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A prospective study for the association between kidney disease and pre-diabetes

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Abstract
Background: Globally, diabetes is the leading cause of kidney disease and kidney failure. Prediabetes is approximately twice as common as diabetes, affecting 20-35% of adults. The fasting glucose and glycated haemoglobin (HbA1c) levels consistent with prediabetes are independent risk factors for hyper filtration in the kidneys and the presence of albumin in the urine -both indicators of kidney damage.
Aims and Objectives: To study the association between pre-diabetes and kidney diseases.
Materials and Methods: This is a prospective study which was conducted on 150 subjects with 50 normoglycemic controls and 100 pre-diabetes patients having fasting plasma glucose (FPG) more than 100 mg/dl and less than 126 mg/dl or Postprandial Blood Sugar (PPBS) more than 140mg/dl or less than 199mg/dl and /or HbA1c 5.6 to 6.4%. Physio-chemical parameters were recorded and assessed to understand the correlation between pre-diabetic conditions and kidney disease.
Results: Kidney disease prevalence is high among people with prediabetes. Majority of the cases had fasting blood between 100-109 mg/dl, all controls had FBS range less than 100 mg/dl. Mean FBS in cases was 111.28±7.06 mg/dl and mean FBS in controls was (77.62±10.2 mg/dl. Post prandial blood sugar in pre diabetic cases ranged from 160- 179, all controls had PPBS< 140 mg/dl, mean PPBS in cases was 171.4±13.63 mg/dl and mean PPBS in controls was 116.52±12.86 mg/dl. Hb1c in pre-diabetic cases ranged from 5.7 – 6.0%, all controls had HbA1c <5.7%, mean HbA1c in cases was 6.03±0.19 and mean HbA1c in controls was 4.5±0.61%. 18% cases and none of the controls showed evidence of kidney disease. This difference of evidence of kidney disease between cases and controls was statistically significant.
Conclusion: Kidney disease prevalence was high among the prediabetes patients. Thus prediabetes can be target for early intervention for prevention of chronic kidney diseases by lifestyle changes.

Keywords: Prediabeets, kidney disease, glomerular filtration rate, glycated hemoglobin

Introduction
Diabetes-related kidney diseases accounts for almost 50% of patients with end-stage renal disease, even with optimal treatment of new-onset diabetes, a large percentage of patients will develop chronic kidney disease (CKD) [1].
Prediabetes is approximately twice as common as diabetes, affecting 20-35% of adults, and it progresses to diabetes in 45-50% of individuals after 10 years [2]. Pre-diabetes with impaired fasting glucose, is associated with abnormally high GFR or glomerular hyper filtration [3].
Hyper filtration has been established as an early manifestation of diabetic nephropathy and has been shown to predict albuminuria and GFR decline in diabetes [4]. Hence present study was planned to evaluate the association between kidney disease and pre-diabetes.

Materials and Methods
The present study was conducted in Consultation Chamber, Gwalior.
As per criteria recommended by American diabetes association (ADA) pre-diabetes was diagnosed.
Patients willing to be a part of study, both men and women > 20 years of age, patients with FPG ≥ 100 mg / dl but ≤ 126 mg/dl and / or PPBS ≥ 140mg/dl but ≤199 mg/dl and/or HbA1c 5.7-6.4% were considered as prediabetes.
Healthy individuals of either sex and who were >20 years of age with FPG < 100 mg/dl and/or PPBS < 140mg/dl and/or HBA1C< 5.7% were taken as normoglycemic patients.
Patients who were pregnant, patients who were known diabetic, patients on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) use to treat hypertension/CKD and patients who do not give consent were excluded from the present study.
Patients with risk factors for Pre-diabetes on OPD basis or from wards were taken and screened for Prediabetes as per the ADA criteria. Under aseptic precautions blood samples were drawn in morning (after 12 hours of fasting) and were analysed for plasma glucose. Blood samples were also drawn 2hrs post meal and were analysed for Post Prandial Blood sugar. The values were measured in mg/dl. Blood samples were also drawn for HBA1C.
Estimated glomerular filtration rate (eGFR) was calculated according to modification of diet in renal disease (MDRD) study by measuring serum creatinine.
Urinary albumin creatinine ratio of 30 to 300 mg /g (microalbuminuria) and > 300 mg /g (macroalbuminuria) were

taken as kidney damage.

Spot urine sample was collected and measured for urine albumin creatinine ratio (UACR). Any of the two above or both the criteria (reduced eGFR and albuminuria) were considered as a marker of renal impairment.

