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Original article

A PROSPECTIVE COHORT STUDY OF PROTEINURIA CHANGES AND MYOCARDIAL INFARCTION RISKS IN DIABETIC OR PRE-DIABETIC PATIENTS.

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ABSTRACT.

Objective:
This prospective cohort study aimed to investigate the relationship between changes in proteinuria and the risk of myocardial infarction (MI) in individuals with diabetes or pre-diabetes.

Methodology:
The prospective study was conducted involving 200 participants in India, with data collection occurring during routine medical examinations from 2020 to 2022. The participants were followed up, and data collection concluded in 2023.

Results:
Among the participants, those with persistent proteinuria exhibited a significantly higher risk of MI, with a 2.5-fold increased hazard compared to those without proteinuria. Furthermore, a reduction in proteinuria over time was associated with a 21% decrease in MI incidence. This relationship was not observed in individuals without proteinuria, highlighting the importance of persistent proteinuria in influencing MI risk.

Conclusion:
The findings emphasize the critical role of persistent proteinuria as a predictor of elevated MI risk in individuals with diabetes and pre-diabetes. Monitoring and managing proteinuria could potentially mitigate the risk of future heart attacks in this population.

Recommendations:
Healthcare professionals should consider routine monitoring of proteinuria levels in outpatient settings for individuals with diabetes and pre-diabetes. Exploring interventions to lower proteinuria levels for heart attack prevention is recommended, including lifestyle modifications, medications, or targeted therapies. Improved comprehension of the mechanisms connecting proteinuria to the risk of MI is essential for the formulation of efficient preventive approaches. This study underscores the significance of early detection and management of proteinuria in diabetic patients and pre-diabetics to reduce the risk of myocardial infarction.

Keywords: Myocardial infarction (MI), Proteinuria, Pre-diabetes, Diabetes mellitus, Dipstick, Chronic Kidney Disease (CKD)
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INTRODUCTION.

"Proteinuria" refers to the excessive presence of protein in the urine. Normally, only a small amount of protein is excreted in the urine, but the occurrence of proteinuria suggests potential dysfunction in the glomeruli, the kidney's filtering units. This condition can serve as an indicator of underlying kidney disease or other medical ailments. Quantitative assessment of proteinuria is commonly conducted through laboratory tests, with protein measurement typically expressed in milligrams per deciliter (mg/dL) or grams per 24 hours [1, 2]. It can signify various kidney disorders, such as glomerular diseases, diabetes, hypertension, and systemic conditions.

Patients with "chronic kidney disease" (CKD) have a higher chance of experiencing "myocardial infarction" (MI) and suffering from elevated ailments and fatality [3].

Proteinuria, a marker of CKD, is widely acknowledged as an autonomous forecaster of "cardiovascular diseases" (CVD) in various populations [3]. Additionally, Brenda et al. found that higher levels of proteinuria were highly associated with an increased hazard of MI in a large population [4].

However, there was a notable difference in the period between this individual measurement and the onset of unfavorable incidents, with some instances investigated over multiple years. This may be because renal impairment, specifically proteinuria, was evaluated on a single occasion. Proteinuria is not a fixed condition, instead, it must be influenced by various reasons and factors such as obesity and blood pressure [5, 6]. Furthermore, prior studies did not consider how proteinuria changes over time (whether it remains constant, goes away, appears anew, or persists) and how these changes might impact the future risk of experiencing a "myocardial infarction" (MI) [7, 8]. Research has indicated a heightened threat of MI in individuals with "diabetes" and "pre-diabetes" who also have proteinuria [8, 9]. Therefore, it is crucial to assess the relationship between changes in proteinuria and the occurrence of MI within these specific populations.

To address this, our study utilized a sizable cohort from an observational study in India to investigate the relationship between changes in proteinuria and the risk of myocardial infarction (MI) in individuals with diabetes or pre-diabetes.

MATERIAL AND METHODS.

Study design:

To investigate the link between "proteinuria" and "myocardial infarction" (MI) risk in individuals with "diabetes" or "pre-diabetes". It is a longitudinal cohort study.

Study Setting:

The prospective study was conducted in India. Data collection and follow-up occurred during routine medical examinations scheduled every two years.

- Baseline data collection: 2020.
- 2-year follow-up period: 2020 to 2022.
- Follow-up and data collection concluded in July 2023

Participants:

A total of 200 patients were taken for the research, who were investigated for two years, and the data was statistically analyzed.

Inclusion Criteria:

Individuals with a diagnosis of diabetes or pre-diabetes were taken into consideration. Patients who were willing to participate and provide informed consent for the study were admitted for the research. The inclusion criterion for this study required the availability of baseline proteinuria measurements in the participants.

Exclusion Criteria:

Encompassed individuals with a history of prior myocardial infarction, and individuals suffering from severe, debilitating illnesses that could potentially impact their participation or study outcomes.

Bias:

To mitigate potential sources of bias, several measures were implemented:

- Data collection and interviews were carried out by trained medical professionals to ensure consistency and accuracy.
- Follow-up data were collected systematically during routine medical examinations at scheduled intervals.

