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The Frequency of Prediabetes and Contributing Factors in Patients with Chronic Kidney Disease

Effat Razeghi[1], Peimaneh Heydarian[2], and Mahshid Heydari[1]

[1] *Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran.* [2] *Department of Endocrinology and Metabolism, Tehran University of Medical Sciences, Tehran, Iran. Address correspondence to: Mahshid Heydari, e-mail: smahshidheydari@gmail.com*

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■ Abstract

AIMS: Uremia is a prediabetic state, but abnormal glucose metabolism and relative risk factors in non-diabetic chronic kidney disease (CKD) patients are not studied extensively. This study aimed to evaluate prediabetes and contributing factors in patients with CKD. **METHODS:** We studied the frequency of prediabetes (defined as fasting plasma glucose 100-125 mg/dl and 2-h plasma glucose 140-199 mg/dl) and contributing risk factors in 91 (34 women and 57 men) non-diabetic CKD (GFR < 60) patients who were referred to Sina Hospital between November 2010 and November 2011. Impaired fasting glucose and impaired glucose tolerance were regarded as prediabetic state. **RESULTS:** Thirty-eight patients (41.8%), 28 male and 10 female, with mean age of 57.4 ± 17.1 yr, had prediabetes. Among these, 18.7% had impaired fasting glucose, 7.7% impaired glucose tolerance, and 15.4% combined impaired fasting glucose and impaired glucose tolerance. CKD patients with impaired glucose tolerance had more frequently hypertriglyceridemia (85.7% vs. 42.0%, p = 0.001), hypertension (66.6% vs. 31.4%, p = 0.004), and metabolic syndrome according to National Cholesterol Education Program Adult Treatment Panel III (52.3% vs. 25.7%, p = 0.02). Also, mean systolic blood pressure (134.2 ± 13.9 vs. 124.5 ± 20.0, p = 0.004) was higher in CKD patients with impaired glucose tolerance compared to CKD patients with normal glucose. **CONCLUSIONS:** Prediabetes is a frequent condition in CKD patients. Also, hypertriglyceridemia and hypertension are more prevalent in prediabetic CKD patients than in non-diabetic CKD patients.

Keywords: prediabetes · impaired fasting glucose · impaired glucose tolerance · chronic kidney disease · metabolic syndrome · oral glucose tolerance test

Introduction

Chronic kidney disease (CKD) is the most important cause of mortality and morbidity affecting survival and quality of life in the general population [1]. Renal function impairment deteriorates the health status of individuals and may be associated with the development of diabetes, resulting in even poorer outcomes [2, 3]. Prediabetes is defined as a state of abnormal glucose metabolism, with fasting plasma glucose (FPG) of 100-125 mg/dl and a 2-hour plasma glucose (2h-PG) of 140-199 mg/dl. Insulin resistance is the hallmark of this state. The prediabetic state is assumed to be associated with CKD as compensatory mechanisms protecting the body against abnormal blood glucose levels seem to be impaired in CKD patients [3-5]. Therefore, these patients are susceptible to hyperglycemia, which is revealed by the mean values of FPG and oral glucose tolerance test (OGTT).

Although the impact of diabetes as a leading cause of CKD is relatively clear, the glucose metabolism status in patients with non-diabetic CKD is not studied extensively, and previous reports have provided conflicting results [6, 7]. According to our knowledge, no previous study has determined prediabetes and relative risk factors in CKD patients. The present study was performed to address this question, and to determine the frequency of prediabetes, by focusing on OGTT, and relative risk factors in non-diabetic CKD patients referred to a tertiary university hospital.

Abbreviations:
2h-PG - 2-hour plasma glucose
ACEI - angiotensin converting enzyme inhibitors
ADA - American Diabetes Association
BMI - body mass index
CKD - chronic kidney disease
Cr - creatinine
DBP - diastolic blood pressure
FPG - fasting plasma glucose
GFR - glomerular filtration rate
HbA1c - glycated hemoglobin
HDL - high-density lipoprotein
Hx - history
IFG - impaired fasting glucose
IGT - impaired glucose tolerance
NCEP-ATP III - National Cholesterol Education Program Adult Treatment Panel III
NGT - normal glucose tolerance
NHANES - National Health and Nutrition Examination Survey
NS - not significant
OGTT - oral glucose tolerance test
PG - plasma glucose
SD - standard deviation
WC - waist circumference

