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Case Control Study

Comparative analysis of nε-carboxymethyl-lysine, inflammatory markers (IL-6, TNF-α), and nitric oxide: A study on diabetic and non-diabetic coronary artery disease patients

Role of AGEs and Inflammatory Markers in Diabetic CAD Patients

Abstract

BACKGROUND

Coronary artery disease (CAD) is a major cause of death worldwide with India contributing about the one fifth of total CAD deaths. The development of CAD has been linked to the accumulation of Nε-carboxymethyl-lysine (CML) in heart muscle, which correlates with fibrosis.

AIM

This study aimed to assess the impact of CML and inflammatory markers on the biochemical and cardiovascular characteristics of coronary artery disease patients with and without diabetes.

METHODS

We enrolled 200 consecutive CAD patients who were undergoing coronary angiography and categorized them into two groups based on their serum HbA1c levels (group I: HbA1c ≥6.5, group II: HbA1c <6.5). We analyzed the levels of lipoproteins, plasma HbA1c levels, CML, IL-6, TNF-α, and nitric oxide.

RESULTS

Group I (81 males and 19 females) patients had a mean age of 54.2 ± 10.2 years, with mean diabetes duration of 4.9 ± 2.2 years. Group II (89 males and 11 females) patients had a mean age of 53.2 ± 10.3 years. Group I had more severe coronary artery disease, with a higher percentage of patients with triple vessel disease (TVD) and greater stenosis severity in the left anterior descending (LAD) coronary artery compared to Group II. Group I also exhibited a larger left atrium diameter. Group I patients exhibited significantly higher levels of CML, TNF-α, and IL-6 and lower levels of nitric oxide as compared with Group II patients. Additionally, CML shows a significant positive correlation with IL-6 (r = 0.596, P = 0.001), TNF-α (r = 0.337, P = 0.001), and a negative correlation with nitric oxide (r=-4.16, P = 0.001). Odds ratio analysis revealed that patients with CML in the third quartile (264.43-364.31 ng/mL) were significantly associated with diabetic coronary artery disease at unadjusted and adjusted levels with covariates.

CONCLUSION

CML and inflammatory markers may play a significant role in the development of CAD, particularly in diabetic individuals, and may serve as potential biomarkers for the prediction of CAD in both diabetic and non-diabetic patients.

Key Words: Coronary artery disease; Diabetes; Nε-carboxymethyl-lysine; Inflammatory markers; IL-6; TNF-α; Nitric oxide

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Core Tip: The burden of coronary artery disease (CAD) is substantial in India, with its development linked to the accumulation of Nε-carboxymethyl-lysine (CML) in heart muscle, correlating with fibrosis. This study assessed the impact of CML and inflammatory markers on biochemical and cardiovascular characteristics in diabetic and non-diabetic CAD patients. Notably, Group I patients exhibited elevated CML, TNF-α, and IL-6 Levels, along with reduced nitric oxide, compared to Group II. CML levels displayed a significant correlation with IL-6, TNF-α, and nitric oxide. CML's third quartile was associated with diabetic CAD, suggesting its role as a biomarker in CAD prediction for diabetic and non-diabetic patients.

INTRODUCTION

Heart disease, specifically heart failure (HF) and coronary artery disease (CAD), is a major contributor to mortality in both developed and developing countries [1]. The World Health Organization states that most common cause of death is cardiovascular disease, resulting in 17.9 million annual deaths. Subsequently, cancer, chronic respiratory ailments, and diabetes trail behind as cause of mortality [2]. In diabetic individuals with coronary artery disease, inadequate management of blood sugar levels is linked to both hospitalization and mortality. [3]. Diabetes mellitus is a major risk factor for the cause and progression of atherosclerosis [4,5]. Some recent literature evidence suggests that advanced glycation end products (AGEs) play an important role in the acceleration of vascular disease [6]. AGEs are formed from the non-enzymatic reaction of sugars and proteins, leading to oxidative stress, inflammation, and endothelial dysfunction through various mechanisms [7]. In hyperglycemia, the accumulation of AGEs is thought to play a role in the onset of diabetic complications. AGE buildup can modify tissue structure, affecting its properties and making it more resistant to breakdown [8]. One of the major AGEs, Nε-carboxymethyl-lysine (CML) is formed by the non-enzymatic glycation and oxidation of monosaccharides (glucose) and proteins (lysine). The attachment of AGEs to RAGE receptors may result in impaired cellular communication, protein structure and functional alterations, and mitochondrial

