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Ageing and type 2 diabetes in an elderly chinese population: the role of insulin resistance and beta cell dysfunction

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Abstract. – OBJECTIVE: The aim of this longitudinal study was to examine the effects of ageing on glucose regulation in elderly Chinese men and women.

SUBJECTS AND METHODS: A total of 4,566 older Chinese men and women (mean age: 70.4 ± 6.7 years) were enrolled in the study. Oral glucose tolerance tests were performed in all participants at baseline and in 3,174 individuals (69.5%) after 3 years of follow-up. Insulin resistance and beta cell function were estimated by the homeostasis model assessment for insulin resistance (HOMA-IR) and beta function (HOMA%-β), respectively.

RESULTS: At baseline, 1,143 had type 2 diabetes (T2D), 517 had prediabetes and 2,906 had normal glucose tolerance (NGT). After 3 years of follow-up, 769 (42.2%) of 1,821 individuals with NGT at baseline progressed to prediabetes and 153 (8.4%) progressed to T2D. Of individuals with prediabetes at baseline, 17.3% progressed to T2D. In individuals who maintained NGT during follow-up ageing was associated with increased insulin resistance ($p \leq 0.001$) and a compensatory increase in beta function ($p \leq 0.001$). Individuals with NGT or prediabetes who progressed to T2D during follow-up had a significantly increased insulin resistance and a decreased beta cell function ($p < 0.01$). In contrast, individuals who regressed from prediabetes to NGT increased both insulin resistance and beta cell function ($p < 0.01$).

CONCLUSIONS: Ageing is associated with development of insulin resistance in an Elderly Chinese population. Therefore, maintenance of normal glucose regulation depends on the ability to compensatory increase of the beta cell function.

Key Words:
Ageing, Type 2 diabetes, Insulin resistance, Beta cell function.

Abbreviations

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D, type 2 diabetes; NGT = normal glucose tolerance; HOMA-IR = homeostasis model assessment for insulin resistance; HOMA-β = homeostasis model assessment for beta cell function

Introduction

Ageing is a significant risk factor for development of type 2 diabetes (T2D) and impaired glucose tolerance. In the National Health and Nutrition Examination Survey (NHANES), the standardized incidence rate of T2D in 60-74 year old Americans was 17.5% in 2005-2006[1]. In addition to the high diabetes mellitus incidence, 60% of Americans aged 60-74 years meet the diagnostic criteria for prediabetes (1). Even worse are recent numbers from China showing that almost one fifth of the older population (ages > 60) have diabetes and 44.9% meet the current diagnostic criteria for diabetes and prediabetes[2].

The underlying pathogenesis of type 2 diabetes in elderly is controversial. Some studies[3-9], but not all[10-15], support the theory that insulin resistance is contributing to age-related diabetes. However, when percentage body fat and visceral fat are taken into account, the role of insulin sensitivity *per se* is less clear[16]. The causes of age-related insulin resistance can be many, including increased adiposity[4,16], physical inactivity, and/or changes in dietary habits[17].

There is also inconsistency regarding beta cell function in older individuals. Evidence from animal studies suggests that pancreatic beta cell function decreases with ageing[17,18]. In contrast, human studies of elderly have shown increased beta cell function with ageing[16,19]. Other studies found no difference in insulin secretion between old and young individuals[20]. Recently, a clinical research study using an intravenous injection of glucose demonstrated that an age-related decrease in insulin secretion contributes to glucose intolerance in elderly people[21]. The latter study was carefully controlled for body mass index (BMI), fasting plasma glucose and insulin sensitivity, and it included a wide age-range of individuals with NGT and impaired glucose toler-

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ance. Together, results from the different studies suggest that the effect of ageing on insulin secretion or/and insulin resistance is somewhat controversial.

Because of the high prevalence of prediabetes and diabetes[2] combined with a shift in the age-distribution towards a larger proportion of older people in China[22], the need for understanding the underlying mechanisms for age-related progression to prediabetes and diabetes is overwhelming. Moreover, a better understanding of the mechanisms associated with normal glucose regulation during ageing is important. Therefore, we aimed to study the effect of aging on insulin resistance and beta cell function in elderly Chinese men and women who maintained normal glucose tolerance or progressed to prediabetes or diabetes during 3 years of follow-up.