The urinary albumin: creatinine ratio was measured using the first morning urine sample where practicable<30mg/g is normal range, 30- 300 mg/g is microalbuminuria and >300 mg/g is macro albuminuria. Protein was also tested using Urine dipstick for macro albuminuria. C - reactive protein (CRP) latex slide test (Serology kit) is used for the qualitative and semi-quantitative measurement of C-reactive protein (CRP) inhuman serum.

All the data was recorded using structured schedule (Case proformas) and entered in Microsoft Excel Sheet and tabulated for analysis along with graphical representation.

Collected data was analysed using Epilnfo TM 7.1.5 and SPSS for windows version 20.0 Microsoft Office word and Microsoft Office Excel are used to generate tables. P value of <0.05 was considered as significant.

Results

Table 1: Characteristics of study population

Parameters	Pre-diabetic cases	Normoglycemic controls.
	Mean ± SD	Mean±SD
Age(years)	49.05±14.71	44.82±14
FBS(mg/dl)	111.28±7.06	77.62±10.2
PPBS(mg/dl)	171.4±13.63	116.52±12.86
HbA1c (%)	6.03±0.19	4.56±.61
UACR(mg/g)	32.45±7.69	9.61±7.16
eGFR(ml/min/1.73m$^{2)}$	75.8±21.94	87.52±15.58

Mg/dl: milligrams per decilitre, mg/g: milligrams per gram, ml/min/1.73m^2: ml/min/1.73m^2

Majority of the cases and Control were in the age group of 60-79 and 40-59 yrs respectively. The difference in age group between cases and controls was found statistically significant and thus as age advances, the prevalence of pre-diabetes increases.

There was no significant difference recorded in distribution of sexes between cases and controls. Thus, there is no association between sex and prevalence of prediabetes.

Table 2: Estimated glomerular filtration rate in pre diabetic cases and controls

eGFR Stages(ml/min/1.73 m)	Number of Cases	Controls
Stage 1 (90)	53	35
Stage 2 (60-89)	31	15
Stage 3 A (30-44)	5	0
Stage 3 B (30-44)	5	0
Stage 4 (15-29)	6	0
Stage 5 (<15)	0	0
Total	100	50

Urine albumin creatinine ratio in pre diabetic cases was maximum and all controls did not show albumin in urine; a clear correlation between CPR and reduction is stage of eGFR was observed. Four cases and none of the controls were found CPR positive, a clear correlation between CPR albuminuria was observed.

Table 3: Overall assessment of pre-diabetic cases for GFR

GFR(ml/min/1.73 m)	Macro-albuminuria	Microalbuminuria	No Albuminuria
>90	2	0	54
60-89	0	0	28
30-59	2	6	2
15-29	3	3	0
<15	0	0	0

Evidence of kidney disease in prediabetes

18% cases and none of the controls showed evidence of kidney disease. This difference of evidence of kidney disease between cases and controls was statistically significant. Thus there is association of Prediabetes with Kidney disease.

Discussion

The present study evaluated the association of Prediabetes with kidney diseases in the form of reduced eGFR and Albuminuria. Most of subjects have age of more than 50 years (44%). Maximum controls were in age group of 40-59 years (42%). This difference of age group between cases and controls was found to be statistically significant. This signifies that as age, advances the prevalence of Prediabetes increases. This is in concordance with older studies by Mainous *et al*. [5] which states that people more than 40 years experienced more Prediabetes than who were under 40 years (p<0.0001). Similarly study by Muthunarayan *et al*. [6] on prevalence of Prediabetes and its associated risk factors among rural adults in Tamil Nadu found that among Prediabetic population, 93.5% were above the age of 40 years (p=0.001).

The Mean age of prediabetic Cases in the present study was 49.05±14.71 years and in controls were 44.82±14 years. This observation is comparable with other studies like Bahar *et al*. [7] on where mean age in pre-diabetic cases was 52 ±11.2 years and in controls was a 40.2±12 year.

Majority of the prediabetes and Control were males (59% and 54% respectively). This difference of gender in cases and controls was not found to be statistically significant (Chi Square- 0.34, p value- 0.560). This signifies that according to present study there is no correlation of sex with prediabetes. Similarly in study by Mainous *et al*, [5] no significant difference between male and female was reported. In contrast the study by Muthunarayan *et al*. [6] prediabetes was higher in women (67.4%) but the difference was statistically insignificant.

In a study by Zhou *et al*. [8] mean FBS was (106.2±5.4) mg/dl which is in agreement to findings of present study. The mean PPBS in Prediabetic cases was 171.413.63) mg/dl, and in controls was 116.52 ±12.86 mg/dl. In a study by Bahar *et al*. [7] mean PPBS range in Prediabetic cases was 160.36±17.4) mg/dl.

