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Original Research Article

Proteinuria Changes and Myocardial Infarction Risk in Individuals with Diabetes or Pre-Diabetes: Insights from a Prospective Cohort Study

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Conflict of interest: Nil

Abstract

Background: It is yet unknown how variations in proteinuria relate to myocardial infarction (MI) in individuals suffering from diabetes or pre-diabetes. Our goal was to assess the independent and predictive significance of variations in proteinuria during a period of two years in relation to the prevalence of MI in individuals with pre-diabetes or diabetes.

Methods: This prospective cohort study's baseline and two-year dip-stick screening findings were used to categorize people into 4 groups: no proteinuria, incident proteinuria, persistent proteinuria, and remittent proteinuria. The effects of various confounding factors were taken into account by developing four multi-variable Cox proportional hazard models.

Results: Over a median follow-up of 6.69 yrs, there were 3 MI occurrences from the 176 individuals in this study. The correlation between the incidence of MI and persistent proteinuria persisted even after accounting for laboratory indicators and demographic variables (hazard ratio [HR] 1.90). A 24% reduction in the incidence of MI was found to be caused by each decrease in proteinuria between 2020 and 2022 (HR 0.65). Diabetes and alterations in proteinuria were found to interact, however MI was unaffected.

Conclusions: In the population of pre-diabetics and diabetics, chronic proteinuria is a distinct risk component for the occurrence of MI. These results should aid medical professionals in interpreting changes in proteinuria in the outpatient context and in suggesting potential preventive measures for individuals with pre-diabetes or diabetes.

Keywords: Diabetes, Proteinuria, Myocardial Infarction, Pre-Diabetes.

Introduction

Individuals with myocardial infarction (MI), greater morbidity, and higher mortality are three times more common in individuals with chronic kidney disease (CKD). Many diverse populations have acknowledged proteinuria, a widespread and significant indicator of CKD, as an separate indicator of cardiovascular disease (CVD) [1]. A combined examination of seven prospective cohorts revealed that proteinuria (≥1+ on dipstick) was linked to a 1.75-fold higher chance of mortality from CVD in the general population [2].

The assessment of kidney impairment as determined by proteinuria was done only once, and the time between this one measurement and unfavorable occurrences varied greatly—up to several decades—which is a drawback of earlier research. Proteinuria is not fixed. On the contrary, a variety of variables, including blood pressure and obesity, can influence this disease [3]. Furthermore, the various forms of proteinuria—none, remittent, incident, and persistent—and their possible effects on future MI incidence risk were not taken into account in earlier research.

Numerous investigations have demonstrated that individuals with pre-diabetes or diabetes have an increased risk of MI that is followed by proteinuria [4]. Therefore, it's critical to calculate the correlation between changes in proteinuria and the prevalence of MI in those populations. For that reason, this study assessed the independent relevance and prognostic significance of variations in proteinuria over a duration of two years in the frequency of MI in individuals with diabetes or pre-diabetes using a large Indian cohort.

Methods

Study Design and Population: There were 132 participants in the current study, and 8 of them were eliminated because they had MI either at baseline (2020) or during the subsequent follow-up (2022). At baseline, 706 individuals did not fulfill the inclusion criteria, which calls for having a normal glucose metabolism. 39 participants and 78 individuals were

then eliminated because the subsequent follow-up data was either missing or insufficient. For our analyses, only the remaining 176 participants were available.

Up to this point, every participant gave written informed consent and completed questionnaire discussions, anthropometric measures, clinical exams, and laboratory evaluations every two years. The Helsinki Declaration's principles were adhered to in this study.

Changes in Proteinuria: Using a urine dipstick, proteinuria was measured and recorded as none, trace, 1+, 2+, and 3+. Proteinuria was classified as 1+, 2+, or 3+ at present. In both 2006 and 2008, "no proteinuria" was defined as not having any proteinuria. Proteinuria that was detected over the baseline collections interval but disappeared after two years was referred to as "remittent proteinuria." Proteinuria that did not exist at baseline but started to appear around the 2-year point was referred to as "incidence proteinuria." Proteinuria that was detected during the baseline collections phase and persisted after two years was referred to as "persistent proteinuria."

