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Albuminuria as a risk marker for developing type 2 diabetes in nondiabetic- A study at tertiary care hospital from central India

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Abstract
This study was conducted amongst rural population of central India at UP University of medical sciences, Saifai, etawah, India wef Apr 2008 to Apr 2020 (12 years) to determine whether the presence of microalbuminuria and macroalbuminuria is associated with the development of diabetes among nondiabetic rural population.
Urine albumin to creatinine ratios (ACRs) were obtained from 1764 rural people aged 20–74 years. Among them 1500 were free of either clinical known diabetes or newly diagnosed diabetes over an 12 years follow-up period, 234 participants developed diabetes. They were defined as cases. Each case was matched by an individual control with same sex and body mass index (BMI) category and age within 2 years. Conditional logistic regression was used to assess the association between albuminuria and diabetes.
The baseline level of ACR was significantly higher among cases than among controls. The odds ratios for future diabetes were 2.36 [95% confidence interval (95% CI) 1.01–5.50] and 3.27 (95% CI 1.38–7.77) for middle and upper tertiles, respectively, with adjustment for age, BMI, serum total cholesterol, serum C-reactive protein values and fasting plasma glucose at the baseline. The adjusted odds ratios were 1.90 (95% CI 0.88–4.06) and 2.51 (95% CI 1.08–5.87) for those with microalbuminuria and macroalbuminuria, respectively. The presence of microalbuminuria and macroalbuminuria predicts diabetes independent of other known risk markers of development of type 2 diabetes in Indian people.

Keywords: albuminuria, marker, developing type, nondiabetic, care, hospital

Introduction
Indian have a higher prevalence of diabetes than many neighbouring Asian counries Physical inactivity and obesity are independent predictors of type 2 diabetese [1, 2] However, current physical inactivity and obesity may not fully explain the high risk of type 2 diabetes in Indian population. There has been considerable focus on the concept of microalbuminuria, not only because it predicts renal disease in diabetes but also because it relates to premature mortality in the diabetic and in the general population. Albuminuria in Indian population is a major risk factor for renal disease[3] and cardiovascular disease [4] Albuminuria can also be present at the time of diagnosis of diabetes. An increased prevalence of microalbuminuria has been observed among those with impaired fasting glucose before developing clinically diagnosed diabetes [4, 5] Mykkanen *et al* [6] reported microalbuminuria predicted the development of diabetes independently of blood pressure level. Brantsman *et al* [7] hypothesized that the presence of increased urine albumin excretion in the non-diabetic population is associated with an increased risk of development of type 2 diabetes. Their 4 year follow-up data suggest that urinary albumin excretion is an independent predictor of diabetes [7, 8, 31]. However, their data were mainly from a Caucasian population in Netherlands. Their findings need to be confirmed in other populations. Confounding is a major concern in most observational studies. People with diabetes have significantly higher levels of most risk factors such as body mass index (BMI), waist circumference, glucose and lipids than those without diabetes. In this study, we examine the association between albuminuria and type 2 diabetes in an Indian population using an individually matched case–control study design.

Material and Method
In 2008 a community-wide renal disease screening programme was started in a rural population of central India at UP University of medica sciences, Saifai, India Participants were offered a baseline examination and testing between 2008 and 2020. 1764 adults aged 20–74 years were followed until April 17, 2020.
During the baseline visit, a fasting venous blood sample was drawn for plasma glucose, and serum total cholesterol and triglycerides measurements. For those free from diabetes at baseline, plasma glucose levels were also measured 2 h after a 75 g oral glucose challenge. An individual with a 2 h plasma glucose level of 140ng to199 mg (7.8–11.0 mmol/l) were considered as having impaired glucose tolerance (IGT).

Urinary albumin concentration was measured by the Beckman immunoassay. A urine albumin to creatinine ratio (ACR) was calculated (mg/mmol). Previous studies in Indian population used 3.4 and 34 mg/mmol as cut-off for microalbuminuria and macro (or overt) albuminuria However, to be consistent with recent studies, this study defined normoalbuminuria as a urine ACR <2.5 mg/mmol, microalbuminuria as a urine ACR 2.5–25 mg/mmol, and macroalbuminuria as a urine ACR >25 mg/mmol [10, 11, 13]. In addition, baseline urine ACR values were categorized into tertiles based on the sex-specific distribution of the total study population.

