Glucose metabolism indices and the development of chronic kidney disease: a cohort study of middle-aged and elderly Chinese persons

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Abstract

Background Chronic kidney disease (CKD) has become a major global health issue, and abnormalities of glucose metabolism are a risk factor responsible for development of CKD. We aimed to investigate associations between glucose metabolism indices and CKD in a Chinese population, and determine which index is superior for predicting incident CKD. Methods This community-based population study included 5232 subjects aged [?]40 years without baseline CKD. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or urinary albumin-to-creatinine ration (UACR) [?]30 mg/g. We examined the associations of glucose metabolism indices, including fasting plasma glucose (FPG), 2-hour (2h) oral glucose tolerance test (OGTT), haemoglobin A1c (HbA1c), fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR), and HOMA-β and the development of CKD. Results With an average follow-up of 3.6 years, 6.4% of the subjects developed CKD. Pearson's correlation analysis revealed that FPG, HbA1c, fasting insulin, and HOMA-IR were all significantly correlated with UACR and eGFR. The association persisted in multivariate linear regression analysis adjusted for age and sex. Compared with other glucose indices, HOMA-IR exhibited the strongest associations with CKD in COX multivariate regression analysis (HR = 1.17, 95% CI: 1.04-1.31). Conclusion HOMA-IR is superior to other routine indices of glucose metabolism for predicting the development of CKD in middle-aged Chinese persons. Screening with HOMA-IR may help prevent the development of CKD in the general population.

What's Known

Chronic kidney disease (CKD) has become a major global health issue, and abnormalities of glucose metabolism are a risk factor responsible for development of CKD. Both diabetes and pre-diabetes increase the risk of developing CKD. Several studies have shown positive associations between CKD and FPG, OGTT, and HbA1c, as well as fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR), and HOMA-β.

What's new

A wide body of evidence supports that abnormalities of glucose metabolism are related with the development if CKD. However, associations have mainly been identified through cross-sectional studies; longitudinal data associating indices of glucose metabolisms and CKD are limited. In addition, few studies have examined if any single index of glucose metabolism is superior for predicting the development of CKD. Thus, the purpose

of this study was to use longitudinal data to investigate associations between glucose metabolism indices and CKD in a Chinese population, and determine which index is superior for predicting CKD.

1 Background

Chronic kidney disease (CKD) was defined as an abnormality of kidney structure or function that can adversely affect health[1]. CKD has become an important public health problem, and is associated with high rates of disability and mortality. In 2016, global years lived with disability among men age 15 to 49 years of age with CKD was 0.81% and deaths were 1.94% [2]. The prevalence of CKD (stages 1-5) is estimated to be 3% to 18% globally[3], and around 8.6% for adult males and 9.6% for adult females in high-incomes countries[4]. A cross-sectional survey based on a nationally representative sample of Chinese adults estimated that around 120 million persons have CKD, with a prevalence of CKD of around 11% [5]. Persons with CKD have a reduced life expectancy due to increased cardiovascular disease and increased all-cause mortality[6]. CKD and associated morbidities are important drivers of increased health care costs[7]. Importantly, in many patients CKD is not diagnosed until it is in a late stage[8]. Thus, it is important to identify factors that may predict the development of CKD so that early interventions may be given to prevent or delay its development.

The association of glucose metabolism and the development of CKD has been extensively investigated over the past decade. Diabetes is the leading cause of CKD, and up to one-third of adults with newly diagnosed diabetes already have CKD[9]. Diabetes is thought to be responsible for almost 40% of new cases of CKD[10]. Pre-diabetes also increases the risk of developing CKD[11,12]. Diabetes and pre-diabetes diagnosed according to an elevated fasting plasma glucose (FPG) and/or 2-hour oral glucose tolerance test (OGTT) and/or elevated hemoglobin (HbA1c) based on World Health Organization (WHO) [13] or American Diabetes Association (ADA)[14] criteria are closely related with the development of CKD. Several studies[11,15,16]have shown positive associations between CKD and FPG, OGTT, and HbA1c, as well as fasting insulin level, homeostasis model assessment of insulin resistance (HOMA-IR), and HOMA-β. A wide body of evidence supports that abnormalities of glucose metabolism are related with the development if CKD. However, associations have mainly been identified through cross-sectional studies; longitudinal data associating indices of glucose metabolisms and CKD are limited. In addition, few studies have examined if any single index of glucose metabolism is superior for predicting the development of CKD.

