Research Article

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Insulin resistance and secretion change after 3 years follow-up and the risk for developing diabetes in non-diabetic adults

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ABSTRACT

Purpose : To determine 3-years natural change of insulin resistance and secretion in non-diabetic Chinese adults and corresponding risk for developing diabetes.

Methods : Population-based cohort study was performed in Chinese adults (35-74 years) from 2009 to 2015. Fasting plasma glucose and serum insulin was determined in 1882 subjects (701 men) at baseline and re-tested in 1087 (377 men). Insulin resistance was estimated with HOMA insulin resistance index (HOMA-IR) and insulin secretion with HOMA insulin secretion index (HOMA-IS). The change of HOMA-IR and HOMA-IS was calculated as: the value at follow-up minus that at baseline.

Results : Normal subjects (NGT) had a lower HOMA-IR (1.51[95%CI 1.45-1.58] vs 1.95[1.84-2.07]) and higher HOMA-IS (72.89[69.76-76.10] vs 62.68[59.03-66.49]) than those with pre-diabetes. After 2.62 years on average, diabetes occurred in 28 participants with NGTs and in 38 with pre-diabetes. HOMA-IS was significantly decreased in participants with worsening glucose metabolism. Decreased HOMA-IS was an independent risk factor for diabetes in both individuals with NGT (HR 0.995[0.991-0.998]) and pre-diabetes (HR 0.993[0.988-0.998]); but, increased HOMA-IR was observed only in NGTs with incident diabetes (HR 1.34 [1.09-1.64]).

Conclusion : The deficiency of insulin secretion played a key role in Chinese adults with worsening glucose metabolism.

Keywords : incident diabetes, insulin resistance, impaired insulin secretion

INTRODUCTION

According to a report by the International Diabetes Federation (IDF) on December 6, 2021, it is expected that by 2045, China will still rank first in the number of people aged 20-79 with diabetes, and the number of people with diabetes will increase from 140.9 million in 2021 to 174.4 million in 2045. This once again highlights the urgent need to prevent diabetes in China [1]. It is well known that insulin resistance and impaired insulin secretion of islet beta cells are two major pathogenic mechanisms of diabetes [2]. Previous studies, mostly based on data collected from cross-sectional surveys, have reported that insufficient insulin secretion from islet beta cells may contribute more to the development of diabetes than insulin resistance in Asian populations [3,4,5]. None of studies have examined the natural changes in impaired insulin action and secretion in the general non-diabetic population. In our study, insulin resistance and natural variations in insulin secretion by islet beta cells were identified using data collected in a prospective study based on a population-based survey.

STUDY POPULATION AND METHOD

Study population

From 2009 to 2015, a population-based cohort study was conducted on the permanent resident population who had lived in Qingdao for more than 5 years. A total of 6200 adults

(aged 35-74 years) were sampled by stratified random sampling. To put it simply, 3 urban areas and 3 rural areas were randomly selected from the 12 administrative regions of Qingdao. Then, depending on the administrative division and geographical location, there were 2-5 streets in each urban area and towns in each rural area. Further 1 to 4 blocks or villages were randomly drawn from each selected street or town, depending on population size and the proportion of administrative divisions. Then about 70 to 100 people (half male, half female) were randomly selected from these neighborhoods or villages. A total of 5,110 residents participated in the baseline survey from 2009 to 2011, with a response rate of 82.4%. Of the 5,110 participants, 830 who had been diagnosed with diabetes according to the 2006 World Health Organization Diabetes Guidelines were excluded from follow-up examinations. Follow-up examinations were conducted from 2012 to 2015, and all 3 795 non-diabetic participants and without missing key variables were invited. Eventually, 2 428 non-diabetic participants attended the follow-up examination, giving a responding rate of 64.0%.

At the baseline survey, a subgroup of 2 740 participants (1009 men) were randomly selected and invited to undergo fasting serum insulin test. Of them, 166 participants refused blood sample collection, 211 failed to have fasting serum insulin test, and 483 were diagnosed with diabetes, who were all excluded from the follow-up survey. Thus, 1 882 participants without diabetes and with fasting serum insulin values at baseline were invited to have a repeated fasting insulin test in the follow-up examination. A total of 1 088 individuals who fulfilled the repeated tests were included in the current analyses.

