a predictor and an outcome variable. However, as a result, we were not able to assess risk factors associated with the conversion from normal glucose tolerance to IFG or from IFG to type 2 diabetes.

In conclusion, both decreased insulin sensitivity and impaired β-cell function are associated with type 2 diabetes in Asian Indians. However, impaired β-cell function appears to have a stronger relationship with prediabetes and type 2 diabetes. This association remained robust even after adjusting for visceral adiposity and other well known risk factors such as age, family history of diabetes, and hypertension, indicating a possible excess susceptibility to β-cell dysfunction in this ethnic group. Larger longitudinal studies in migrant Asian Indians are needed to provide further insight into acquired and/or epigenetic risk factors that may play a role in the development of β-cell dysfunction and eventual overt type 2 diabetes in this population.

Acknowledgements

We thank the MASALA study participants, the study coordinators and interns for their help with participant enrollment and retention. We thank the nurses and staff of the San Francisco General Hospital Clinical Research Unit for their help with the oral glucose tolerance testing, phlebotomy and sample processing.

References

American Diabetes Association. (2008). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *31*, S55–S60.

Bergman, R. N., Finegood, D. T., & Kahn, S. E. (2002). The evolution of β-cell and insulin resistance in type 2 diabetes. *European Journal of Clinical Investigation*, *32*(Suppl 3), 35–45.

Bild, D. E., Bluemke, D. A., Burke, G. L., Detrano, R., Diez Roux, A. V., Folsom, A. R., et al. (2002). Multi-ethnic study of atherosclerosis: objectives and design. *American Journal of Epidemiology*, *156*(9), 871–881.

Bonora, E., Kiechl, S., Willeit, J., Oberhollenzer, F., Egger, G., Meigs, J. B., et al. (2004). Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes*, *53*(7), 1782–1789.

Chiu, M., Austin, P. C., Manuel, D. G., Shah, B. R., & Tu, J. V. (2011). Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care*, *34*, 1741–1748.

Chiu, K. C., Cohan, P., Lee, N. P., & Chuang, L. M. (2010). Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. *Diabetes Care*, *23*(9), 1353–1358.

Florez, J. C. (2008). Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? *Diabetologia*, *51*(7), 1100–1110.

Gastaldelli, A., Ferrannini, E., Miyazaki, Y., Matsuda, M., & DeFronzo, R. A. (2004). Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*, *47*(1), 31–39.

Gujral, U. P., Pradeepa, R., Weber, M. B., Narayan, K. M., & Mohan, V. (2013). Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. *Annals of the New York Academy of Sciences*, *1281*(1), 51–63.

Gupta, L. S., Wu, C. C., Young, S., & Perlman, S. E. (2011). Prevalence of diabetes in New York City, 2002–2008: comparing foreign-born South Asians and other Asians with U.S.-born whites, blacks, and Hispanics. *Diabetes Care*, *34*, 1791–1793.

Kahn, S. E. (2003). The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia*, *46*(1), 3–19.

Kahn, S. E., Prigeon, R. L., McCulloch, D. K., Boyko, E. J., Bergman, R. N., Schwartz, M. W., et al. (1993). Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*, *42*(11), 1663–1672.

Kanaya, A. M., Wassel, C. L., Mathur, D., Stewart, A., Herrington, D., Budoff, M. J., et al. (2010). Prevalence and correlates of diabetes in South Asian Indians in the United States: findings from the metabolic syndrome and atherosclerosis in South Asians living in America study and the Multi-Ethnic Study of Atherosclerosis. *Metabolic syndrome and related disorders*, *8*(2), 157–164.

Kasuga, M. (2006). Insulin resistance and pancreatic beta cell failure. *The clinical investigator*, *116*(7), 1756–1760.

Kleinbaum, D. G., & Klein, M. (2002). Logistic regression: a self-learning text. In K. Dietz, M. Gail, K. Krickeberg, J. Samet, & A. Tsiatis (Eds.), New York, NY: Springer-Verlag.

Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*, *22*(9), 1462–1470.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*, 412–419.

Misra, R., Patel, T., Kotha, P., Raji, A., Ganda, O., Banerji, M., et al. (2010). Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. *Journal of Diabetes and its Complications*, *24*(3), 145–153.

Mohan, V., Anandakumar, A., Ranjani, H., Anjana, R. M., Staimez, L. R., Ali, M. K., et al. (2013). Associations of β-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. *Diabetes Technology & Therapeutics*, *15*(4), 315–322.

Mohan, V., Deepa, M., Anjana, R. M., Lanthorn, H., & Deepa, R. (2008). Incidence of diabetes and pre-diabetes in a selected urban south Indian population (CUPS-19). *Journal of the Association of Physicians of India*, *56*, 152–157.

Oza-Frank, R., Ali, M. K., Vaccarino, V., & Narayan, K. M. (2009). Asian Americans: diabetes prevalence across U.S. and World Health Organization weight classifications. *Diabetes Care*, *32*, 1644–1646.

Saad, M. F., Knowler, W. C., Pettitt, D. J., Nelson, R. G., Charles, M. A., & Bennett, P. H. (1991). A two-step model for development of non-insulin-dependent diabetes. *American Journal of Medicine*, *90*(2), 229–235.

Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, *87*, 4–14.

Staimez, L. R., Weber, M. B., Ranjani, H., Ali, M. K., Echouffo-Tcheugui, J., Phillips, L. S., et al. (2013). Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. *Diabetes Care*, *36*, 2772–2778.

Utzschneider, K., Prigeon, R., Faulenbach, M., Tong, J., Carr, D. B., Boyko, E. J., et al. (2009). Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care*, *32*(2), 335–341.

Valdes, S., Botas, P., Delgado, E., Alvarez, F., & Cadorniga, F. D. (2007). Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. *Diabetes Care*, *30*(9), 2258–2263.

WHO Expert Committee on Physical Status. (1995). The use and interpretation of anthropometry: report of a WHO expert committee. *World Health Organization Technical Report Series*. (pp. 854)Geneva, Switzerland: World Health Organization.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care*, *27*, 1047–1053.

Please cite this article as: Gujral, U.P., et al., The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in mig..., *Journal of Diabetes and Its Complications* (2013), http://dx.doi.org/10.1016/j.jdiacomp.2013.10.002