Thus, the purpose of this study was to use longitudinal data to investigate associations between glucose metabolism indices and CKD in a Chinese population, and determine which index is superior for predicting CKD.

2 Research design and methods

2.1 Participants

The study population was from the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a IONgigudinal (REACTION) study, which was a multicenter prospective observational study with the aim of evaluating chronic diseases in the Chinese population. Detailed information about the study design and protocols has been published previously[17]. A total of 9916 subjects from a community in Guangzhou, China signed the informed consent and were included in the baseline survey, from June to November 2011. All baseline examinations were performed in 2011, and follow-up examinations were carried out from 2014 to 2016. Of the 9,166 individuals included in baseline survey, 2,917 were lost to follow-up. Thus, a total of 6,999 participants were included in the final dataset (follow-up success rate = 71%). With a mean of 3.6 years' follow-up, 125 subjects died and 995 subjects completed questionnaire by telephone interview. The subjects who failed to provided baseline information of albumin-to-creatinine ratio (ACR) (n=78), creatinine (n=8), FPG (n=7), PPG (n=35), OGTT 2h glucose (n=35) and HbA1c (n=19) were excluded from the analyses. The individuals who failed to provided follow-up information of ACR (n=50), creatinine (n=3), OGTT 2h glucose (n=23) and HbA1c (n=5) were excluded from the analyses. For the current study, subjects with baseline CKD were excluded (n=378). Thus, a total of 5,273 individuals were included in the current analyses. Detailed patient selection for this study is shown in Figure 1.

The study protocol was approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (2014[3]). The study was performed in accordance with the principles of the Helsinki Declaration, and all participants provided written informed consent.

2.2 Clinical and biochemical measurement

A standardized questionnaire was used to collect baseline data, and was administered by trained interviewers during a face-to-face interview. Information collected included lifestyle factors, socio-demographic characteristics, and family history. Current smoking and drinking status were divided into 3 groups: never, ever (the cessation of smoking and drinking for more than half a year), and current (smoking or drinking regularly in the recent half year). The frequency and duration of physical activity were obtained using the International Physical Activity Questionnaire (IRAQ), and the level of physical activity was evaluated by calculating the metabolic equivalent hours per week (MET-h/week).

Anthropometrical examinations were conducted by trained staff using standard protocols. Body weight and height were measured with subjects wearing light indoor clothing without shoes, and recorded to the nearest 1.0 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2), and BMI was used to define obesity. Obesity was defined as a BMI [?] 28.0 kg/m^2, and overweight when 24.0 kg/m^2 [?] BMI < 28.0 kg/m^2. Waist circumference (WC) was measured at the umbilical level to the nearest 0.1 cm with subjects in the standing position using a non-elastic measuring tape. Central obesity was defined as a WC [?] 90 cm in men and [?] 80 cm in women. Blood pressure was obtained with the subject seated 3 consecutive times at 5 minutes intervals using an automated electronic device (OMRON, Omron Company, Dalian, China). The average of the 3 measurement was used in the analysis. Hypertension was defined as a systolic blood pressure (SBP) [?] 140 mmHg or a diastolic blood pressure (DBP) [?] 90 mmHg or the subject reporting that they were receiving regular anti-hypertensive treatment

After an overnight fast of at least 10 hours, venous blood samples were collected and stored at 80 ^{o}C until testing. All patients also received a 2h OGTT. Measurements of FPG, 2h OGTT, fasting serum insulin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferse (γ-GGT) was done using an automated electronic device (Beckman CX-7 Biochemical Autoanalyzer, Brea, California, USA). HbA1c was measured by high-performance liquid chromatography (BioRad, Hercules, CA). HOMA-β was calculated using the formula: HOMA-β = 20 × (fasting plasma insulin, μU/mL) / (FPG, mmol/L) – 3.5. HOMA-IR was calculated using the formula: HOMA-IR = (FPG, mmol/L) × (fasting plasma insulin, μU/ml) / 22.5[18]. The abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for the Chinese population was used to calculate the estimated glomerular filtration rate (eGFR) expressed as mL/min per 1.73 m^2. The formular is: eGFR = 175 × (serum creatinine × 0.011)$^{-1.234}$ × (age)$^{-0.179}$ × (0.79 if female), with serum creatinine was expressed as μmol/L. Diabetes was diagnosed according to the 1999 WHO diagnostic criteria, the level of FPG [?] 7.0 mmol/L or the level of 2h OGTT [?] 11.1 mmol/L[19].