High sensitivity C-reactive protein concentrations were measured using the immunoturbidimetric C-reactive protein assay with a detection limit of 0.03 mg/l. The assay's analytical range was from 0.1 to 20 mg/l. Samples with values >20 mg/l were measured using dilution techniques. The imprecision of the assay is <5%. Other risk factors were measured, such as blood pressures, serum cholesterol, triglycerides, BMI, cigarette smoking, alcohol drinking and the presence of diabetes and have been described elsewhere [14, 16].

A total of 264 participants who either had known diabetes before the baseline examination or were newly diagnosed as having diabetes at the baseline examination according to the World Health Organisation (WHO) 1999 criteria [17]. On fasting and 2 h post-load glucose values were excluded. During a median 12 year follow-up period, newly diagnosed cases of diabetes were determined through clinical and hospital records among 1500 participants free from diabetes at baseline. A total of 234 participants developed clinically diagnosed diabetes according to their symptoms, fasting and/or 2 h post-load glucose values. Each case was matched by a control of the same sex and BMI category of <25, 25–29, and >30 kg/m^2 and the closest age (within 2 years). Participants who died or had cardiovascular disease during the follow-up period before the diagnosis of diabetes were also excluded.

Statistical analysis

We used a matched *t*-test to assess differences in means and the McNemar test to assess for differences in proportions. Since the urine ACR, plasma glucose, and C-reactive protein values were skewed, the logarithmic transformed values were used and their geometric means were presented. Conditional logistic regression was used to examine the association between diabetes and urine ACR values. Crude and adjusted odds ratios and their 95% confidence intervals (95% CIs) were calculated with the lowest urine ACR group as reference. Since each case was matched by a control with the same sex, sex cannot be a possible confounder. However, the potential residual confounding effects of age and BMI were further assessed in the multiple conditional logistic regressions along with other non-matched variables such as serum cholesterol, C-reactive protein, fasting plasma glucose, and impaired plasma glucose status. Interactions between ACR and other variables were tested. We also used a logarithmic transformation of ACR as a continuous variable to assess its association with diabetes and its interactions with other factors as conducted in one of previous studies [17]. All analyses were performed using Stata 9.0 [19].

Results

Baseline characteristics of study participants who were subsequently diagnosed with diabetes (cases) and those remaining free from diabetes (controls) are shown in Table-1. Since sex, age and BMI are matching variables, as expected for successful matching, cases and controls are similar in those variables. Cases had higher serum cholesterol, plasma glucose, and C-reactive protein levels and a higher proportion of participants with IGT than controls. There were no statistically significant differences in blood pressures, triglycerides, smoking and drinking, and waist circumferences.

Table 1: Baseline characteristics of new diabetes cases and controls

Variable	Controls	Cases	*P*-value
Number	234	234	---
Age, years	36.1 (10.3)	36.4 (10.4)	0.80
BMI, kg/m	26.2 (5.7)	26.7 (5.4)	0.46
Waist circ. cm	94.7 (13.8)	95.9 (12.4)	0.48
Systolic pressure, mm Hg	123.4 (16.8)	123.1 (19.5)	0.91
Diastolic pressure, mm Hg	76.5 (12.2)	77.3 (13.8)	0.63
Total cholesterol, mmol/l	4.7 (1.0)	5.0 (1.2)	0.08
Triglycerides, mmol/l	2.1 (1.8–2.4)	2.0 (1.8–2.2)	0.40
CRP, mg/dl	5.9 (4.8–7.2)	8.0 (6.6–9.6)	0.031
Urine ACR, mg/mmol	4.8 (3.3–7.0)	11.0 (7.8–15.6)	0.0014
Fasting plasma glucose, mmol/l	4.9 (4.7–5.1)	5.7 (5.3–6.1)	0.0003
2 hr post-load glucose, mmol/l	6.0 (5.7–6.4)	6.7 (6.2–7.3)	0.025
Male (%)	44 (37.6)	44 (37.6)	0.33
Smoking (%)	78 (66.7)	85 (72.6)	0.32
Drinking (%)	71 (60.7)	65 (55.6)	0.43
Impaired glucose tolerance (%)	10 (8.5)	25 (21.4)	0.0060

Mean (standard deviation).