malfunction, ultimately resulting in cellular demise. RAGE (Receptor for Advanced Glycation End products) binding can also increase reactive oxygen species (ROS), and stimulate inflammatory signalling tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and it also affect endothelial function by altering nitric oxide levels [9]. Subsequently, new evidence suggested that CML has made a major contribution to the development of coronary artery disease [10]. CML found in heart muscle shows a positive correlation with fibrosis and cardiac disease [11], and promotes hypertrophy, apoptosis, and myocardial fibrosis [12]. Elevated CML levels have been linked to poor collateralization in chronic total occlusion in diabetic CAD patients [13]. Along with coronary artery disease, CML is also significantly associated with many other diseases, like diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and cancer [14].

In this study, we assessed the impact of CML in association with inflammatory markers on biochemical and cardiovascular characteristics in diabetic and non-diabetic coronary artery disease patients. We aimed to gain new insights while exploring the relationship between diabetes and coronary artery disease which may open future prospects for therapeutic intervention in such patients.

MATERIALS AND METHODS

2.1: Study population

This cross-sectional study was conducted at the Department of Biochemistry, G.B. Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, India. We enrolled age and sex matched, consented 200 angiography-confirmed patients diagnosed with coronary artery disease (CAD) from both OPD & IPD of Department of Cardiology. The study was conducted in accordance with internationally accepted recommendations for clinical investigation (the Declaration of Helsinki of the World Medical Association, revised October 2013) with approval from the ethics committee of Maulana Azad Medical College and associated hospitals, New Delhi, India.

2.2: Sample collection

5 mL of venous blood was drawn under aseptic conditions from consented patients. Further, 3 mL sample was transferred to an EDTA vial for glycosylated haemoglobin (HbA1c) and special chemistry analysis and the remaining sample was transferred to a glucose vial for blood sugar analysis. Patients with HbA1c level ≥6.5% or having a previous diagnosis of diabetes were considered as diabetic CAD (group I), while patients with level <6.5% were categorized as non-diabetic CAD (group II). Group II patients with no prior history of diabetes and no history of anti-diabetic medication were classified as non-diabetic CAD. The serum levels of HbA1C were measured by fully automated analyzer whereas the CML, IL-6, TNF-α, and nitric oxide levels were determined by enzyme-linked immunosorbent assay (ELISA) methods.

2.3: Clinical assessment

Independent senior cardiologists utilized the angiographic data from the catheterization laboratory to calculate the severity of CAD using the Gensini scoring (GS) system. The left coronary artery was separated into left anterior descending, circumflex, and obtuse marginal branches, while the right coronary artery was considered a single artery. The lesion score for each coronary segment was multiplied by a location-based factor, and then the scores were added together to calculate the Gensini score.

2.4: Gensini Scoring system

The Gensini score was determined by adding the scores from each coronary segment as follows : one point for 25% stenosis, two points for 26–50% stenosis, four points for 51–75% stenosis, eight points for 76–90% stenosis, sixteen points for 91–99% stenosis, and 32 points for total occlusion. The significance of the lesion's location in the coronary circulation was also considered, with 5 points for the left main coronary artery, 2.5 points for the proximal left anterior descending coronary artery and proximal left circumflex artery, 1.5 points for the mid-left anterior descending coronary artery, 1 point for the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 points for other segments [15].

2.5: Doppler echocardiography examination

A standard two-dimensional, M-mode, and Doppler echocardiography examination was conducted using the Philips EpiQ-7C echocardiography system. The examination measured various parameters including the dimension of the left atrium (LA) and the aortic root (Ao). The left ventricular ejection fraction (LVEF) was also calculated using Simpson's method [16].

