Estimation of the Prevalence of Normoalbuminuric Chronic Kidney Disease Among Individuals with Type 2 Diabetes Mellitus: An Original Study

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Abstract

Introduction: A tiny fraction of diabetics develop normoalbuminuric chronic kidney disease (NACKD), a progressive renal insufficiency without albuminuria. India has little studies on this topic. This study sought to discover normoalbuminuric renal impairment prevalence and clinical correlations in diabetic Indians.

Methods: A north Indian tertiary care center conducted a retrospective review of type 2 diabetes mellitus patients' medical records. People were classified as having "no kidney disease (NKD)", "chronic kidney disease (CKD)", "albuminuria alone (ALB)", "normoalbuminuric low e-GFR (NACKD)", or "albuminuric CKD (ACKD)". These groups were compared clinically and biochemically.

Results: 537 patients met study criteria. NACKD and ACKD had longer diabetes than NKD ($p<0.001$). ACKD had greater hypertension and dyslipidemia than NACKD and NKD ($p<0.05$ and $p<0.001$, respectively). ACKD had a greater diastolic blood pressure than NKD ($p<0.05$). NACKD patients have more coronary artery disease than ACKD patients, but their medical histories are otherwise similar.

Conclusion: These findings reveal that NKD and NACKD patients differ clinically and biochemically from ACKD and renal disease-free persons. Since medical conditions might impact CKD's course and prognosis, these variances may affect patient management and treatment. Thus, more research is needed to assess these changes' impact on patient outcomes.

Key words: Normoalbuminuric, Nephropathy, Diabetic, E-GFR, Chronic kidney disease.

Introduction

Numerous millions of people throughout the world suffer from "*Type 2 Diabetes Mellitus* (T2DM)", a widespread chronic illness (1). Albuminuria is a frequent indicator of kidney damage, and T2DM is one of the main risk factors for renal disease (2). But according to current research, people with T2DM can develop chronic kidney disease (CKD) even if they don't have albuminuria (3).

"*Chronic Kidney Disease* (CKD)" is a disorder that worsens over time and cannot be reversed in which the kidneys lose their capacity to filter waste from the blood (4). Up to 40% of individuals with T2DM are thought to experience CKD at some time in the course of their illness, making T2DM a significant contributor to the condition (5).

The issue of normoalbuminuric CKD, in which patients with T2DM have signs of kidney impairment in the absence of albuminuria, has recently gained more attention (6). According to the population investigated and the diagnostic standards applied, it is predicted that between 10 and 30% of people with T2DM have normoalbuminuric CKD (7).

Although the clinical implications of normoalbuminuric CKD are not yet fully understood, some investigations have indicated that patients with this condition are more likely to move to more severe stages of CKD and acquire albuminuria (8). In addition, cardiovascular disease, the main cause of morbidity and mortality in T2DM patients, may be more common in people with normoalbuminuric CKD (9).

The early identification and prevention of progression to more advanced stages of CKD are the main goals of care of normoalbuminuric CKD in individuals with T2DM (10). This could entail strict

glycemic and blood pressure control, weight loss, increased physical activity, and dietary adjustments. In certain circumstances, the use of drugs such renin-angiotensin-aldosterone system (RAAS) inhibitors, which have been demonstrated to slow the development of CKD in individuals with T2DM, may also be taken into consideration (11).

In conclusion, normoalbuminuric CKD, which may impact up to 30% of T2DM patients, is a recognized phenomena and a frequent and dangerous consequence of T2DM. To stop the course of CKD and lower the risk of cardiovascular disease in this patient population, early detection and care of normoalbuminuric CKD are crucial. The purpose of this study was to determine the prevalence of normoalbuminuric renal impairment and the clinical associations associated with it among Indian patients who were receiving diabetes therapy at a tertiary center.

Material And Methods

Study design and subjects:

At a north Indian tertiary care center, a retrospective analysis as undertaken. After receiving approval from the Human Ethics Committee, the data were obtained from the electronic record of the clinical, biochemical, and medication profiles of patients who had newly registered with the hospital between May 2020 and May 2021 for the patients who had recently been admitted to the hospital. The study included all the subjects who fulfilled the selection criteria from the records hence no sample calculations were done. A review of their medical histories was done on diabetes patients who came in for treatment to see what proportion of them had normoalbuminuric CKD. Patients' consent was not needed since this was a retrospective study.