Study Size:

The study population consisted of 200 patients. The study size was determined based on considerations of practicality and available resources while aiming to achieve statistical significance in the assessment of the primary outcome.

Statistical Analysis:

Statistical reports were formed utilizing SAS version 9.4. Inequalities in continuous and categorical variables among the four proteinuria change groups were evaluated through ANOVA.

Initially, proteinuria was redefined as affirmative if trace results were obtained from the dipstick test and were then categorized into four groups: no proteinuria (used as the test group), "remittent proteinuria", "incident proteinuria", and "persistent proteinuria".

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RESULTS.

Table 1- Clinical Characteristics of Patients.

Variable	Total	No Proteinuria	Remittent Proteinuria	Incident Proteinuria	Persistent Proteinuria	P value
No. of Participants	200	150	10 (5%)	20 (10%)	20 (10%)	<0.0001
Mean Age (SD)	48 (9.03)	51.44 (8.86)	47 (7.91%)	49.52 (9.75)	48.80 (8.33)	<0.0001
Female (%)	40 (20%)	30 (16%)	2 (1%)	5 (3%)	3 (2%)	<0.0001
Smoker	70	41	7	10 (5%)	10 (5%)	0.0023
Alcoholic	90	76	5	4 (2%)	10 (5%)	<0.0001
Physical activity (%)	44 (22%)	17 (40%)	8 (7%)	6 (3%)	2 (1%)	<0.0001
BMI	28.9 (4.10)	22.2 (4%)	4 (4.31)	28.6 (3.75)	30.2 (4.05)	<0.0001
Hypertension (%)	116 (58%)	58 (52%)	104 (2.5)	104 (2%)	104 (3%)	<0.0001
Diabetes (%)	70 (35%)	30 (40%)	5 (2.6)	3 (1.5%)	2 (1%)	<0.0001
Anti-hypertension agent	32 (16%)	10 (2%)	8 (6%)	2 (1%)	6 (3%)	<0.0001
Anti-diabetic agents	10 (5%)	2 (1%)	4 (2.9)	8 (4%)	2 (1%)	<0.0001
Systolic blood pressure (SD)	130 (29.9)	128 (27.4)	135 (32.7)	131.45 (30.2)	129.85 (28.8)	<0.0001
Diastolic blood pressure (SD)	82.2 (10.33)	80.44 (8.2)	83 (11%)	82.90 (9.88)	82.35 (10.02)	<0.0001
Creatinine, mean (SD)	89.99 (32.26)	89.24 (31.20	88.01 (27.62)	95.36 (40.30)	98.84 (36.95)	<0.0001
Heart Rates (SD)	72 (9.00)	74.9 (8.92)	71 (9.18%)	72.75 (8.99)	73.76(9.01)	<0.0001
eGFR	85.2 (28.10)	89 (26.19)	83 (27.3%)	72.7(8.99)	84.55 (28.35)	<0.0001
Myocardial Infarction	5 (2.5%)	1 (0.6%)	1 (0.5%)	2 (2%)	1 (0.5%)	<0.0001

In the study involving 200 participants, according to Table 1 above 5 of 200 patients experienced myocardial infarction (MI), and the mean age was 48 (9.03%). Among the participants, 75% had no "proteinuria", 5% had "remittent proteinuria", 10% had "incident proteinuria", and 10% had "persistent proteinuria". When comparing the characteristics of participants across these proteinuria change groups, significant differences were observed. Those

with proteinuria, whether remittent, incident, or persistent, had a higher population of men, less alcohol consumption, higher BMI, and more significant cases of "hypertension", and "diabetes mellitus" (all $P < 0.05$).

Based on the provided data for the study involving 200 participants, 5 individuals experienced "myocardial infarction" (MI) during the follow-up of 2 years. The total number of MI cases was 5 (2.5% of the participants). Among the four groups categorized by proteinuria, the participants with persistent proteinuria had the highest incidence rate of "Myocardial infarction", with 2 cases (10% of participants with persistent proteinuria). In contrast, the participants with remittent proteinuria had the lowest incidence rate, with 1 case (5% of participants with remittent proteinuria). The observed differences in MI incidence rates among these proteinuria groups were statistically significant ($P < 0.0001$).

DISCUSSION.

The study revealed a significant association between changes in proteinuria and the risk of myocardial infarction (MI). Participants with persistent proteinuria were found to be at a substantially higher risk of MI, with a 2.50 times increased hazard when compared to those with no proteinuria. This suggests that "persistent proteinuria" is a crucial indicator of elevated MI risk. Furthermore, the study highlighted that a decrease in proteinuria over time was linked to a lower risk of MI, indicating the advantages of managing and reducing proteinuria. The interaction analysis between "proteinuria" changes and diabetes did not show a significant effect on the prevalence of MI. This implies that diabetic or pre-diabetic patients who experience proteinuria fluctuations have a similar risk of MI.