Informed consent was collected from all participants. The study was approved by the Qingdao Municipal Health Commission and local ethics committee.

Methods

The field work team was composed of doctors, nurses, local Centre for Disease Prevention and Control staff and nutrition master's students. A one-week training program to all members of the field work team was conducted before the field investigation. All subjects were invited to present in a survey center, which were temporally built in community clinics or health centers near the residential area of survey participants. Standardized questionnaires were employed to collect information on demographic characteristics, family history of diabetes, personal medical history, physical activity, smoking and drinking habits, eating habits, and diabetes awareness. If a subject reports a history of diabetes, medical records regarding diabetes diagnosis and treatment are required and reviewed by a physician on a field work team. Medication history was recorded in the questionnaire. When height and weight were measured, the subjects wore light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m). Waist circumference was measured at the middle horizontal abdominal girth between the thorax and iliac bone; and hip circumference at the maximum horizontal girth between the waist and thighs. Blood pressure was determined from the right arm of sitting subjects.

All participants were asked not to eat after 20:00 in the night before the blood sugar test and not to drink water after 22:00. All subjects were invited to undergo a standard 2-hour 75g oral glucose tolerance test (OGTT). Blood samples were collected from the anterior cubical vein before and 120 minutes after ingestion of 75g glucose. Blood samples were centrifuged in time after collection, temporarily stored in a -20□ refrigerator in the survey center during the morning, and transported to the Central Laboratory of Qingdao Endocrinology and Diabetes Hospital in an ice-sealed container every day in the afternoon. Glucose and insulin were measured immediately after receiving the samples. Glucose was measured by glucose oxidase and insulin was measured by chemiluminescence immunoassay (Seimens, ADVIACentaur XP immunoassay system).

To evaluate the ability of β-cell insulin secretion, β-cell function index (HOMA-IS) based on homeostasis model was calculated as: HOMA-IS = (20× fasting serum insulin [μIU/ml]) / (fasting plasma glucose [mmol/L] - 3.5) [6]; and, insulin resistance index (HOMA-IR) was calculated as HOMA-IR = (FPI×FPG) / 22.5 to determine insulin resistance [6]. Natural change in HOMA-IS (ΔHOMA-IS) and HOMA-IR (ΔHOMA-IR) of each participant between followup and baseline survey was calculated as: ΔHOMA-IS (ΔHOMA-IR) = value of HOMA-IS (HOMA-IR) at follow-up survey - value of HOMA-IS (HOMA-IR) at baseline.

Classification of subjects

In individuals who reported a history of diabetes prior to baseline or follow-up examination, diabetes can be confirmed by oral antidiabetic medication or insulin injection regardless of FPG level, or FPG≥7.0mmol/L. For patients without a history of diabetes, as defined by the World Health Organization/International Diabetes Federation: 1) normal glucose metabolism (NGT): FPG below 6.1mmol/L, blood sugar (2hPG) below 7.8mmol/L 2 hours later; 2) pre-diabetes: impaired fasting blood glucose (FPG≥7.0mmol/L,2hPG<11.1mmol/L) and impaired glucose tolerance (FPG<7.0mmol/L,2hPG≥7.8mmol/L, less than 11.1mmol/L); 3) Diabetes mellitus: FPG≥7.0mmol/L, and/or 2hPG≥11.1mmol/L.

Statistical Analysis

Plasma glucose, serum insulin, HOMA-IS, and HOMA-IR was logarithmically transferred for all analyses and the geometric means was presented. Age and sex-adjusted mean values of

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BMI, blood pressure, plasma glucose, fasting serum insulin, HOMA-IS, and HOMA-IR were calculated with general linear model; and the difference was tested with ANOVA. As value of ΔHOMA-IS (ΔHOMA-IR) might be positive or minus, Kruskai-Wallis test was employed to test the differences in ΔHOMA-IS (ΔHOMA-IR). Hazard ratio for diabetic risk factors was estimated by Cox proportional model for interval censor data. All statistical analyses were performed using SPSS 29.0 software. A p value less than 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

As expected, glucose levels, HOMA-IR levels, and diabetes incidence were statistically higher in the pre-diabetic subjects compared with those with NGT at baseline survey ($P < 0.05$, shown in Table 1). Compared with individuals with NGT, participants with pre-diabetes tended to be older, more obese and having a higher level of blood pressure. However, there was no significant difference in HOMA-IS between individuals with or without pre-diabetes. HOMA-IR of female subjects was higher than the one of males.