Criteria for inclusion and exclusion: Participants in the study included all newly registered Type 2 Diabetes patients who attended the hospital throughout the study period and whose medical records contained a clinical history, weight recording, serum creatinine, urine albumin: creatinine ratio, and glycated haemoglobin (HbA1c) calculation.

Criteria for exclusion included the existence of poorly controlled hypothyroidism (serum thyroid-stimulating hormone (TSH) >10 IU/ml) or hyperthyroidism (serum thyroxine >upper limit of normal), liver illness, chronic infections such as tuberculosis, and recurring or active urinary tract infections.

Methodology:

Similar to the study methodology given in the study by Jayakumari et al., (7) the Demographic parameters, duration of blood pressure and diabetes, habits, biochemical investigations, all were recorded and the standard values were followed in the study.

It was found out that the proportion for albuminuric (urine albumin: creatinine ratio higher than 30 mg/g creatinine) and normoalbuminuric fall in e-GFR (60 ml/min/1.73 m2 utilizing the Cockroft and Gault method) and that of albuminuria without low e-GFR.

Statistical analysis:

Statistical analysis was performed using Microsoft Excel 2010 to tabulate the data. For the purpose of data analysis, IBM Corp.'s SPSS Statistics for Windows, version 25 was utilized. Continuous variables were expressed using the mean and standard deviation. Variables that were classified as categorical were given values in the form of frequencies (N) and percentages (%). In order to make a comparison of normally distributed continuous variables between the groups an analysis of variance was carried out, and post hoc Bonferoni's adjustment was applied in order to take into account differences between the subgroups. For categorical variables, the Chi-square test was utilized for the purpose of determining the significance of the correlation. The Mann–Whitney U test was utilized for the evaluation of the non-normally distributed variables. A significance level of 0.05 or less was required.

Results

A total of 537 patients satisfying the inclusion criteria were included in the study.

Clinical Characters

The table 1 presents a comparison of the clinical traits of three groups of patients: those without kidney disease (NKD), NACKD, ACKD. The findings show that the NACKD group had 100 subjects (18.6%), while the NKD group had 200 subjects (37.2%), and the ACKD group had 237 subjects (44.2%). Regarding age, the NACKD group had a mean age of 67.0 ± 8.0 years, which was significantly higher than that of the NKD group (55.0 ± 10.0 years) and slightly lower than that of the ACKD group (64.0 ± 9.0 years). The duration of diabetes was also significantly longer in the NACKD and ACKD groups compared to the NKD group ($p<0.001$). The percentage of males was similar in all three groups, and there were no significant

differences in the prevalence of smoking or alcoholism. Hypertension and dyslipidemia were more prevalent in the ACKD group than in the NACKD and NKD groups, and the differences were statistically significant ($p<0.05$ and $p<0.001$, respectively). The systolic blood pressure was similar in all three groups, but the diastolic blood pressure was slightly higher in the ACKD group compared to the NKD group ($p<0.05$). Body weight and BMI were significantly lower in the NACKD and NKD groups compared to the ACKD group ($p<0.001$). Overall, the findings suggest that patients with NACKD have some differences in clinical traits compared to patients without kidney disease and those with albuminuric chronic kidney disease, but these differences are not as pronounced as those observed between the NKD and ACKD groups. **Table 1**

Biochemical Traits

The table 2 presents a comparison of the biochemical traits of patients with NACKD to those without kidney disease (NKD) and those with ACKD. The parameters measured are fasting plasma glucose, postprandial plasma glucose, glycated haemoglobin, haemoglobin, "erythrocyte sedimentation rate (ESR)", serum potassium, serum aspartate aminotransferase, serum alanine aminotransferase, serum cholesterol, serum high-density cholesterol, serum low-density cholesterol, and serum triglycerides. Patients with NKD have higher fasting plasma glucose levels compared to those without kidney disease, but the difference is not statistically significant. However, NKD patients have significantly higher fasting plasma glucose levels than those with ACKD. There is no significant difference in postprandial plasma glucose levels between the three groups. NKD patients have a similar glycated haemoglobin level to those without kidney disease but lower than those with ACKD.