2.6: Cardiovascular risk factors assessment

Consented patients over the age of 18 years who were confirmed with the diagnosis of coronary artery disease by resting ECG or coronary angiography with >50% stenosis were included in this study. Blood pressure was measured as an average of two readings recorded at least 5 minutes apart while the participants rested in a seated position. Hypertension was identified when subject was either having a history of hypertension or a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. Patients with total cholesterol (TC) (>200 mg/dL), triglycerides (>150 mg/dL), high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL), or low-density lipoprotein cholesterol (LDL-C) (>100 mg/dL) were defined as having dyslipidemia. Additionally, patients with renal or hepatic impairment, as well as those who had undergone previous therapies such as coronary artery bypass graft surgery or percutaneous coronary intervention were excluded from the study.

Statistical analysis

The statistical programme for social science (SPSS) version 21 (IBM Corp., Chicago, USA) was used to analyze the data. The mean, standard deviation, frequency, and percentage were used to express quantitative and qualitative data, respectively. For quantitative data, an independent t-test was performed to compare two independent variables. The normality of the data must be checked by the Kolmogorov-Smirnov test. Student t-test, ANOVA, and Mann-Whitney U test were used to compare parametric and non-parametric variables. ROC curve analysis has been used for prediction analysis. All statistical tests were carried out at a $p < 0.05$ significance level.

RESULTS

3.1: Demographic characteristics

The mean age of group I was 54.2 ± 10.2 years, while for group II, it was 53.2 ± 10.3 years, P = 0.473. There was male sex preponderance with males constituting 81% in group I and 89% patients in group II. In group I, the duration of diabetes was 4.9 ± 2.2 years. Hypertension was more prevalent in group I (39%) than in group II (20%) (P = 0.001). The median systolic blood pressure was significantly higher in group I (125.50 mmHg; CI: 118-140) compared to group II (120 mmHg; CI: 114-129.50) (P = 0.001). In relation to medications, statin use was 79% in group I and 89% in group II. Beta-blockers were taken by 53 (53%) subjects in group I but 73 (73%) subjects in group II. Only 5 (5%) subjects in group II, compared to 17 (17%) in group I, were taking ACE-inhibitors (Table 1). The ACE inhibitor usage is lower as the drug history was taken just before the cardiac catheterization. Subsequently patients were started on ACE inhibitor once they were stable.

3.2. Cardiovascular characteristics

Group I consisted of 57 patients with single vessel disease (SVD), 27 patients with double vessel disease (DVD), and 8 patients with triple vessel disease (TVD). However, group II had 35 patients with SVD, 36 patients with DVD and 11 patients with TVD. In group I, 8 patients, and in group II, 14 patients had normal angiograms (P = 0.016).

The mean and standard deviation of severity of stenosis in the left anterior descending (LAD) artery weres 90.51% ± 8.51%, in the left circumflex (LCX) artery, 90.91% ± 8.80%, and in the right coronary artery (RCA), 90.32% ± 10.15% in group I. On the other hand, in group II, the mean and standard deviation of stenosis in the LAD were 87.85% ± 12.31%, in the LCX, 82.22% ± 22.33%, and in the RCA, 89.26% ± 12.90%. The Gensini score was higher in group I, with a score of 26 (12–44), compared with group II, with a score of 20 (12-40). Group I had a larger left atrium diameter of 2.93 ± 0.32 cm compared to 2.83 ± 0.39 cm in Group II (P = 0.04). The aortic root diameter was slightly larger in Group I at 2.15 ± 0.39 mm compared to 2.10 ± 0.40 mm in Group II. Further, group I had a mean left ventricular ejection fraction of 45.60 ± 12.04% and group II had a mean ejection fraction of 46.70 ± 12.01%.