Patients and methods

A descriptive cross-sectional study was performed, with consecutive non-diabetic CKD outpatients who were referred to the nephrology clinic and hemodialysis unit of Sina Hospital, Tehran University of Medical Sciences, between November 2010 and November 2011. Known or recently diagnosed diabetic patients (FPG ≥ 126 mg/dl or 2h-PG ≥ 200 mg/dl), patients with a history of drug use affecting blood glucose levels such as corticosteroids, patients with severe infectious diseases, and patients with GFR ≥ 60 (ml/min/1.73 m^2) were excluded. Demographic data such as age, sex, CKD duration (from initial diagnosis by physician to start of study), use of angiotensin converting enzyme inhibitors (ACEI) or erythropoietin, and family history of diabetes were recorded. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at two visits, or taking antihypertensive medication. The waist circumference was measured with a tape placed at the level of the iliac crest from the anterior view.

Fasting plasma glucose, serum triglycerides, serum total cholesterol, serum HDL cholesterol, and serum uric acid were measured after 12 hours fasting in a morning venous blood sample. The OGTT was performed as a blood sample for plasma glucose two hours after ingestion of 75 grams anhydrous glucose dissolved in water. Plasma glucose was measured by the glucose oxidase technique. Serum triglycerides and serum total cholesterol were measured by cholesterol oxidase and cholesterol esterase techniques. Serum HDL cholesterol was measured after precipitation of apolipoprotein B containing lipoprotein with phosphotungstic acid. Serum creatinine (Cr) was measured using the Jaffe method. Pars-chemi kit (Tehran, Iran) was used for all measurements. The analyses of laboratory samples were performed using Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands).

Based on the definitions of the National Health and Nutrition Examination Survey (NHANES), CKD was defined as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for at least three months. Cockcroft Gault formula was used to estimate creatinine clearance as follows:

Creatinine clearance = ((140 - age) x weight (kg)) / 72 x Cr (mg/dl) (x 0.85 in women)

CKD patients with stage 3 or above were included. Stage 3 disease was specified as a GFR of 30-59 ml/min/1.73 m^2, stage 4 disease as a GFR of 15-29 ml/min/1.73m^2, and Stage 5 or end-stage renal disease as a GFR of less than 15 ml/min/ 1.73m^2 [3].

According to American Diabetes Association (ADA) criteria [8], people without previously diagnosed diabetes were categorized as follows:

- **Normal glucose tolerance** (NGT): FPG < 100 mg/dl and 2h-PG < 140 mg/dl.
- **Isolated impaired fasting glucose** (IFG): FPG 100-125 mg/dl and 2h-PG < 140 mg/dl.
- **Isolated impaired glucose tolerance** (IGT): 2h-PG 140-199 mg/dl and FPG < 100 mg/dl.
- **Combined IFG and IGT** (IFG/IGT): FPG 100-125 mg/dl and 2h-PG 140-199 mg/dl.
- **Prediabetes**: FPG 100-125 mg/dl and 2h-PG 140-199 mg/dl.

- **Diabetes**: FPG ≥ 126 mg/dl or 2h-PG ≥ 200 mg/dl.

According to the definitions mentioned above, diabetic patients diagnosed through FPG and OGTT (FPG ≥ 126 or 2h-PG ≥ 200 mg/dl) were excluded from the study.

For the definition of metabolic syndrome, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria were used. Metabolic syndrome was regarded as diagnosed when three or more of the following risk factors were present:

- Waist circumference >102 cm in men and >88 cm in women.
- Serum triglycerides ≥ 150 mg/dl.
- HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women.
- Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg.
- FPG ≥ 110 mg/dl [9].

The study was approved by the ethical committee of Tehran University of Medical Sciences. The informed consent form was filled by all patients.

Chi-square test was used to compare frequency distribution. Student's *t*-test was used for comparison of means in the two groups. For the statistical analysis, SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA) was used and p-values <0.05 were considered significant.

Results

Ninety-one non-diabetic CKD patients (34 women and 57 men) with mean age 54 ± 17.4 years were evaluated. These patients have been divided into four groups (NGT, IFG, IGT, IFG/IGT). Table 1 shows the characteristics of the patients with IGT and NGT. There were significant differences for cardiovascular (hypertension, blood pressure) and diabetes (metabolic syndrome, FPG) risk factors between the two groups. Similarly, there were also significant differences for hypertension, blood pressure, hypertriglyceridemia, and metabolic syndrome between the NGT and combined IFG/IGT groups, and there were differences for hypertriglyceridemia and metabolic syndrome between the NGT and IFG groups (not shown in table).