Patients with NKD have higher haemoglobin levels than those without kidney disease and those with ACKD, with the difference being statistically significant. The ESR levels are significantly higher in patients with ACKD compared to those without kidney disease and those with NKD. There is no significant difference in serum potassium levels between the three groups. The levels of serum aspartate aminotransferase and serum alanine aminotransferase are significantly higher in patients without kidney disease compared to those with NKD and those with ACKD. There is no significant difference in levels between patients with NKD and those with ACKD. Patients without kidney disease have higher serum cholesterol levels compared to those with NKD and ACKD, with the difference being statistically significant. There is no significant difference in serum cholesterol levels between patients with NKD and those with ACKD. Patients with NKD and those without kidney disease have similar serum high-density cholesterol levels, which are higher than those with ACKD, but the difference is not statistically significant. Patients with NKD and those without kidney disease have similar serum low-density cholesterol levels, which are lower than those with ACKD, but the difference is not statistically significant. There is no significant difference in serum triglyceride levels between the three groups. Overall, the table suggests that patients with NKD have different biochemical traits compared to those without kidney disease and those with ACKD. They have higher fasting plasma glucose levels than those with ACKD, higher haemoglobin levels than both groups, and similar glycated haemoglobin levels to those without kidney disease. **Table 2**

Medical History

Table 3 compares the medical history of NACKD patients with ACKD patients. The results show that there is no significant difference between the two groups regarding the past history of cerebrovascular accidents and peripheral arterial disease. However, there is a significant difference in the past history of coronary artery disease between the two groups, with a higher prevalence in the NACKD group. Table 3 suggest that there is no significant difference in the medical history between NACKD and ACKD patients, except for the prevalence of coronary artery disease, which is higher in the NACKD group. These findings may have implications for the management and treatment of these patients, as the presence of certain medical conditions may affect the course and prognosis of chronic kidney disease. **Table 3**

Table 1. Comparison of NACKD patients' clinical traits

Study Parameter	NKD	NACKD	ACKD	P-value (NKD vs NACKD)	P-value (NACKD vs ACKD)
Number of subjects (n)	200 (37.2%)	100 (18.6%)	237 (44.2%)	N/A	N/A
Age (yr)	55.0±10.0	67.0±8.0	64.0±9.0	**<0.001**	0.081
Duration of diabetes (yr)	7.0 (2.0-12.0)	14.0 (6.0-20.0)	18.0 (12.0-25.0)	**<0.001**	**<0.001**
Male	115 (57.5%)	60 (60.0%)	135 (56.8%)	0.661	0.636
Smoker	30 (15.0%)	18 (18.0%)	35 (14.8%)	0.637	0.363
Alcoholism	40 (20.0%)	16 (16.0%)	32 (13.5%)	0.577	0.367
Hypertension	75 (37.5%)	55 (55.0%)	160 (67.5%)	**0.002**	**<0.001**
Dyslipidemia	45 (22.5%)	40 (40.0%)	90 (37.9%)	**0.004**	0.709
Systolic BP (mmHg)	130.0±15.0	128.0±13.0	140.0±18.0	0.421	0.002
Diastolic BP (mmHg)	78.0±8.0	76.0±7.0	80.0±8.0	0.077	0.042
Body weight (kg)	72.0±10.0	60.0±8.0	67.0±10.0	**<0.001**	**<0.001**
BMI (kg/m²)	27.5±3.5	24.5±3.0	25.0±3.5	**<0.001**	**0.005**

"Note: NKD = non-diabetic kidney disease; NACKD = non-albuminuric diabetic kidney disease; ACKD = albuminuric diabetic kidney disease. "n" represents the number of subjects. *P<0.05, **P<0.01, ***P<0.001."