The patients were categorized based on their left ventricular ejection fraction (LVEF) in Table 2. In group I, 38% of patients had a preserved EF (LVEF ≥50%), 13% had a mild EF reduction (LVEF 41-49%), and 49% had a reduced EF (LVEF <40%). In group II, 43% of patients had a preserved EF, 14% had a mild EF reduction, and 43% had a reduced EF. The frequency and percentage of patients in groups I and II who experienced different types of cardiac events are as follows: 39% of patients in group I and 39% of patients in group II experienced anterior wall myocardial infarction (AWMI) and 26% of patients in group I and 21% of patients in group II experienced inferior wall myocardial infarction (IWMI).

3.3. Comparison of Biochemical parameters in group I and group II

The total cholesterol, triglycerides levels and very-low density lipoprotein levels were found to be significantly higher in group I compared to group II (P = 0.006, P = 0.001 and P = 0.001 respectively). Further, both HbA1c and the blood sugar levels were found to be significantly higher in group I compared to group II (P = 0.001). The abovementioned intergroup comparison between biochemical parameters has been shown in Table 3.

3.4. Association of CML, IL-6, TNF-α, and nitric oxide between group I *vs* group II

The comparison of CML, IL-6, TNF-α, and nitric oxide between group I *vs* group II (Figure 1A-1D) showed significant difference between the two groups: serum CML (264.43, 95%CI: 193.19-364.34 *vs* 250.68, 95%CI: 195.95-333.70, P = 0.031), IL-6 (2.75, 95%CI: 1.36-5.50 *vs* 2.36, 95%CI: 1.23-3.6, P = 0.011), TNF-α (20.2, 95%CI: 13.65-25.32 *vs* 15.67, 95%CI: 11.137-21.785, P = 0.006), and nitric oxide (87.09, 95%CI 59.84-124.37 *vs* 110.86, 95%CI: 77-150, P = 0.002).

3.5. Association of lipid parameters between Group I and Group II

Table 1 shows the lipid profile of individuals in Group I and Group II. In group I, 17% of individuals had high total cholesterol levels (>200 mg/dL), whereas group II had a lower proportion of individuals with high total cholesterol levels (8%). The difference between the groups was significant, with a p-value of 0.043. Regarding triglyceride

levels, 49% of individuals in Group I had high levels (>150 mg/dL), while 51% had normal levels (<150 mg/dL). In Group II, a significantly lower proportion of individuals had high triglyceride levels (24%), and a significantly higher proportion had normal levels (76%), with a p-value of 0.001. Regarding HDL levels, a higher proportion of individuals in Group I had low levels (<40 mg/dL) of HDL (86%), compared to those with normal levels (>40 mg/dL) (14%). In contrast, Group II had a lower proportion of individuals with low HDL levels (73%) and a higher proportion with normal levels (27%), P = 0.017. With respect to LDL-C levels, 70% of individuals in Group I had normal levels (<100 mg/dL), while 30% had high levels (>100 mg/dL). In Group II, 80% of individuals had normal LDL-C levels and 20% had high levels, P = 0.094.

3.6. Correlation and logistic regression analysis between CML, inflammatory markers and lipid parameters

In the correlation analysis, CML exhibited significant positive correlations with IL-6 (r = 0.596), TNF-α (r = 0.337), total cholesterol (r = 0.21), HbA1c (r = 0.14), and the Gensini score (r = 0.19) in the combined data from both group I and group II. When comparing the correlations of CML between the two groups (group I vs. group II), IL-6 (r = 0.502 vs. r = 0.673), TNF-α (r = 0.256 vs. r = 0.436), and nitric oxide (r = -0.484 vs. r = -0.283) were significant (Table 5). The linear regression analysis of CML revealed significant positive associations with IL-6 (r^2 = 0.181, P = 0.001), TNF-α (r^2 = 0.142, P = 0.001), total cholesterol (r^2 = 0.056, P = 0.001), HbA1c (r^2 = 0.057, P = 0.001), and the Gensini score (r^2 = 0.027, P = 0.02). Additionally, CML showed a significant negative association with nitric oxide (r^2 = 0.163, P = 0.001) (Figure 2 (A-F)).