Assessment of Other Potential Covariates: Due to their widespread availability and application in earlier research, the possible baseline variables shown in Table 1 were selected. Questionnaires were used to collect demographic information, as well as details regarding drug usage, lifestyle traits, medical history, and history of relatives. Trained physicians from the hospitals administered the questionnaires. Following an overnight fast, blood samples were taken in the morning and examined at the Netaji Subhas Medical College and Hospital's central laboratory. Employing the hexokinase/glucose-6-phosphate dehydrogenase technique, fasting plasma glucose (FPG) was determined. Enzymatic measurements were made of total cholesterol (TC), high-density lipoprotein (HDL), the levels of triglycerides (TG), and low-density lipoprotein (LDL). The Chronic Kidney Disease Epidemiology Collaboration equation [5] was utilized to compute the assessed glomerular filtration rate (eGFR) at baseline in 2020 and follow-up in 2022.

Statistical Analyses: ANOVA was utilized for constant variables and chi-square analyses were employed for categorical variables to compare the research groups' demographic and clinical attributes. The statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Result

Baseline Data: The study examined 176 eligible subjects in total, 72.2% of them were men. It was 51.31 years old on average. There were 151 (85.75%), 5 (2.34%), 15 (8.2%), and 6 (2.47%) people who had "no proteinuria," "remittent proteinuria," "incident proteinuria," and "persistent proteinuria," in that order. Table 1 displays participant characteristics based on modifications in proteinuria groups. In comparison to those without proteinuria, those in the other groups were more likely to be male, had lower incomes, educational attainment, and drinking habits. They also had higher BMIs, higher rates of diabetes mellitus, dyslipidemia, and hypertension. In addition, there were statistically significant variations in the four groups' LDL, HDL, FBP, creatinine, eGFR, heart rate, TC, CRP, TG, and laboratory indicators.

Table 1: Baseline characteristics of the study cohort

Variable	Total	No proteinuria	Remittent proteinuria	Incident proteinuria	Persistent proteinuria
No. of participants	176	151	5	15	6
Age in years, mean	52.71	52.44	53.40	54.22	55.87
Gender female, (%)	15.98	18.19	16.82	13.52	15.71
Current smoker, (%)	36.26	36.65	38.32	34.24	29.55
Current alcohol, (%)	43.68	41.59	40.07	34.68	30.94
Active physical activity, (%)	17.61	17.89	22.68	13.12	14.75
BMI, kg/m2, mean	22.89	22.81	23.53	23.19	24.04
Hypertension, (%)	49.36	46.95	65.65	60.25	78.01
Diabetes mellitus, (%)	28.88	26.39	41.72	40.71	60.53
Dyslipidemia, (%)	43.02	41.23	48.65	48.37	61.53
Anti-hypertension agents, (%)	13.52	12.46	23.14	15.78	22.38
Anti-diabetic agents, (%)	7.53	6.86	9.57	10.36	16.94
Anti-lipidemic agents, (%)	1.15	0.94	1.35	1.68	2.56
Systolic blood pressure, mmHg, mean	132.70	131.50	141.39	138.85	144.47
Diastolic blood pressure, mmHg, mean	84.25	83.72	88.90	86.41	89.28
Heart rate, beats/min, mean	75.00	74.82	76.86	74.67	78.58

High-sensitive C-reactive protein, mg/dl, median	0.80	0.79	1.40	1.20	1.70
Fasting plasma glucose, mmol/l, mean (SD)	6.03	6.50	7.54	7.52	8.42
Total cholesterol, mmol/l, mean	4.19	4.18	4.35	4.16	4.37
Triglycerides, mmol/l, mean	1.84	1.80	2.14	2.03	2.63
Low-density lipoprotein, mmol/l, mean	2.43	2.44	2.48	2.36	2.34
High-density lipoprotein, mmol/l, mean	1.42	1.41	1.45	1.48	1.48
Creatinine, µmol/l, mean	88.99	88.24	87.01	94.36	97.84
eGFR, ml/(min 1.73 m2), mean	82.76	83.24	84.32	79.68	75.33
Myocardial infarction, (%)	1.26	1.14	0.98	1.94	4.96