Subjects and Methods

Study Population

This study was approved by The Human Rights Committee of the Shanghai Fifth's Hospital of Fudan University and supported by the Chinese government. The study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all study participants, A total of 4,566 Chinese participants (aged ≥ 60 years) who lived in Shanghai Jiangchuan Community were consecutively enrolled during 2008. After an overnight fast for at least 8 hours, all participants received a standard 75 g oral glucose tolerance test (OGTT). Blood samples were drawn before and after 120 min of the OGTT. Based on the World Health Organization criteria, all participants were divided into groups of NGT (n=2,906), prediabetes (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT); n=517), and T2D (n=1,143). Among these individuals, 306 died of cancer, cardiovascular disease and other reasons after inclusion in the study. A total 1,086 could not be traced or refused to participate in the follow-up examination. Accordingly, 3,174 of the baseline participants completed a follow-up examination after 3 years during 2011.

Measures of Anthropometry and Blood Pressure

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively, and BMI was calculated. Systolic and diastolic blood pressure was measured by a nurse in the sitting position.

Study Procedures and Biochemical Measurements

Blood samples were drawn from the antecubital vein after an overnight fast to detect glucose, insulin and lipid concentrations. All blood samples were stored at –80°C until assayed. Plasma glucose was measured by the glucose oxidase method with a Hitachi 7170S analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). Fasting serum insulin concentration was determined by immunochemiluminescent assay (Roche Diagnostic, Mannheim, Germany). Lipid profile (triglycerides and total cholesterol) were determined in the biochemical laboratory of the Shanghai Fifth's Hospital. Homeostasis model assessment was used to measure beta cell function (HOMA%-β) and insulin resistance (HOMA-IR), using the following equations: HOMA%-β = 20 × insulin / (glucose – 3.5); HOMA-IR = glucose × insulin / 22.5.

Statistical Analysis

The clinical characteristics among groups were compared by ANOVA for continuous variables and the ^{2} test for categorical variables. For within group comparisons between baseline and follow-up the paired t test was used. Values of HOMA-IR, HOMA%-ß and triglycerides were logarithmically transformed before analysis because of skewed distributions.Data are expressed as means ± SD or medians (25^{th}, 75^{th} percentile). $p \leq 0.05$ was considered statistically significant. All analyses were performed using the Statistical Package for the Social Science (SPSS) for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics at Baseline

The clinical characteristics of the 4,566 participants are shown in Table I. All groups had similar diastolic blood pressure and total cholesterol ($p > 0.05$). As expected, individuals with T2D had higher levels of BMI, fasting insulin, 2-hour plasma glucose and HOMA-IR, and lower HOMA%-β compared to the NGT and prediabetes groups ($p < 0.05$).

Progression to Prediabetes and Diabetes

Of the 1,821 individuals with NGT at baseline, 153 (8.4%) progressed to T2D and 769 (42.2%) developed prediabetes 277 (15.2%) developed

Table I. Clinical and biochemical characteristics of study participants with normal glucose tolerance (NGT), prediabetes or type 2 diabetes (T2D) at baseline.

	NGT	Prediabetes	T2D
N	2906	517	1143
Sex (male/female)	1346/1560	267/250	544/599
Age (years)	69.9 ± 6.5	70.7 ± 7.2	71.4 ± 6.7*
BMI (kg/m^2)	23.4 ± 3.2	23.5 ± 3.0	24.1 ± 3.2*,$^\Delta$
Systolic blood pressure (mmHg)	130.2 ± 14.6	131.1 ± 15.4	131.0 ± 14.6*
Diastolic blood pressure (mmHg)	80.0 ± 8.6	80.5 ± 8.5	80.4 ± 7.9
Triglycerides (mmol/L)	1.8 (1.3, 2.3)	1.8 (1.3, 2.4)	1.9 (1.4,2.7)*
Total cholesterol (mmol/L)	5.8 ± 1.1	5.8 ± 1.0	5.8 ± 1.2
Fasting serum insulin (μU/ml)	6.8 ± 12.3	6.7 ± 4.4	8.6 ± 8.5*,$^\Delta$
Fasting plasma glucose (mmol/L)	5.1 ± 0.7	5.1 ± 0.6	7.5 ± 2.6*,$^\Delta$
2-hour plasma glucose (mmol/L)	6.6 ± 1.4	9.0 ± 1.1*	13.9 ± 9.0*,$^\Delta$
HOMA-IR	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)	2.1 (1.3, 3.4)*,$^\Delta$
HOMA%-β	76.3 (51.0, 115.8)	71.7 (49.7, 107.2)	42.4 (25.5, 71.9)*,$^\Delta$