2.3 Definition of chronic kidney disease

CKD was defined according to the latest guidelines of the American Diabetes Association Standards of Medical Care[20]. First morning spot urine samples were collected for determination of the urine albumin-to-creatinine ratio (UACR). Urine albumin was measured by a chemiluminescence immunoassay (Siemens Immulite 2000, United States), and creatinine was measured by the Jaffe's kinetic method (Biobase-Crystal, Jinan, China) using an automatic analyzer. UACR was calculated by dividing the urine albumin concentration by the urine creatinine concentrations, and the result was expressed in mg/g. CKD was defined as a UACR [?] 30 mg/g or an eGFR < 60 mL/min/1.73 m^2.

2.4 Statistical analyses

Baseline characteristics of study participants were expressed as mean ± standard deviation for continuous

variables with a normal distribution, or median and interquartile range (IQR) for continuous variables with a skewed distribution. Categorical variables were summarized as count and percentage. UACR, FPG, 2h OGTT, HbA1c, fasting insulin, HOMA-IR, HOMA-β, TG, ALT, AST, γ-GGT, and MET-h/week were logarithmically transformed prior to analysis due to skewed distributions. Characteristics between groups were compared using one-way ANOVA. Comparisons between categorical variables were performed with the χ^2 test. Correlations between the indices of glucose metabolism (FPG, 2h OGTT, HbA1c, fasting insulin, HOMMA-IR, and HOMA-β) with UACR and eGFR were examined with Pearson's correlation analysis and multivariate linear regression. Cox proportional hazards analyses were used to calculate incidence of CKD, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI). Model 1 was unadjusted; Model 2 was adjusted for age, sex and BMI; Model 3 was further adjusted for current smoking status, current drinking status, physical activity level, SBP, γ-GGT, and LDL-C. The relations of indices of glucose metabolism with CKD were also examined in subgroups stratified by age ([?] 58 or $<$ 58 years old), sex (male or female), degree of obesity categorized by BMI (normal, overweight, or obese), central obesity (yes or no), diabetes (yes or no), and hypertension (yes or no). Interactions were tested by including strata factors, the quartile of glucose metabolism index and the respective interaction terms (strata factors multiplied by quantiles of glucose metabolism index) simultaneously in the models.

All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-sided, and values of $P < 0.05$ were considered statistically significant.

3 Results

3.1 Clinical characteristics of the study population

The 5,273 subjects had a mean age at baseline of 58.7 ± 7.2 years, and after a mean follow-up interval of 3.6 ± 0.7 years, 335 (6.4%) had developed new CKD. The clinical and biochemical characteristics of the subjects at baseline are summarized in Table 1. Compared to those who did not develop CKD, subjects that did had increased FPG, 2h OGTT, HbA1c, fasting insulin, and HOMA-IR (all, $P < 0.001$). However, HOMA-β was not different between the 2 groups.

3.2 Associations of baseline glucose indices with UACR and eGFR

As shown in Table 2, Pearson's correlation analysis revealed that baseline FPG, 2h OGTT, HbA1c, fasting insulin and HOMA-IR were significantly correlated with follow-up UACR and eGFR. No significant relation between HOMA-β and UCAR was observed in the correlation analysis. Multivariate linear regression analysis adjusted for sex and age indicated that the correlations of the baseline glucose indices, with the exception of HOMA-β, with UACR persisted (all, P<0.001). HOMA-IR was most strongly correlated with UACR (β=0.13, P<0.001) and eGFR (β=-0.05, P=0.0001).