Mean HbA1C in Prediabetic cases was 6.03± 0.19 and in controls was 4.56 ±0.61 %. Majority of the cases had HbA1c of 5.7-6.0% and that in controls was HbA1C < 5.7 %. In a study by Weiping *et al*. [9] mean HbAIc in IGR was 5.81±0.5%. This difference may be attributed to difference in laboratory methods of assessment of HbA1C. In a study by Ketema *et al*. [10] on correlation of fasting and postprandial

plasma glucose with HbA1c showed that PPG has a closer association with HbA1c than FPG. Hence, PPG is better in predicting overall glycemic control in the absence of HbA1c. In another study by David B *et al*. [11] showed that by retrospective analysis of data derived from self-monitoring of blood glucose by patients in the DCCT identified a linear correlation between HbA1c and average blood glucose. These differences in correlation of HbA1C with plasma sugar level maybe attributed to differences in study population (diabetic, pre-diabetic, normoglycemic) and differences in laboratory methods to assess plasma glucose and HbA1C.

In the present study total 4% cases were CRP Positive (1% in stage 3A, 1% in stage 3B, 2% in stage 4 of eGFR). This was statistically significant (Chi square 23.61 p= 0.001). This signifies correlation of CRP with reduction of eGFR. This is in concordance with study by Fox *et al*. [12] where CRP was significantly associated with CKID based on eGFR criteria (p= < 0.0001).

In the present study among the CRP positive cases, 3% had microalbuminuria and 1% had macro-albuminuria. Total 4% cases had albuminuria and this was statistically significant. (Chi square-25.59, p <0.0001).This signifies association of CRP with albuminuria. A study conducted by Abhijit *et al*. [13] showed positive association of CRP with microalbuminuria. (p <0.0003). Similarly in study by Fox *et al*. [14] CRP was significantly associated with albuminuria in the age and sex adjusted model (p=0.0001).

In the present study, 5% cases were in stage 3A, 5% in stage 3B, 6 % in stage 4 of eGFR and none of the controls were in stages 3 and 4 of eGFR. This difference in eGFR between cases and controls was significant. (Chi Square=9.65, p =0.05) Overall 16% cases were in stage 3 and 4 of CKD. A study conducted by Platinga *et al*. [14] showed that of total 17.7% patients with prediabetes had stage1 CKD and 56.2% had stage 3. In contrast study by Zhou *et al*. [8] showed 14.1% prevalence of CKD in Prediabetes in which only 2.6% showed reduced eGFR. This difference in eGFR in various studies may be due to difference in study population and different methods of eGFR calculation used. Also duration of hyperglycaemia in study population which was not known may have cause hyper filtration followed by reduced eGFR which may also contributed to differences in eGFR.

In the present study albuminuria was found in 16% cases. Microalbuminuria was found in 9% cases (UACR- 30-300mg/g). Macroalbuminina was found in 7% cases (UACR->300mg/g). None of the controls showed microalbuminuria or microalbuminuria. This difference of albuminuria between cases and controls was statistically significant. In study conducted by Bahar *et al*. [7] on correlation and microalbuminuria, prevalence rate of between Prediabetic conditions microalbuminuria was 15.5% in prediabetic group (p = 0.005). In study by Zhou *et al*. [8] albuminuria was found in 12.9% with Prediabetes. This difference in prevalence of albuminuria in various studies may be attributed to differences in the population indices, laboratory techniques for urine albumin measurement, differences in definitions of albuminuria and prediabetes and laboratory techniques to measure it.

The overall evidence of kidney disease was found in 18% cases and none of the controls had kidney disease. This difference in evidence of kidney disease between cases and controls was found to be statistically significant (chi square 19.78, p value <0.0001). A study conducted by Zhou *et al*. [8] showed 14.1% prevalence of CKD in Prediabetes and 9.2% in normoglycemic patients (p <0.05). Similarly study conducted by Platinga *et al*. [14] showed that 17.7% with prediabetes had CKD. A study by Caroline *et al*. [15] showed that IFG or IGT conferred a 65% increased odds of developing CKD.

Also a study by Shottker *et al*. [16] showed that relative risk of IFG to develop reduced kidney function was 0.97 (95% CI: 0.75-1.25) and HbA1c defined prediabetes was 1, 03 (95% CI: 0. 86-1.23) which is agreement to present study findings.

Conclusion

Current study shows that out of the 100 Prediabetic cases and 50 normoglycemic controls, 9% cases and none of the controls showed micro-albuminuria, 7% cases and none of the controls showed macro-albuminuria 16% cases and none of the controls were under stage 3 and 4 of CKD. Overall 18% prediabetic cases and no normoglycemic controls showed evidence of kidney disease. There was also association of CRP with reduced eGFR and albuminuria

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