Data are n, means ± SD, and median (25,75th percentile). *$p < 0.05$ vs. NGT group. $^\Delta p < 0.05$ vs. prediabetes group.

isolated IFG, 464 (25.5%) developed isolated IGT, and 28 (1.5%) developed combined IFG/IGT) during the 3 years of follow-up. Of the 450 individuals with prediabetes at baseline, 130 (28.9%) regressed to NGT and 78 (17.3%) progressed toT2D. The progression rates to T2D were 3.0% per year from i-IFG, 7.4% per year from i-IGT and 2.8% per year from NGT.

As shown in Table II and III, concentrations of fasting plasma glucose and fasting serum insulin as well as systolic blood pressure increased in all groups – also in those regressing from prediabetes to NGT – without changes in BMI or TG over the 3 year study period ($p < 0.05$). The 2-hour plasma glucose levels decreased in those regressing from prediabetes to NGT ($p < 0.05$), was stable in those who maintained their prediabetes or diabetes status ($p > 0.05$), and increased in all other groups ($p < 0.05$).

Effect of Aging on Insulin Resistance and Beta Cell Function

Figure 1 shows the change in insulin resistance (1) and beta cell function (2) from baseline to 3-years of follow up in the different glucose tolerance groups. Of note, HOMA-IR increased in all groups over the 3-year follow-up period ($p < 0.05$). HOMA%-β increased significantly in

Table II. Clinical and biochemical characteristics in individuals with normal glucose tolerance (NGT) at baseline and NGT, prediabetes or type 2 diabetes (T2D) at follow-up.

	NGT → NGT		NGT → Prediabetes		NGT → T2D	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
N	899		769		153	
Sex (male/female)	436/463		294/475		64/89	
Age (years)	68.8 ± 6.4	71.7 ± 6.4*	68.5 ± 6.0	71.5 ± 6.1*	68.3 ± 6.8	71.3 ± 6.8*
BMI (kg/m^2)	23.5 ± 3.9	23.5 ± 4.2	23.5 ± 3.9	24.0 ± 3.9	24.1 ± 3.5	25.6 ± 5.9
Systolic blood pressure (mmHg)	127.7 ± 14.5	138.9 ± 18.5*	128.0 ± 15.5	139.2 ± 18.8*	135.2 ± 15.3	140.3 ± 25.2*
Diastolic blood pressure (mmHg)	78.0 ± 7.7	80.3 ± 10.9*	78.4 ± 7.6	79.9 ± 9.8	77.7 ± 9.9	78.7 ± 13.3
Triglycerides (mmol/L)	1.8 (1.2, 2.2)	1.8 (1.1, 2.2)	1.7 (1.2, 2.2)	1.7 (1.3, 2.1)	1.6 (1.4, 2.0)	1.7 (1.3, 2.1)
Total cholesterol (mmol/L)	5.8 ± 1.0	5.9 ± 1.0	5.6 ± 1.0	5.8 ± 1.1*	6.0 ± 2.4	6.0 ± 1.0
Fasting serum insulin (μU/ml)	6.4 ± 6.3	11.5 ± 4.4*	8.9 ± 8.7	12.6 ± 5.5*	7.7 ± 4.9	14.7 ± 8.6*
Fasting plasma glucose (mmol/L)	4.9 ± 0.5	5.4 ± 0.4*	5.0 ± 0.5	5.8 ± 0.5*	5.4 ± 0.5	7.0 ± 0.8*
2-hour plasma glucose (mmol/L)	6.4 ± 0.9	6.6 ± 0.8*	6.4 ± 1.1	8.6 ± 1.1*	6.7 ± 0.9	12.5 ± 1.8*
HOMA-IR	1.1 (0.6, 1.9)	2.7 (2.0, 3.9)*	1.3 (0.9, 1.8)	2.9 (2.1, 4.3)*	1.2 (0.5, 1.9)	3.6 (2.1, 5.1)*
HOMA%-β	78.3 (47.4, 100.8)	114.6 (91.2, 143.1)*	82.6 (53.4, 115.3)	120.0 (100.8, 158.3)*	78.2 (56.7, 103.8)	69.1 (48.4, 89.9)*

Data are n, means ± SD, and median (25,75th percentile). *$p < 0.05$ vs. baseline.