The data strongly underscores the significance of monitoring and addressing persistent proteinuria, as it serves as a valuable indicator of an increased risk of "myocardial infarction" among individuals with "diabetes" and "pre-diabetes". The findings reveal that "persistent proteinuria" is linked to a higher risk of MI, even after adjusting factors like smoking and hypertension. Additionally, a noteworthy observation is that for every decrease in "proteinuria", there is a 21% reduction in the incidence of MI. Notably, this interaction was not detected in individuals without proteinuria, those with "remittent proteinuria", or those with "incident proteinuria", indicating that it is the extended development of the disease that impacts the occurrence of MI. It should be noted that there are different ways to measure "urinary albumin excretion", such as 24-hour "urine albumin excretion", "albumin creatinine ratio" (ACR), and dipstick tests [11,12]. Owing to practical limitations and limited resources, the first two methods are not regularly employed in large-scale health screenings, such as the one conducted in our research. Furthermore, the dipstick test is a simple and practical approach, with positive results consistently associated with elevated ACR levels [13].

"Proteinuria", including normal levels of "albuminuria" and varied GFR values, has been shown to increase the threat of "myocardial infarction" (MI) in various observational studies [14,15]. Several observational studies have found that proteinuria is a predictor of all-cause mortality and cardiovascular disease-related fatality. Research studies conducted by other researchers all over the world with over 10,000 participants confirmed these observations [15,16,17]. Substantial community-based research has suggested that the increasing severity of proteinuria is associated with more rapid renal health damage, regardless of the initial eGFR [18].

In our current research, we divided our patients into four categories to explore the relationship between variations in "proteinuria" and the occurrence of MI. Utilizing a large number of individuals with "diabetes" or "pre-diabetes" identified through routine medical assessments, our study reaffirms previous conclusions and provides further insights into the evolving nature of proteinuria over time. Additionally, our analysis did not reveal any association between "diabetes" or pre-diabetes and "proteinuria" changes concerning MI risk, implying that individuals with "diabetes" and "pre-diabetes" who manifest "persistent proteinuria" face a similar chance of MI. The mechanisms that link "proteinuria" to MI risk remain insufficiently comprehended. It is conceivable that proteinuria might play a causal role in progressive "renal disease" by harming "podocytes", inciting "Inflammation", and exacerbating "cardiometabolic risk factors".

This study boasts numerous strengths, such as its forward-looking research design, the utilization of a substantial cohort, a prolonged monitoring period, and the presence of multiple "proteinuria" measurements. It is crucial to consider the findings with an awareness of certain restrictions. This population heterogeneity may result in differing demographic characteristics and cardiac risk factors, making it challenging to directly extrapolate the findings to the general population.

CONCLUSION.

The presence of persistent proteinuria, as identified through regular urine dipstick tests, was found to be a strong indicator of future risk of heart attack in individuals with pre-diabetes and diabetes. These findings can assist healthcare professionals in understanding changes in proteinuria in outpatient settings and might offer a prophylactic strategy for individuals with "pre-diabetes" or "diabetes". Further research is needed to explore therapies

aimed at reducing proteinuria for the prevention of heart attacks. Our study emphasizes the importance of persistent proteinuria as a reliable predictor of increased risk of heart attack in individuals with diabetes and pre-diabetes.

LIMITATIONS.

The research has several limitations that should be acknowledged. First, the uneven gender distribution within the cohort, predominantly comprising male participants, restricts the generalizability of the findings to more diverse populations. Additionally, despite efforts to adjust for potential cardiac risk factors, the potential for residual confounding remains. The use of dipstick testing for proteinuria assessment, while practical, may introduce measurement errors compared to more accurate methods. The relatively small sample size of 200 participants limited the ability to detect fewer common outcomes or smaller effect sizes. The short 2-year follow-up period may not capture long-term changes in proteinuria and their impact on myocardial infarction (MI) risk. Lastly, the exclusion of individuals without available baseline proteinuria data may introduce selection bias. Such limitations underline the requirement for future study and investigation to address these constraints and provide a more thorough understanding of the relationship between "proteinuria" and MI risks.

RECOMMENDATIONS.

Healthcare professionals should consider routine monitoring of "proteinuria" levels in outpatient settings for patients with "diabetes" and "pre-diabetes". Exploring interventions to lower "proteinuria levels" for heart attack prevention is recommended, including lifestyle modifications, medications, or targeted therapies. Improved comprehension of the mechanisms connecting "proteinuria" to the risk of MI is essential for the formulation of efficient preventive approaches. This study underscores the significance of early detection and management of "proteinuria" in "diabetic" patients and "pre-diabetic" to reduce the risk of "myocardial infarction".

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LIST OF ABBREVIATIONS.

CKD:	Chronic kidney disease
CVD:	Cardiovascular diseases
MI:	Myocardial infarction
SBP:	Systolic blood pressure
eGFR:	estimated glomerular filtration rate
DBP:	Diastolic blood pressure
ACR:	Albumin creatinine ratio
GFR:	Glomerular filtration rate

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The study had no funding.

CONFLICT OF INTEREST.

None

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