Transformation of glucose metabolism

The incidence was twice as high in subjects with pre-diabetes (10.1%) as in those with NGT (3.9%) (Table 1). The incidence of pre-diabetes was 18.3% in men and 19.0% in women with NGT. More than half of subjects with pre-diabetes at baseline were defined as normal at follow-up examination (56.2% of men and 56.3% of women). There was no gender difference in glucose metabolism conversion rate ($P > 0.05$).

Table 1 : Characteristics of participants with normal glucose metabolism or prediabetes at the baseline examination.

	Normal	Pre-diabetes
Men		
Number of cases	225	153
Age, year	54.1(0.76)	55.3(0.86)
Body mass index, Kg/m2	24.7(0.23)	25.3(0.28)
Waist circumference, cm	84.9(0.71)	86.3(0.86)
Systolic blood pressure, mmHg	134.7(1.26)	137.5(1.52)
Diastolic blood pressure, mmHg	84.9(0.76)	86.6(0.92)
Fasting plasma glucose, mmol/L	5.37(1.01)	6.05(1.01)*
2-hour post-challenged plasma glucose, mmol/L	5.69(1.02)	7.43(1.02)*
Fasting serum insulin, μlu/ml	5.34(1.04)	5.89(1.05)*
HOMA insulin resistance index	1.28(1.04)	1.58(1.05)*
HOMA insulin secretion index	58.38(1.04)	47.18(1.05)
Family history of diabetes, yes, %	20.4	15.0
Cases with incident diabetes	11	19*
Maxium follow-up years, year	4.38	4.38
Women		
Number of cases	485	225
Age, year	51.4(0.44)	54.9(0.64)*
Body mass index, Kg/m2	24.8(0.16)	26.3(0.24)*
Waist circumference, cm	82.1(0.44)	83.1(0.65)
Systolic blood pressure, mmHg	129.3(0.86)	138.3(1.27)*

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Diastolic blood pressure, mmHg	81.2(0.49)	85.3(0.72)*
Fasting plasma glucose, mmol/L	5.28(1.00)	5.83(1.01)*
2-hour post-challenged plasma glucose, mmol/L	6.04(1.01)	8.14(1.01)*
Fasting serum insulin, μlu/ml	7.01(1.02)	8.58(1.03)*
HOMA insulin resistance index	1.65(1.02)	2.22(1.03)*
HOMA insulin secretion index	81.04(1.02)	75.26(1.04)
Family history of diabetes, yes, %	28.2	20.4
Cases with incident diabetes	17	19*
Maxium follow-up years, year	3.93	3.88

* Compared with participants with normal glucose metabolism, $p < 0.05$

Baseline HOMA-IR and HOMA-IS and risk for developing diabetes

For men and women with worsening glucose metabolism at follow-up examination, HOMA-IR levels at baseline were already elevated in individuals either with NGT or pre-diabetes (Table 2); however, there was no significant difference in HOMA-IS levels. Increased fasting insulin (HR 2.06 [95% CI 1.21-3.51]) or HOMA-IR (HR 2.52 [1.53-4.13]) at baseline were associated with an increased risk for incident diabetes. HOMA-IS at baseline was not a risk predictor of developing diabetes (HR 0.86 [0.53-1.41]). A total of 28 patients (accounting for 42.2% of all cases, and among them 15 with NGT at baseline and 13 with pre-diabetes), who developed diabetes, were not insulin resistant (defined as HOMA-IR values above the sex-specific HOMA-IR upper quartile in patients with NGT) at baseline. In these 28 participants, 14 patients (accoutning for 21.1% of all cases, 5 with NGT at baseline and 9 with pre-diabetes) were not insulin resistant both at baseline and at follow-up examinations. And the baseline HOMA-IS of these 14 patients (37.64, 95% CI, [29.02-48.86]) was significantly lower than those who were insulin resistant and either without developing diabetes (101.19 [96.64-105.95]), or with developing diabetes (92.39 [80.72-105.64]).