Table III. Clinical and biochemical characteristics in individuals with prediabetes or type 2 diabetes (T2D) at baseline and normal glucose tolerance (NGT), prediabetes or T2D at follow-up.

	Prediabetes → NGT		Prediabetes → Prediabetes		Prediabetes → T2D		T2D → T2D	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
N	130	93/149	242	377/526	78		903	
Sex (male/female)	55/75		24/54					
Age (years)	66.3 ± 5.5	69.2 ± 5.5*	69.8 ± 7.4	72.7 ± 7.4*	68.6 ± 6.7	71.5 ± 6.7*	69.6 ± 5.9	72.5 ± 5.9*
BMI (kg/m^2)	24.1 ± 2.8	24.7 ± 4.5	24.1 ± 3.2	24.0 ± 4.3	23.5 ± 3.0	23.2 ± 5.4	23.9 ± 3.0	24.4 ± 4.5
Systolic blood pressure (mmHg)	128.5 ± 16.5	134.3 ± 15.2*	131.5 ± 13.9	140.4 ± 21.8*	132.3 ± 16.4	141.3 ± 17.2*	134.3 ± 15.5	139.3 ± 20.1*
Diastolic blood pressure (mmHg)	79.1 ± 9.7	79.0 ± 10.3	81.2 ± 8.7	79.9 ± 10.8	81.7 ± 8.0	80.3 ± 8.6	81.0 ± 8.7	79.3 ± 10.1*
Triglycerides (mmol/L)	1.9 (1.3, 2.7)	1.8 (1.1, 2.5)	1.9 (1.4, 2.6)	1.7 (1.2, 2.3)*	1.9 (1.6, 3.1)	2.1 (1.4, 2.4)*	2.0 (1.4, 3.0)	1.9 (1.3, 2.5)
Total cholesterol (mmol/L)	5.9 ± 1.0	5.8 ± 1.1	5.8 ± 1.1	5.9 ± 1.1	6.3 ± 1.1	6.0 ± 1.2	5.9 ± 1.2	5.8 ± 1.2
Fasting serum insulin (μU/ml)	6.4 ± 3.1	13.0 ± 7.9*	7.2 ± 6.7	12.9 ± 5.2*	6.7 ± 2.6	13.5 ± 4.5*	8.6 ± 7.6	17.3 ± 3.5*
Fasting plasma glucose (mmol/L)	55.2 ± 0.6	5.5 ± 0.4*	5.2 ± 0.6	5.8 ± 0.5*	5.8 ± 0.8	7.0 ± 1.0*	8.5 ± 2.3	9.1 ± 2.9*
2-hour plasma glucose (mmol/L)	8.9 ± 0.8	6.8 ± 0.8*	9.2 ± 1.1	9.0 ± 1.0	9.2 ± 1.2	11.6 ± 2.6*	14.7 ± 4.2	14.0 ± 3.8
HOMA-IR	1.3 (0.9, 1.9)	2.8 (2.0, 3.6)*	1.2 (0.9, 1.6)	2.8 (2.2, 3.5)*	1.6 (1.2, 2.2)	4.4 (3.7, 5.9)*	1.9 (1.3, 3.0)	3.9 (2.7, 5.8)*
HOMA%-β	73.2	110.6	79.6	116.1	83.0	61.3	43.1	38.3
	(48.0, 116.7)	(84.0, 134.5)*	(56.2, 130.5)	(91.3, 147.5)*	(64.7, 114.4)	(47.9, 74.0)*	(26.6, 68.5)	(19.2, 60.6)

Data are n, means ± SD, and median (25,75th percentile). *$p < 0.05$ vs. baseline.

those who maintained NGT or who regressed from prediabetes to NGT ($p < 0.05$). However, beta cell function decreased by 11.5% in individuals who progressed from NGT to T2D and by 25.2% in those progressing from prediabetes to T2D during the follow-up ($p < 0.05$).