In this study, the mean FPG and 2h-PG values were 93.6 ± 14.2 mg/dl and 116.7 ± 30.5 mg/dl, respectively. Table 2 shows the status of OGTT re-

Table 1. Clinical characteristics of patients with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT)

Variable	IGT* (n = 21)	NGT (n = 70)	p
Age (yr)	56.0 ± 18.9	53.6 ± 17.0	NS
Gender (m/f)	16/5	41/29	NS
CKD duration (yr)	4.3 ± 2.5	5.0 ± 4.8	NS
Hx of ACEI drugs (n, %)	6 (28%)	19 (27%)	NS
Hx of erythropoietin (n, %)	5 (23%)	16 (22%)	NS
Family Hx of diabetes (n, %)	3 (14%)	6 (8%)	NS
Height (cm)	161.5 ± 7.3	163.7 ± 8.6	NS
BMI (kg/m^2)	26.5 ± 5.0	28.2 ± 18.8	NS
Waist circumference (cm)	91.8 ± 14.2	90.8 ± 12.7	NS
Hypertension (n, %)	14 (66.6%)	22 (31.4%)	0.004
SBP (mmHg)	134.2 ± 13.9	124.5 ± 20.0	0.04
DBP (mmHg)	81.9 ± 9.2	78.6 ± 11.3	NS
GFR ($ml/min/1.73\ m^2$)	27.3 ± 16.2	23.9 ± 16.0	NS
Creatinine (mg/dl)	4.4 ± 3.6	5.0 ± 3.7	NS
Cases in CKD stages#	11/3/7	22/22/26	NS
Total cholestrol (mg/dl)	172.0 ± 53.9	169.6 ± 44.2	NS
LDL cholesterol (mg/dl)	82.9 ± 38.8	98.6 ± 35.6	NS
LDL chol. >100 mg/dl (n, %)	14 (66.6%)	34 (48.5)	NS
HDL cholestrol (mg/dl)	40.6 ± 11.1	41.5 ± 15.3	NS
Triglycerides (mg/dl)	168.0 ± 38.7	150.4 ± 67.6	NS
Uric acid (mg/dl)	7.5 ± 2.3	6.8 ± 1.4	NS
Uric acid >7 mg/dl	11 (52%)	29 (41%)	NS
Hemoglobulin (g/dl)	12.0 ± 2.1	12.1 ± 2.0	NS
≥3 MS criteria	11 (52.3%)	18 (25.7%)	0.02
WC > 102 cm in men	3 (18.7%)	4 (10.8%)	NS
WC > 88 cm in women	3 (75.0%)	19 (57.9%)	NS
Triglycerides ≥150 (mg/dl)	18 (85.7%)	30 (42.0%)	0.001
HDL-C <40 mg/dl in men	10 (66.7%)	24 (60.0%)	NS
HDL-C <50 mg/dl in women	3 (75.0%)	21 (75.1%)	NS
SBP ≥130 (mmHg)	15 (71.4%)	31 (44.2%)	0.02
DBP ≥85 (mmHg)	8 (38.0%)	20 (28.5%)	NS
FPG ≥110 (mg/dl)	8 (38.0%)	5 (7.1%)	< 0.001

Legend: Data of the quantitative variables are mean ± SD. The frequencies of qualitative variables are shown as number and percentage. * 2h-PG 140-199 mg/dl and FPG < 100 mg/dl. # stage III/stage IV/stage V. IGT: impaired glucose tolerance. NGT: normal glucose tolerance. CKD: chronic kidney disease. Hx: history. ACEI: angiotensin converting enzyme inhibitors. BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. GFR: glomerular filtration rate. LDL: low-density lipoprotein. HDL: high-density lipoprotein. C: cholesterol. MS: metabolic syndrome. WC: waist circumference. FPG: fasting plasma glucose. NS: not significant.

sults according to FPG levels. The sensitivity of OGTT to identify states of prediabetes in patients was 45% (compared to 66% for FPG) and the specificity was 88%. Moreover, the positive predictive value for OGTT to identify states of prediabetes in patients was 66% and the negative predictive value was 75%.