Table 2 : The HOMA insulin resistance and insulin secretion index at baseline and followup in individuals with different glucose metabolic status transformation

	Number of cases	**Fasting insulin at baseline, ulu/ml**	**HOMA-IR at baseline**	**HOMA_IS* at baseline**	**Fasting insulin at* followup, ulu/ml**	**HOMA-IR* at followup**	**HOMA-IS at followup**
Normal to Normal	442	6.22 (5.96-6.49)	1.46 (1.40-1.52)	71.95 (68.72-75.34)	5.56 (5.33-5.80)	1.25(1.20-1.31)	73.85 (70.25-77.63)
Normal to pre-dabetes	113	6.98 (6.40-7.61)	1.68 (1.53-1.84)†	74.89 (68.17-82.27)	6.74 (6.18-7.35)†	1.60 (1.47-1.75)†	75.57 (68.24-83.60)
Normal to diabetes	20	8.74 (7.23-10.57)†	2.08 (1.70-2.53)†	96.83 (78.96-118.75)†	9.66 (7.99-11.68)*	2.44 (2.01-2.96)*	92.76 (74.51-115.58)
Pre-dabetes to NGT	201	7.11 (6.5-7.66)†	1.85 (1.71-2.00)†	61.93 (57.28-66.89)	5.71 (5.32-6.13)	1.39 (1.29-1.49)	60.40 (55.76-65.37)
Pre-diabetes to Pre-diabetes	120	7.21 (6.547.94)†	1.91 (1.73-2.11)†‡	59.50 (53.84-65.76)	6.33 (5.77-6.93)	1.64 (1.49-1.80)‡	56.37 (50.91-62.49)
Pre-diabetes to diabetes	32	9.63 (8.06-11.51)†	2.69 (2.24-3.23)†‡	70.11 (58.32-84.27)	8.50 (7.19-10.05)†‡	2.44 (2.06-2.90)‡	58.44 (48.42-70.60)

Data was showed as genomic means (95% CI). Normal is normal glucose metabolism.

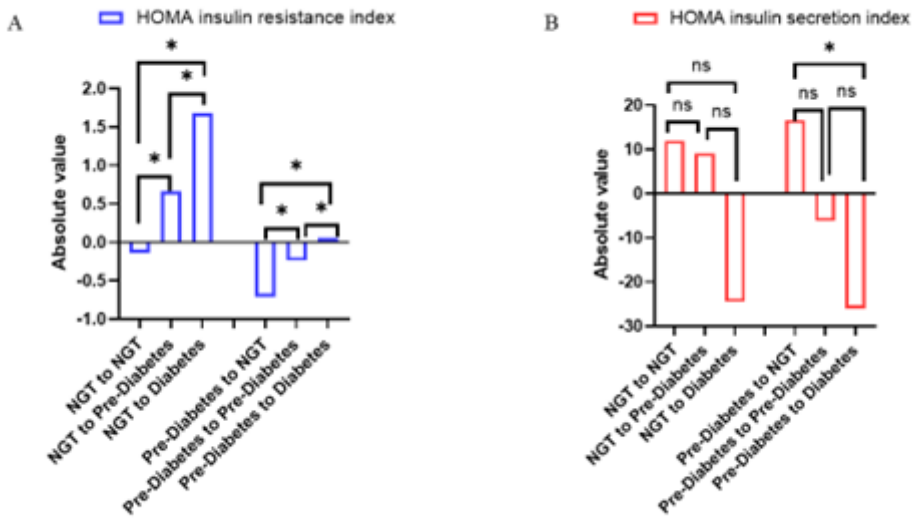
* The means was calculated with general linear model for repeated measures; †Compared with individuals who kept as normal glucose metabolism, $p < 0.05$. ‡Compared with individuals who returned to NGT, $p<0.05$., ‡

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Natural change of HOMA-IR and HOMA-IS and risk for developing diabetes