Both HOMA-IR and HOMA%-ß increased in those who maintained NGT status over the 3 years of follow-up ($p < 0.05$). The group who progressed from NGT to prediabetes exhibited an increase in both HOMA-IR and HOMA%-β levels over the same period ($p < 0.05$). Among individuals who progressed from NGT to prediabetes, the 3-year change in HOMA-IR did not differ between those who developed i-IFG (1.5±1.1) or i-IGT (1.5±1.1; $p = 0.577$). However, the change in HOMA%-ß among individuals with NGT who progressed to i-IFG (19.5±12.7) was slightly, but significantly, lower than in those who progressed from NGT to i-IGT (24.3±7.2) during the 3-year follow-up ($p = 0.013$). The group who progressed from NGT to T2D significantly increased HOMA-IR and decreased HOMA%-β levels during the follow-up ($p < 0.05$). Of interest, individuals who regressed from prediabetes to NGT had a pronounced increase in both HOMA-IR and HOMA%-β levels ($p < 0.05$), whereas those who progressed from prediabetes to T2D increased HOMA-I Rand decreased HOMA%-β from baseline to follow-up ($p < 0.05$).

Discussion

In this study we demonstrated that ageing is associated with a significant reduction of insulin sensitivity among older Chinese people independent of changes in glucose regulation. The reduction in insulin sensitivity was accompanied by a worsening of beta cell function in those developing diabetes, but improvement of beta cell function in those maintaining NGT status, progressing from NGT to prediabetes or regressing from prediabetes to NGT. These findings underscore the close relationship between insulin sensitivity and beta cell function in regulation of glucose homeostasis. Moreover, we found that the progression rates from NGT to T2D and prediabetes after three years of follow-up were 8.4% and 42.2%, respectively, in older Chinese people (> 60 years of age).

Many[3-7,9,23,24], but not all[10-15], previous studies have reported that insulin resistance is the main cause of diabetes development in elderly sub-

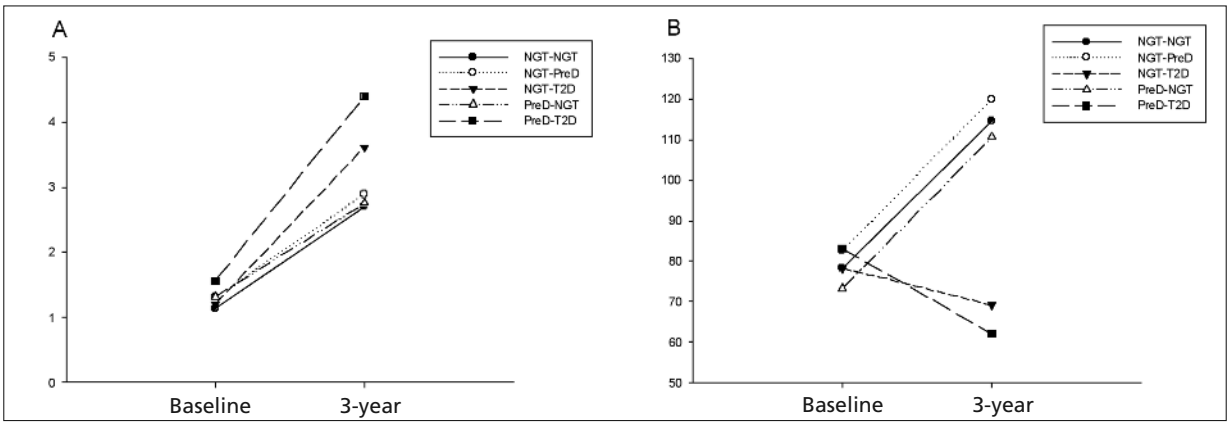

Figure 1. Median values of HOMA-IR and HOMA%-β in individuals with normal glucose tolerance (NGT) orprediabetes (PreD) at baseline and NGT, prediabetes or T2D at 3-year follow-up.

jects. However, we demonstrated that insulin resistance is associated with ageing independent of diabetes development. Thus,beta cell function seems to play an even more important role than insulin resistance in regulating glucose homeostasis in the elderly.

The effects of ageing on beta cell function have been debated widely. Previous investigations reported beta cell function to be elevated[16,19], decreased[5,8-10,18,21,25-27], or unchanged[6,11,13,14,20,24] in the elderly. In general, individuals developing T2D is characterized by a progressive decline in both insulin resistance and beta cell function, whereas those maintaining NGT or progressing to prediabetes is characterized by a compensatory elevated beta cell function. This finding is in contrast to our previous study[28] showing that non-obese, middle-aged, first-degree relatives of T2D patients have a 50% reduced beta cell function after 5 years follow-up despite maintenance of normal glucose tolerance. The differences between the studies can be explained by the fact that the first-degree relatives were younger and had a significantly elevated beta cell function at baseline despite normal insulin sensitivity. Furthermore, a genetic predisposition to T2D is more likely to be associated with beta cell dysfunction than with insulin resistance[29].