3.3 Associations between baseline glucose indices and risk of CKD

Figure 2 shows the incidence of CKD in quartiles of the different baseline glucose indices. The incidence of CKD tended to increase with increasing FPG, 2h OGTT, HbA1c, fasting insulin, and HOMA-IR (all, P for trend $<$ 0.001). No differences of CKD were found in HOMA-β quartiles (P=0.734). HOMA-IR exhibited the strongest correlations with increased risk of CKD in all of the Cox regression analysis models (Table 3). The HR for the risk of CKD in the first (lowest) quartile of HOMA-IR was 1.00 (reference); for the second quartile the HR=1.15 (95 % CI: 0.79-1.69); for the third quartile the HR=1.22 (95% CI: 0.84-1.78); and for the fourth quartile (highest) the HR=1.61 (95% CI: 1.10-2.34).

3.4 Subgroup analyses of HOMA-IR with risk of CKD

As shown in Figure 3, multivariate analyses of subgroups indicated that the association of baseline HOMA-IR with the development of CKD was different in different subgroups. Significant difference of such relationship was detected in subjects with age $<$ 58 years, women subjects, those BMI in normal range, those with diabetes and those without hypertension.

5 Discussion

In this study we evaluated the relations between different indices of glucose metabolism and the development of CKD in a large population of middle-aged Chinese individuals from the REACTION study. The results showed that 3 indices of glucose metabolism, 2h OGTT, HbA1c, and HOMA-IR were significantly associated the development of CKD, independent of potential confounding risk factors. Of the 3 indices, HOMA-IR exhibited the best predictive ability. To the best of our knowledge, this is the first and largest population-based cohort study to examine the best index of glucose metabolism for predicting the development of CKD. Because the only effective treatment for ESRD is transplantation, controlling risk factors for the development of CKD, and screening methods to determine persons at greater risk of developing CKD are important for decreasing the number of patients develop ESRD. The findings of the present study may assist in identifying persons who are at risk of developing CKD and who may benefit from early interventions.

CKD is becoming a global health problem, and global deaths from kidney disease have risen by 83% since 1990[21]. Glucose metabolism has been shown to be an important factor in the development of CKD[12,22,23]. Our finding that an elevated 2h OGTT and an elevated HbA1c level are independent risk factors for development of CKD is consistent with that of prior studies[23,24]. Gabir et al. [24] studies 5023 Pima Indian adults, and with a follow-up period of 10 years showed that a 2h OGTT can predict the development of CKD. Markus et al.[23] studies 7728 subjects with a median follow-up of 8.7 years; 871 (11.3%) developed CKD and HbA1c was an independent predictors for the development of CKD.

However, there have been conflicting reports of the association of CKD development and glucose metabolism. In a study in Germany, Schottker et al. [25] followed 3,538 participants during for 8 years and found that pre-diabetes might not contribute to the development of CKD, and that preventive efforts such as regular exercise might reduce the risk of developing CKD[26]. An animal study using rats showed that physical training increased insulin sensitivity by enhancing muscle glucose uptake and glucose utilization via glycolysis [27]. A study of hemodialysis patients showed that moderate physical training, using of plasma insulin level for patients reduces by the 40%[28]. In addition, some cross-sectional studies showed that neither glucose tolerance nor insulin secretion were associated with CKD. Hanssen et al.[29] studies 1796 persons with normal glucose metabolism, 478 with pre-diabetes, and 669 with type 2 DM, and reported no association of CKD with 2h OGTT or HbA1c. However, the follow-up was relatively short, and the results can be interpreted as short or intermediate follow-up periods might not capture the associations of 2h OGTT or HbA1c with CKD. It is possible that there might be geographic or race variability with respect to the association of 2h OGTT and HbA1c and the development of CKD, as study has shown that both are predictors of insulin resistance, which is strongly associated with the development of CKD[30]. Clinical significance of each indicator is expected to be studied in the future and further explored with long-term and multi-stage longitudinal measures to better define the relationship.