Geometric means (95% CI).Number (%).The geometric means of urine ACR was significantly higher among cases than among controls Table-2 shows higher proportions of microalbuminuria, macroalbuminuria, and participants in higher tertile groups among cases than among controls.

Table 2: ACR distribution amongst controls n cases

ACR tertiles	cases	controls	P values
Lower	88(37.6%)	44 (18.8%)	0.006
Middle	64 (27.4%)	70 (29.9%)	0.005
Upper	82 (35.0%)	120 (51.3%)	0.004
Albuminuria	cases	controls	P values
Normal	106 (45.3%)	64 (27.4%)	0.050
Microalbuminuria	66 (28.2%)	84(35.9%)	0.015
Macroalbuminuria	62 (26.5%)	86 (36.8%)	0.017

Table 3: Crude and adjusted odds ratios of diabetes according to baseline urine albumin/creatinine ratio values

	ACR tertile vs lower			**Albuminuria vs normal**	
	Middle	**Upper**	**Micro**	**Macro**	**Log_{10} (ACR)**
Crude OR	2.22 (1.11–4.48)	3.32 (1.61–6.85)	2.22 (1.15–4.29)	2.69 (1.30–5.56)	1.81 (1.26–2.58)
Adjusted OR 1	2.07 (1.00–4.29)	3.05 (1.44–6.46)	2.03 (1.02–4.03)	2.58 (1.21–5.49)	1.70 (1.18–2.45)
Adjusted OR 2	2.38 (1.11–5.09)	3.12 (1.45–6.69)	2.15 (1.06–4.35)	2.51 (1.17–5.38)	1.66 (1.15–2.40)
Adjusted OR 3	2.53 (1.11–5.79)	3.50 (1.51–8.09)	2.20 (1.04–4.65)	2.87 (1.25–6.56)	1.81 (1.20–2.72)
Adjusted OR 4	2.65 (1.13–6.22)	3.12 (1.32–7.38)	2.17 (1.02–4.60)	2.45 (1.04–5.76)	1.71 (1.12–2.59)
Adjusted OR 5	2.36 (1.01–5.50)	3.27 (1.38–7.77)	1.90 (0.88–4.06)	2.51 (1.08–5.87)	1.71 (1.13–2.59)

OR 1: Adjusted for age and BMI; OR 2: Adjusted for age, BMI, and total cholesterol; OR 3: Adjusted for age, BMI, total cholesterol, and CRP; OR 4: Adjusted for age, BMI, total cholesterol, CRP, and IGT; OR 5: Adjusted for age, BMI, total cholesterol, CRP, and fasting plasma glucose.

In age, sex, and BMI matched analysis, the odds ratios of incident diabetes were 2.22 (95% CI 1.11–4.48) and 3.32 (95% CI 1.61–6.85) for middle and upper tertiles, respectively, with the lower tertile group as reference. Similarly, odds ratios for microalbuminuria and macroalbuminuria were 2.22 (95% CI 1.15–4.29) and 2.69 (95% CI 1.30–5.56), respectively, relative to the normal albuminuria group. Interactions between albuminuria and other variables were examined and no significant interaction terms were observed. Adjusting for age and BMI had little impact on the effect estimate, as both were matching variables. Even after adjusting for possible confounding factors collected in this study, the associations between diabetes and elevated levels of ACR remained statistically significant. The adjusted odds ratios were 2.36 (95% CI 1.01–5.50) and 3.27 (95% CI 1.38–7.77) for middle and upper tertiles, and 1.90 (95% CI 0.88–4.06) and 2.51 (95% CI 1.08–5.87) for microalbuminuria and macroalbuminuria groups, respectively. Crude and adjusted odds ratios for log (ACR) as a continuous variable were significantly higher than the null effect.