On the other hand, our results agree with other previous studies. Gumbiner et al[19] performed a carefully BMI matched study of 10 elderly men with abnormal glucose tolerance and 8 young individuals with normal glucose tolerance. After analysis of C-peptide kinetics during a hyperglycemic clamp test, the results showed that the beta cell secretory response to intravenous glucose was significantly lower in the glucose intolerant older group. However, because of the study design, it cannot be concluded whether the reduction in beta cell function was due to ageing or glucose intolerance per se. Another study[5] showed that beta cell function in response to arginine stimulus was 48% decreased in old compared with young individuals with NGT, suggesting that ageing is associated with reduction in beta cell function. Chang et al[21] studied old people with NGT (n=16) or IGT (n=14) and young people with NGT (n=15) carefully matched to have similar baseline BMI and insulin sensitivity measured by a frequently sampled intravenous glucose tolerance test. The young and older groups with NGT were also closely matched for glucose tolerance status by OGTT. In these carefully matched groups, acute insulin response to intravenous glucose was reduced by 30% in old people with NGT and by 67% in old people with IGT compared with young people with NGT, indicating that both ageing and glucose intolerance are independently associated with beta cell dysfunction. In contrast, Beccaro et al[30] found no difference in insulin resistance, but a deteriorated beta cell function in older compared with younger non-obese Italian men with NGT. To sum up, most studies find an age-related decline in beta cell function, whereas we suggest that only those with a relatively high degree of insulin resistance have lost the ability to compensatory increase beta cell function, and thus are prone to develop type 2 diabetes. Prevention of severe insulin resistance in the elderly therefore seems important in order to further prevent beta cell loss and onset of T2D.

From our study we can only guess about the underlying mechanisms linking ageing to insulin resistance and beta cell dysfunction. Ageing is associated with sarcopenia, which may contribute to development of insulin resistance[31]. Many factors may contribute to an age-related decline in beta cell function, including age-associated loss of silent information regulator1-mediated glucose-stimulated insulin secretion and beta cell mass[32], reduced beta cell sensitivity to the incretin hormones[27,13], iron excess-related decreased in mitochondrial function, reduced expression of (2)-adrenergic receptor[33], as well as increased oxidative stress and glucolipotoxicity[34,35]. There is also evidence that amyloid deposition increases with ageing in the islet beta cell[36] and that age-dependent beta cell replication rather than beta cell apoptosis is decreasing[37]. In addition to these findings, hyperphosphorylated tau protein can accumulate within the islet of Langerhans[38], causing beta cell failure.

We would like underline the lack of availability of body composition or central adiposity measures in our study. An increase in adiposity has been well-documented with advancing age and decreased beta cell function. Thus, more detail measures of body composition would allow a more thorough analysis of the role of sarcopenia and body fat on changes in glucose metabolism in the elderly. Moreover, we used HOMA to estimate insulin resistance and beta cell function. Since HOMA is based on fasting insulin and glucose levels, it is assumed to reflect hepatic insulin resistance and stationary beta cell function to a larger extend than peripheral insulin resistance and dynamic beta cell function[39]. Ideally, estimates of insulin resistance and beta cell function should be based on "gold standard" tests such as the glucose clamp technique. However, this is not feasible in large-scale epidemiological studies.

Conclusions

We found in this large prospective observational study that ageing is associated with increased insulin resistance in an elderly Chinese population. Individuals who were able to compensatory elevate their insulin secretion in response to insulin resistance did not develop diabetes, but maintained NGT, progressed from NGT to prediabetes, or even regressed from prediabetes to NGT during the 3-year observation period. In contrast, individuals who exhibited severe defects in insulin resistance in combination with a progressive loss of beta cell function developed diabetes. Whether physical activity, dietary interventions, smoking cessation and/or metformin therapy can reduce insulin resistance related to ageing and, thus, decreasing the risk of type 2 diabetes in the elderly needs to be examined in future studies.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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