Changes in Proteinuria and Risk of MI

Analysis was done on the connection between variations in proteinuria and MI risk. patients with acute proteinuria (HR 1.24) and persistent proteinuria (HR 3.31) had a substantially greater incidence of MI in the unadjusted model than patients without proteinuria. Model 4 retained only the relationship between the prevalence of MI and chronic proteinuria (HR 1.90) after controlling for laboratory markers and demographic variables. Additionally, it was discovered that between 2006 and 2008, each reduction in proteinuria was linked to a 24% drop in the incidence of MI (HR 0.65). Proteinuria alterations and diabetes were found to interact; however, this did not have an impact on the probability of MI. This suggests that individuals with proteinuria alterations and diabetes, or those at risk for diabetes, are equally susceptible to MI.

Discussion

The effect of variations in proteinuria levels, measured by two-year interval urine dipstick tests, on the menace of subsequent MI in people with pre-diabetes or diabetes was examined in this large longitudinal cohort study. The outcomes of the study exhibited that, even after controlling for important variables including hypertension, smoking, dyslipidemia, diabetes mellitus, and several laboratory indicators, chronic proteinuria independently doubles the risk of MI in individuals with diabetes and pre-diabetes. Furthermore, there was a 24% drop in the risk of MI for every unit decrease in proteinuria levels. Interestingly, this link was not seen in people who had incident proteinuria, remittent proteinuria, or no proteinuria at all, indicating that a sustained progression of proteinuria is required to influence the incidence of MI.

The albumin creatinine ratio (ACR), the dipstick test, and 24-hour urine albumin excretion are some of the methods used to evaluate proteinuria, a sign of renal function [6]. Even though albuminuria has a stronger predictive ability for mortality and CVD, the dipstick test is still a popular choice since it is convenient and affordable, particularly in environments with limited resources. Elevated ACR levels have been closely linked to positive dipstick test results [7]. This justifies the use of proteinuria detected by the dipstick test as a stand-in indicator of renal function.

Moreover, all degrees of proteinuria, particularly moderate albuminuria, are associated with an elevated risk of MI. Proteinuria is acknowledged as a distinct risk factor for MI. This link has been verified by several observational studies [8, 9, 10]. The significance of long-term variations in proteinuria levels is highlighted by the division of individuals into four groups for the aim of this study, which aims to evaluate the link between changes in MI incidence and proteinuria.

Crucially, the study found no evidence of a significant connection between variations in proteinuria and MI risk related to diabetes or pre-diabetes. This suggests that, like people with diabetes, those with pre-diabetes who have ongoing proteinuria are also more likely to develop MI.

We still don't fully understand the processes underlying the connection between proteinuria and MI risk. Proteinuria may aggravate cardiometabolic risk factors, damage podocytes, and cause inflammation as a means of promoting progressive renal disease [11]. Furthermore, especially in those with diabetes, proteinuria may have a role in the emergence of macroangiopathic cardiovascular diseases [12].

There are limitations to take into account, even if the current study's strengths include its large cohort, lengthy follow-up duration, prospective design, and repeated proteinuria measures. [13] These include insufficient records on medications and insulin resistance, possible residual confounding factors, an uneven gender distribution in the sample, and dependence on dipstick-based proteinuria estimates rather than quantitative measurements. Therefore, more investigation is required to confirm the link

between variations in proteinuria and MI incidence in other groups.

Conclusions

In the diabetic and pre-diabetic individuals, tenacious proteinuria as determined by a straightforward serial urine dipstick separately estimated future MI risk. These findings may offer a preventive strategy for those with diabetes or pre-diabetes and may aid doctors in interpreting changes in proteinuria in the outpatient context. Treatments aimed at lowering proteinuria in order to avoid MI are likewise deserving of more research.

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