Discussion

In this matched case–control study, we found that an elevated urine ACR value is associated with the development of diabetes in Indian people. This association is independent of age, sex, BMI, serum cholesterol, C-reactive protein, and fasting plasma glucose. Our findings suggest that albuminuria can precede and predict the development of diabetes in Indian people.

Albuminuria has usually been considered a consequence of diabetes [20] It has been associated with increased cardiovascular risk in populations with and without diabetes [13, 20, 21, 22]. In Indian people, albuminuria predicts the risk of coronary heart disease independent of traditional risk factors [19, 20]. Several studies have demonstrated that microalbuminuria occurs in individuals without diabetes [19, 23].

Only two studies have examined whether it predicts the development of diabetes among people without diabetes [7, 8, 23]. Both studies were conducted in Caucasian populations. Diabetes cases were determined during 4.2 years of follow-up in Brantsma *et al*.'s study [7]. and over 3.5 years in the study by Mykkanen *et al*. [6] This nested case–control study is the one of few in a high-risk indigenous population and has the long follow-up of 12 years.

The mechanism of the association is not clear. Confounding effects are a major concern for an observational epidemiological study. Albuminuria is associated with the insulin resistance and metabolic syndrome [23, 24] and the presence of the metabolic syndrome and insulin resistance increases the risk of diabetes [25, 27] In this study, we did not identify individuals with metabolic syndrome but the major risk components of metabolic syndrome were adjusted for either through the matched study design or multiple conditional logistic regressions. After such adjustment, the association between diabetes and albuminuria remained. Albuminuria and diabetes may also share other risk factors that are not currently known. Since the onset of type 2 diabetes is generally held to be at least several years before clinical diagnosis [28] the pathophysiology of diabetes related vascular complications probably begins before the diagnosis of diabetes. Microalbuminuria is a marker of endothelial dysfunction, which may occur with early renal disease [29] and before the current diagnosis of diabetes.

Although the underlying mechanism of the association is still not clear, it is important to know that the presence of microalbuminuria and macroalbuminuria can precede diabetes and independently predict the risk of future diabetes. Improving kidney function may be potentially beneficial to preventing diabetes. Our results suggest that microalbuminuria and macroalbuminuria can at least be useful for identifying persons at increased risk of diabetes regardless of whether the association is causal.

Our findings have particular clinical and public health implications for Indian population since a high prevalence of albuminuria has also been found in many different western communities [30] We have already reported that, in this study population, >30% of adults have microalbuminuria and 20% have macroalbuminuria [4].

Our study had several limitations. First, the diabetes events were identified through hospital records and clinical records. It is likely that some undetected cases were included in the control group. The effect is likely to be underestimated owing to this bias. Second, those with albuminuria may be more likely to visit their doctors for other health problems. Therefore, the presence of diabetes among them is more likely to be identified. If this bias is present, it will overestimate the true association between albuminuria and diabetes, although there is no evidence on this. Third, albuminuria in this study was defined using random urine ACR values rather than 24 h urine collection for urinary albumin excretion. However, it has been found that spot ACR is a good screening test for microalbuminuria [30, 31] Fourth, because the study participants were adults from a remote rural population of central India, the results may not be generalizable to other populations.

Branstma *et al*. found that the predictive value of urine albumin excretion for diabetes was modified by the level of C-reactive protein. Urinary albumin excretion predicts the development of diabetes most strongly when the level of C-reactive protein is low[7] No significant interaction between C-reactive protein and urine ACR was observed in our study. This may be due to a relatively small sample size.

Compared with two previous studies [6, 7], this study used a different study design and different measuring method for albuminuria in a different population. However, the findings that the presence of microalbuminuria and macroalbuminuria predicts the future development of diabetes are consistent The association between albuminuria and diabetes is independent of conventional risk factors for diabetes. The presence of microalbuminuria and macroalbuminuria can precede diabetes and independently predict the risk of future diabetes. Improving kidney function is potentially beneficial to preventing diabetes.

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None

Conflict of Interest
None

Ethical Clearance
Taken from Ethical committee of UPUMS, Saifai

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