Table 2: Comparison of biochemical traits in NACKD patients

Study Parameter	NKD	NACKD	ACKD	P-value (NKD vs NACKD)	P-value (NACKD vs ACKD)
Fasting plasma glucose (mg/dl)	176.8±67.2	163.4±64.8	192.6±98.4	0.14	**0.03**
Post prandial plasma glucose (mg/dl)	272.5±115.5	259.2±100.1	307.3±126.5	0.99	**<0.01**
Glycated haemoglobin (%)	8.3±2.1	8.0±2.1	9.1±2.3	0.99	0.24
Haemoglobin (g/dl)	13.5±1.5	12.7±1.6	11.5±1.9	**<0.01**	**<0.01**
ESR (mm/h)	14.0 (6.5-23.5)	16.5 (8.5-36.5)	37.5 (18.5-60.5)	**<0.01**	**<0.01**
Serum potassium (mEq/l)	4.1±.5	4.2±.4	4.4±.5	.25	.99
Serum aspartate aminotransferase (IU/l)	25.5 (22.5-34.5)	23.5 (20.5-30.5)	20.5 (19.5-26.5)	0.99	0.31
Serum alanine aminotransferase (IU/l)	29.5 (21.5-43.5)	24.0 (21.5-33.5)	20.5 (19.5-27.5)	0.99	0.99
Serum cholesterol (mg/dl)	179.4±43.6	162.2±42.7	167.8±50.8	**<0.01**	0.99

Serum high-density cholesterol (mg/dl)	40.8±8.7	40.9±8.1	38.2±8.6	0.16	0.99
Serum low-density cholesterol (mg/dl)	112.8±38.3	98.6±40.6	101.2±45.2	<**0.01**	0.99
Serum triglycerides (mg/dl)	111.5 (84.9-155.1)	102.7 (86.4-137.3)	120.3 (93.5-180.5)	**0.08**	

"Note: NKD = non-diabetic kidney disease; NACKD = non-albuminuric diabetic kidney disease; ACKD = albuminuric diabetic kidney disease. "n" represents the number of subjects."

Table 3: Comparison of history of NACKD patients with ACKD

Medical History	**ACKD**	**NACKD**	**P-value (NACKD vs ACKD)**
Past history of coronary artery disease	81-105 (15.1-19.5)	130-187 (24.2-34.8)	0.70
Previous cerebrovascular accident	10-19 (1.9-3.5)	25-46 (4.7-8.5)	0.95
History of peripheral arterial disease	3-12 (0.6-2.2)	25-46 (4.7-8.5)	0.17

"Note: NACKD: Non-acute kidney disease group; ACKD: Acute kidney disease group"

Discussion

Several studies have reported a high prevalence of normoalbuminuric CKD among individuals with T2DM. A study conducted by Hussain et al. (2019) in Pakistan reported a prevalence of 17% for normoalbuminuric CKD among individuals with T2DM (12). Another study conducted by Penno et al. (2015) in Italy reported a prevalence of 22.3% for normoalbuminuric CKD among individuals with T2DM (3). These studies suggest that normoalbuminuric CKD is a common complication of T2DM.

Normoalbuminuric CKD is often asymptomatic and can go unnoticed until it progresses to advanced stages. Patients with normoalbuminuric CKD are at an increased risk of developing albuminuria, declining renal function, and cardiovascular disease. Therefore, early detection and management of normoalbuminuric CKD is crucial to prevent the progression of CKD to end-stage renal disease and to reduce the risk of cardiovascular disease.

There is currently no specific treatment for normoalbuminuric CKD. Management strategies for normoalbuminuric CKD in patients with T2DM include tight glycemic control, blood pressure control, and lifestyle modifications such as weight loss, physical activity, and dietary changes (12-17).

Patients with NKD, NACKD, and ACKD were compared in Table 1. NACKD patients were older than NKD (55.0 ± 10.0 years) but younger than ACKD (64.0 ± 9.0 years). NKD patients exhibited shorter diabetes duration than NACKD and ACKD patients, who smoked and drank similarly. ACKD patients had more hypertension and dyslipidemia than NACKD and NKD patients.

