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Prediabetes is associated with microalbuminuria, reduced kidney function and chronic kidney disease in the general population
The KORA (Cooperative Health Research in the Augsburg Region) F4-Study

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Abstract *Background and Aims:* We investigated the associations of serum fasting (FG) and 2-h postload (2HG) glucose from an oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), fasting insulin and the homeostasis model assessment-insulin resistance index (HOMA-IR) with urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR).

Methods and Results: We performed cross-sectional analyses of 2713 subjects (1429 women; 52.7%) without known type 2 diabetes, aged 31–82 years, from the KORA (Cooperative Health Research in the Augsburg Region) F4-Study. FG, 2HG, HbA1c, fasting insulin, HOMA-IR and glucose tolerance categories were analyzed for association with ACR and eGFR in multivariable adjusted linear and median regression models, and with isolated microalbuminuria (i-MA), isolated reduced kidney function (i-RKF) and chronic kidney disease (CKD, defined as MA and/or RKF) in multivariable adjusted logistic regression models. Among the 2713 study participants, 28% revealed prediabetes (isolated impaired fasting glucose [i-IFG], isolated glucose tolerance [i-IGT] or both by American Diabetes Association definition), 4.2% had unknown type 2 diabetes, 6.5% had i-MA, 3.1% i-RKF and 10.9% CKD. In multivariable adjusted analysis, all continuous variables (FG, 2HG, HbA1c, fasting insulin and HOMA-IR) were associated with i-MA, i-RKF and CKD.

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The odds ratios (ORs) for i-MA and CKD were 1.54 (95% confidence interval: 1.02–2.33) and 1.58 (1.10–2.25) for individuals with i-IFG. Moreover, the OR for i-RKF was 2.57 (1.31–5.06) for individuals with IFG + IGT.

Conclusion: Our findings suggest that prediabetes might have harmful effects on the kidney.

Introduction

Chronic kidney disease (CKD) is increasingly common affecting over 12% of the population in the developed countries today [1]. The number of deaths attributed to CKD has doubled in the last 20 years [2]. CKD is defined based on the presence of renal damage (usually expressed as urinary albumin-to-creatinine ratio [ACR] ≥30 mg/g) or reduced kidney function (expressed as estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2) for 3 months or more [3]. Importantly, many cases of CKD are undetected, resulting in delayed treatments for CKD-related conditions including hypertension or hyperglycemia that may help avoid the progression to end-stage renal disease and cardiovascular events [4]. Among the established risk factors for CKD, diabetes mellitus is thought to be responsible for almost 40% of new cases in the United States [3]. Noteworthy, up to 30% of individuals with recently diagnosed diabetes mellitus present some degree of renal disease which suggests that the effects of hyperglycemia on the kidney might begin already at glycemic levels below the diabetic range [4]. However, the long-term influences of prediabetes on the kidney are still unknown. It might be possible that screening for CKD in individuals presenting with prediabetes might lead to early detection and interventions resulting in fewer new cases of renal dysfunction.

A report from the National Health and Nutrition Examination Survey (NHANES, from 2009 to 2012) estimated that up to 80.8 million adult Americans (35.3%) have impaired fasting glucose [5]. This indicates that the number of individuals with prediabetes might be four times the number of subjects with type 2 diabetes. In previous analyses of our group, we found that 43.1% adults in Northeast and 30.1% adults in Southeast Germany already present the diagnosis of prediabetes (according to the American Diabetes Association definition) [6].

The diagnosis of diabetes and also prediabetes is based on a dichotomization of biomarkers such as serum glucose or glycated hemoglobin (HbA1c) for ease of use in primary care. However, the use of discrete thresholds to define abnormalities is artificial and distorts understanding of the underlying pathways. It is most likely that there is a non-linear dose–response association between glycemic levels and renal damage, with no clear cut-point where the risk increases. Because leakage of albumin through the glomerular filter and impaired renal function are separate phenomena, the aim of the present study was to investigate the associations of parameters (continuously and with categorization), from an oral glucose tolerance test (OGTT: fasting [FG] and 2-h postload [2HG] serum glucose), HbA1c, fasting insulin and the homeostasis model assessment-insulin resistance index (HOMA-IR), as well as the presence of prediabetes and unknown type 2 diabetes (UT2D), with ACR, eGFR, and isolated microalbuminuria, isolated reduced kidney function and chronic kidney disease (microalbuminuria and/or reduced kidney function) in the population-based KORA (Cooperative Health Research in the Augsburg Region) F4-Study.

Methods

Please see the Online Data Supplement for a more detailed description.

Study sample

The KORA F4 study

The present cross-sectional analysis is based on data from the KORA F4 study, a follow-up of the KORA S4 study, a population-based health survey conducted in the city of Augsburg and 16 municipalities from the surrounding counties (about 600,000 inhabitants). A total sample of 6640 subjects was drawn from the target population consisting of German residents of the region aged 25–74 years. Out of these, 4261 participated in the baseline examination (KORA S4) between 1999 and 2001 (response 64.2%) [7]. Of the initially examined participants of KORA S4, 176 had died, 206 lived outside the study region or were completely lost to follow-up and 12 had demanded deletion of their address data. Of the remaining 3867 eligible persons, 174 could not be contacted, 218 were unable to participate because they were too ill or had no time, 395 were not willing to participate in the follow-up. Finally, altogether 3080 subjects were included in the KORA F4 examination that was conducted between 2006 and 2008. From the 3080 participants, we excluded individuals with known diabetes mellitus (defined as validated by physician diagnosis or current use of hypoglycemic medication expressed as use of agents with the ATC code A10; n = 238) and less than 8 h of overnight fasting (n = 3), as well with missing values for OGTT parameters (n = 80), ACR (n = 21) and other covariates

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