The results of this study showed that HOMA-IR was the strongest predictor of the development of CKD in middle-aged and elderly Chinese. The HOMA-IR reflects a pathological state in which target tissues fail to respond normally to the biological effects of insulin, and is generally considered as an important influential factor for development of CKD. A study using NHANES data showed that individuals with the highest insulin levels had a 2.65 times greater risk for the development of CKD (95% CI: 1.25-5.62)[31]. Ma et al.[32] studied 3,237 middle-aged and elderly Chinese persons with a 3-year follow-up and showed that an elevated HOMA-IR was associated with accelerated progression of CKD. Huh et al.[33] studied 6,065 Korean persons without CKD at baseline, and over a follow-up period of 10 years showed that insulin resistance was independent risk factor for development of CKD. However, a prospective study of 73 non-diabetic subjects with CKD showed that of incident CKD in Korean population. However, a prospective study of 73 non-diabetic subjects with CKD showed that HOMA-IR was not significantly different in patients with or without renal endpoints [34]. And the findings of the study might not extend to our study since it was conducted from one region of Turkey with small sample (n=73).

There are some theories as to why insulin resistance increases the risk of developing CKD. First, normally, insulin binds to the insulin receptor can activate insulin receptor substrate-1 (IRS-1), which can phosphorylated phosphatidylinositol 3-kinase (PI3-K). Under insulin resistance conditions, Impaired PI3-K lead to

reductions in bioavailable nitric oxide (NO) directly resulting in the development of endothelial dysfunction and CKD [35]. Secondly, insulin resistance promotes CKD at the molecular level by inflammation through endoplasmic reticulum (ER) stress, and is involved in the pathophysiology of chronic kidney injury with tubulointerstitial damage [36]. Moreover, insulin resistance can increase the levels of inflammatory, cytokines, which can lead to basement membrane thickening, glomerular mesangial expansion, and the loss of slit pore diaphragm integrity, ultimately leading to glomerulosclerosis and tubule-interstitial injury[37]. Thirdly, insulin resistance may cause overproduction of LDL-C and contribute to hypertriglyceridemia, which can result in renal disease[38]. Triglyceride-rich apolipoprotein B-containing lipoproteins promote the progression of renal insufficiency [39]. Lastly, insulin resistance promotes CKD by worsening renal hemodynamics through mechanisms such as activation of the sympathetic nervous system, sodium retention, decreased Na^+, K^+-ATPase activity, and increased GFR[40,41].

The causes of insulin resistance are complex and multifactorial, and involve genetic factors such as post-receptor signaling defects, an unhealthy lifestyle that includes a lack of physical activity and poor diet which can lead to obesity, obesity, medications, aging, metabolic acidosis, oxidative stress, inflammation, vitamin D deficiency, uremic toxicity, and anemia, as shown by previous human and animal studies. Other co-morbid conditions that are strongly associated with insulin resistance are hypertension, diabetes, and hyperlipidemia.

Several limitations of in this study need to be addressed. First, by including only middle-aged and elderly Chinese subjects, the results might not apply to different races or a population of younger individuals. Secondly, our study population was predominantly female; this was partially because we invited person [?]40 years old to participate and females are predominant in this age range in China. Third, as with any observational study all confounding factors that may contribute to the development of CKD may not have been included in the models. Fourth, the "gold-standard" for documenting insulin resistance is the euglycemic clamp test. However, the euglycemia clamp test is time-consuming and requires trained personal so it is rarely used in large epidemiological studies. HOMA-IR is a common method used to assess insulin resistance in large epidemiological studies, and it is relatively well-correlated with the euglycemia clamp technique (r=0.88)[42]. Fifth, we defined the CKD based on the first measurements of eGFR and UACR; however, the gold standard is two measurement results. This approach may have reduced the accuracy of our results; however, the results of 1 measurement correlate well with those of 2 measurements and use of 1 measurement is common in large epidemiology studies[43]. Finally, the follow-up rate in this study of 71% was relatively low; however, large epidemiological investigations rarely studies can achieve follow-up rate of [?]85%[44,45]. It is worth noting that the follow-up rate of another REACTION study with a defined 3-year follow-up in Shandong Province, China, from 2012 to 2015 was 77.8%, which was similar to that of our study[32].

6 Conclusion

Our study demonstrated that HOMA-IR is superior to other glucose metabolism indices in predicting the development of CKD in a middle-aged and elderly Chinese population. HOMA-IR may be a useful screening method to determine persons at risk for the development of CKD, and who may benefit from early interventions.

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Disclosure

The authors report no conflicts of interest in this work.

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