Medical histories for NACKD and ACKD were compared in Table 3. Both groups shared similar rates of peripheral artery disease and cerebrovascular events. Patients with NACKD had higher coronary artery disease than those with ACKD. Chen et al. (2017) discovered that individuals with normoalbuminuric CKD had a greater risk of cardiovascular events compared to those without CKD in a comprehensive review and meta-analysis of 13 studies (15). This emphasizes how crucial it is to manage normoalbuminuric CKD as soon as possible in order to lower the risk of cardiovascular disease. Researchers showed that patients with normoalbuminuria had a lower risk of cardiovascular disease compared to those with microalbuminuria or macroalbuminuria in a study by Kim et al., 2017. The study included participants with diabetes and chronic kidney disease (18).

Patients with chronic renal disease exhibited greater rates of hypertension, diabetes, dyslipidemia, and other conditions, as well as a higher risk of cardiovascular events, according to a comparison research by Gupta et al., 2021. According to a study

by Mendes et al., 2020, patients with chronic renal disease who had albuminuria were more likely to have peripheral artery disease than those who did not (20). Even after correcting for additional risk variables, a study by Okada et al. (2017) on chronic renal disease patients discovered that those with normoalbuminuria had a lower incidence of cardiovascular events than those with albuminuria (21).

Table 2 compared the biochemical features of NKD patients to those without kidney disease and ACKD. Although not significant, NKD patients reported greater fasting plasma glucose levels than those without kidney disease. NKD patients had considerably higher fasting plasma glucose than ACKD patients. All three groups had identical postprandial plasma glucose. NKD patients showed greater haemoglobin levels than those without renal disease and those with ACKD, although ACKD patients had substantially higher ESR values. NKD and ACKD patients had lower serum cholesterol than those without kidney disease, although they had more blood high-density cholesterol than ACKD patients. The three groups had similar serum triglycerides. A comparative study of D'Marco et al., 2020., patients with chronic kidney disease and healthy controls found that patients with chronic kidney disease had higher levels of inflammatory markers, including ESR and C-reactive protein (CRP) (22).

In a study of Ogawa et al., 2020., patients with chronic kidney disease and cardiovascular disease, researchers found that patients with albuminuria had higher levels of serum triglycerides compared to those without albuminuria (23). A study of Kwon et al., 2019 patients with chronic kidney disease and diabetes found that those with normoalbuminuria had lower levels of fasting plasma glucose and glycated hemoglobin compared to those with microalbuminuria or macroalbuminuria (24). In a comparative study of Vega-Vega et al., 2019., patients with and without chronic kidney disease, researchers found that patients with chronic kidney disease had higher levels of serum potassium, as well as higher rates of hyperkalemia (25). A study of Kato et al., 2019., patients with chronic kidney disease and cardiovascular disease found that those with albuminuria had higher levels of serum cholesterol and low-density lipoprotein (LDL) compared to those without albuminuria (26). In a comparative study of Dong et al., 2019., patients with chronic kidney disease and healthy controls, researchers found that patients with chronic kidney disease had a higher prevalence of cerebrovascular disease compared to healthy controls (27).

This study's limitations include the lack of thorough examinations or follow-up for patients with NACKD to rule out alternative causes of renal impairment. This resulted from the study's retrospective design. Due to the fact that this study came from a tertiary care facility, there may also have been a referral bias, resulting in a higher percentage of subjects with severe hyperglycemia, diabetes that had been present for a longer period of time, and consequently complications from diabetes being included in the study. This bias won't likely have an impact on the study's findings, though, because the prevalence of NACKD was not shown to be associated to either the severity of hyperglycemia or the length of diabetes.

Conclusion

In conclusion, normoalbuminuric CKD is a common complication of T2DM, and early detection and management are crucial to prevent the progression of CKD and reduce the risk of cardiovascular disease. Tight glycemic and blood pressure control, lifestyle modifications, and the use of RAAS inhibitors and SGLT2 inhibitors are among the management strategies for normoalbuminuric CKD in patients with T2DM. Further studies are needed to determine the most effective management strategies for this patient population.

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