Table 2. Results of oral glucose tolerance test (OGTT) according to impaired and normal fasting plasma glucose

Variable	IGT* (n = 21)	NGT (n = 70)	Total (n = 91)
IFG	14 (15.4%)	17 (18.7%)	31 (34.1%)
Normal FPG	7 (7.7%)	53 (58.2%)	60 (65.9%)

Legend: IGT: impaired glucose tolerance. NGT: normal glucose tolerance. IFG: impaired fasting plasma glucose. FPG: fasting plasma glucose.

Discussion

There are many reasons to believe that uremia is a prediabetic state. Hyperinsulinemia, glucose intolerance, and dyslipidemia characterizing prediabetes can be found in non-diabetic patients with kidney disease even before the advanced stages of renal function impairment [10, 11].

Blood glucose levels can be increased by 50% in patients with non-diabetes CKD [12]. The prevalence of IGT varied in previous studies; it was identified in:

- 18% of patients in the Caillard study [13],
- 36% of patients in the Rufino study [14], and
- 54% of patients in the Shehab Eldin study [15].

In a recently published epidemiologic study in Tehranian adults, the prevalence of isolated IFG, isolated IGT, and combined IFG/IGT were 7.3%, 6.7%, and 4.2%, respectively [16]. We detected prediabetes in 38 (41.8%) patients (28 male and 10 female), including 18.7% isolated IFG, 7.7% isolated IGT and 15.4% combined IFG/IGT.

Although hyperglycemic states can be detected by FPG measurements, OGTT can detect the early development of diabetes when FPG may not be elevated. Previous studies revealed that 30% of individuals may have a normal FPG, whereas their OGTT suggests diabetes [17]. In this regard, we found that one-third of our patients with IGT had normal FPG. However, OGTT did not demonstrate a good sensitivity for identifying states of prediabetes (45%). In our study, mean 2h-PG was considerably lower than in a previous study which reported 135 ± 33 mg/dl for 2h-PG and 93 ± 10 mg/dl for FPG [18].

Prior reports have provided conflicting information regarding gender distribution of prediabetic CKD patients. In a study by the International Diabetes Federation, IGT was more prevalent in women [19]. Conversely, a report by Sicree showed no gender differences in IGT [20]. In our study, 76.1% of the patients with IGT were men, but no significant gender-related difference was seen.

In contrast to our results, Ikee *et al*. and Satirapoj *et al*. found that glucose intolerance and insulin resistance were age-related [21, 22].

It is well known that body mass index (BMI) is a leading factor in the metabolic syndrome. Also, high BMI and waist circumference have been associated with glucose intolerance in previous studies [23, 24]. Our study population did not include obese. Therefore, with the data available, there were no findings to confirm the association between BMI and glucose intolerance.

Dyslipidemia is a common condition in CKD, and is mainly described as hypertriglyceridemia and low HDL cholesterol. Dyslipidemia has been related to prediabetes and increased risk of cardiovascular diseases [18, 25]. We reported a significant association between hypertriglyceridemia and IGT: 85.7% of IGT and 42.0% of NGT patients had hypertriglyceridemia, but significant association was not seen between IGT and low HDL or high LDL cholesterol. It is also known that CKD patients are more prone to develop hypertension and dyslipidemia, which are associated with coronary artery disease and insulin resistance [18, 22, 26]. Hypertension was significantly associated with IGT in our study, and IGT patients had higher systolic blood pressure.

According to NCEP-ATP III criteria [9], the frequency of metabolic syndrome was 31.8% in our study, and about one-third of patients with metabolic syndrome had concomitant IGT. These findings confirm results of a previous study, where 30.1% of CKD patients had metabolic syndrome [22].

Serum uric acid has been suggested as a risk factor for abnormal glucose metabolism in the general population [27]. Our IGT patients had higher, but not significant higher, serum uric acid level. The effect of erythropoietin and ACEI on improving insulin resistance and glucose metabolism abnormalities is known [15, 28], but our data could not confirm this association.

As the GFR decreases, insulin resistance aggravates [5]. In this regard, the mean GFR was similar in the two groups. We did not found a correlation between mean GFR and plasma glucose values. Also, the frequency of IGT in the various stages of CKD was not significantly different.

In conclusion, prediabetes is a widespread condition among CKD patients. Previous studies indicated that OGTT can detect more patients with prediabetes than FPG alone. However, our study shows that FPG has an acceptable prediabetes detection sensitivity. Also, hypertriglyceridemic and hypertensive CKD patients are more associated with prediabetes. Considering the prognostic role of IGT and IFG in the progression to diabetes and advanced stages of CKD, routine glycemic control in CKD patients is recommended.

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