HOMA-IS was elevated in individuals who remained normal, progressed from normal to pre-diabetes, or returned to normal from pre-diabetes (Figure 1). HOMA-IS decreased in subjects with incidental diabetes, both in normal and pre-diabetic subjects. An increase in HOMA-IR was observed in participants with pre-diabetes or who progressed from normal to diabetes; however, no significant changes were observed in pre-diabetic patients, regardless of glucose metabolic conversion. The increase of HOMA-IS was an independent protective factor for future diabetes both in NGT individuals (HR 0.995 [0.991-0.998]) and in pre-diabetic patients (HR 0.993 [0.988-0.998]), . However, elevated HOMA-IR is only an independent risk factor for diabetes in NGT patients (HR 1.34 [1.09-1.64]). Changes in fasting insulin did not predict the risk of developing diabetes in either subjects with normal glucose metabolism (HR1.038 [0.98-1.10]) or subjects with pre-diabetes (HR1.01 [0.97-1.05]).

Figure 1. The change of HOMA insulin resistance and insulin secretion index in subjects with different glucose metabolic status transformation. A: the change of HOMA insulin resistance between 3years later each group and each baseline group; B: the change of HOMA insulin secereton index between 3years later each group and each baseline group. * $p < 0.05$,Statistically significant; ns $p>0.05$,Statistically insignificant.



HOMA insulin resistance index = HOMA insulin resistance at follow-up – HOMA insulin resistance index at baseline;HOMA insulin resistance index = HOMA insulin secretion index at follow-up – HOMA insulin secretion at baseline

DISCUSSION

In the current study, we observed that insulin resistance and abnormal islet β-cell insulin secretion had already happened when the glucose metabolism were still normal. It seemed that insulin resistance remained stable through pre-diabetes and diabetes. Although baseline insulin resistance index predicted the risk for diabetes, the key turning point for developing diabetes was the decrease of islet β-cell insulin secretion. In the current study population, about 21% of cases with developing diabetes happened in individuals without significant insulin resistance.

Type 2 diabetes mellitus (T2DM) is an endocrine and metabolic disease characterized by hyperglycemia, dyslipidemia, altered insulin secretion, and decreased insulin sensitivity [8]. Numbers of studies have reported that insulin resistance and altered insulin secretion were the main pathogenesis of diabetes [9]. Generally, insulin resistance was assumed to be primarily occurred and became worse progressively when the glucose level were still normal [10]. Diabetes was diagnosed with an elevated blood glucose when pancreatic islet β-cell insulin secretion couldn't compensate the existing insulin resistance [11]. Results of our study were mostly consistent with those findings.

However, it is noticeable that in the current study population, approximately 21% of diabetes occurred in individuals who did not have significant insulin resistance at baseline and after the onset of diabetes. If insulin resistance remained stable as hypothesized, the pathogenesis of diabetes in them could simply be impaired insulin secretion from islet beta cells. This may

be partly due to age-related decline in β-cell insulin secretion, a high prevalence of latent autoimmune adult diabetes in the Chinese population, and a relatively low degree of insulin resistance in slender Chinese [12-15]. But, no conclusion might be made whether degeneration of insulin secretion with aging may explain the increased risk of glucose metabolism disorders. And it is not possible to determine whether insulin resistance occurred transiently in them with current data. Further research is needed. There are some limitations to our study. The follow-up rate of 64% is not high enough and might bias the findings. But at baseline, there were no significant differences in age, body mass index, waist circumference, fasting and post-challenge blood glucose, and fasting serum insulin between subjects who participated the follow-up examination or not. The small number of cases that developed diabetes limited further detailed analysis. In addition, the reported modeling of insulin resistance indicators HOMA-IR and HOMA-IS may mislead the results to some extent [16].

Overall, insulin resistance is associated with an increased risk of diabetes, and, decreased insulin secretion is the key turning point during the course of incident diabetes. In Chinese population, decreased β-cell insulin secretion may be the sole pathogenesis of 1 in 5 diabetes cases. β-cell insulin secretion should be protected to prevent or delay the occurrence of diabetes in Chinese population.

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Author Contributions

WG Gao, LP Liu, FM Fu, L Zhang, YH Dong participated in the study of concept and design. LP Liu, FM Fu, and WG Gao were responsible for drafting the manuscript. Statistical analysis was conducted by WG Gao, LP Liu. JP Sun were involved in the data collection and manuscript revision. All authors have read and agreed to the published version of the manuscript.

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Competing Interests

The authors declare that they have no competing interests.

Data Availability

Data available on request from the authors.

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