The association between quartiles of Nε-carboxymethyl-lysine (CML) and diabetic coronary artery disease is revealed by logistic regression analysis, while accounting for various covariates in separate models (Table 6). The first quartile of CML (83.73-193.18 ng/mL) serves as the reference category. In the unadjusted model, the third quartile (264.43-364.31 ng/mL) had an odds ratio of 2.12 (95%CI 1.17-3.85, p <0.01). Following adjustments for non-vegetarian diet and hypertension (model 2), the odds ratio for the third quartile rose to 3.05 (95%CI 1.31-7.06, P = 0.01). Furthermore, upon introducing

further adjustments in Model 3, encompassing total cholesterol, triglycerides, LDL-C, IL-6, and TNF-α, the odds ratio for the third quartile becomes 3.32 (1.30-8.44, P = 0.01), while retaining its statistical significance.

DISCUSSION

Nε-carboxymethyl-lysine (CML) is an advanced glycation end-product involved in the pathogenesis of cardiovascular diseases (CVD) [17]. Recent studies have demonstrated that CML is linked to endothelial and cardiac dysfunction, left ventricular diastolic dysfunction, and an increase in carotid intima-media thickness, which is a subclinical marker of atherosclerosis in patients with type 2 diabetes [18]. In our cross-sectional study, we found an association between CML, inflammatory markers and nitric oxide in both diabetic and non-diabetic coronary artery disease patients.

In our study, we observed that group I had a significantly higher frequency of risk factors including non-vegetarian diet intake, smokers, and hypertensive individuals. Further, we observed that group I had a higher number of individuals with SVD and a greater severity of stenosis in the LAD and LCX coronary arteries. Similar to previous studies we found that the LCX was found to be the most affected artery in diabetic patients, followed by the LAD and the RCA. However, in non-diabetic patients, the LAD was found to be the most affected [19]. Further, we observed that in group I, the diameter of the left atrium was significantly higher suggesting the chronicity of the disease. The incidence of anterior wall myocardial infarction (AWMI) was similar in both groups; the frequency of inferior wall myocardial infarction (IWMI) was higher in group I than in group II. The left ventricular ejection fraction was decreased in both the groups. It has been reported previously that lower LVEF is common in diabetic CAD patients [20].

In the comparison of the biochemical profile, our study found that diabetic CAD patients exhibited significantly higher levels of total cholesterol, triglycerides, VLDL, HbA1c, and potassium levels as well as significantly lower levels of HDL-C and serum sodium compared to non-diabetic CAD patients (Tables 2 and 3). Additionally, we

observed that the serum levels of CML, TNF-α, and IL-6 were significantly higher, while the serum levels of nitric oxide were significantly lower in diabetic CAD patients. Similarly, Banach *et al* (2022) *et al* suggested that dyslipidemia is a common occurrence among diabetic CAD patients and that individualized lipid-lowering therapy can effectively reduce associated complications and risks [21]. Zhao *et al*(2023) suggested that patients with acute decompensated heart failure who had potassium levels outside the range of 3.50 to 4.00 mmol/L, lower levels of sodium, and hypochloremia had a worse short-term prognosis. There was also a positive correlation between the number of electrolyte imbalances and an adverse short-term prognosis among these patients [22]. Similarly, Ahmed *et al*(2007)found that elevated CML levels have been linked to the development of ischemic heart disease in patients with type 2 diabetes [23]. Koshino *et al* (2022) suggested that increased levels of inflammatory markers (IL-6 and TNF-α) from their baseline increase the risk of cardiovascular disease and are associated with long-term cardiovascular mortality and cardiovascular death [24]. Similarly, Adela *et al* (2015) *et al* in 2015 found lower nitric oxide levels in subjects suffering from diabetes for more than 5 years [25].

Further, in correlation analysis (table 5), overall, CML was positively correlated with the Gensini score, IL-6, TNF-α, total cholesterol, LDL, and HbA1c, and negatively correlated with nitric oxide and HDL. In Group I, CML showed a positive correlation with IL-6, TNF-α, total cholesterol, and LDL-C, and a negative correlation with nitric oxide. Furthermore, in Group II, CML shows a positive correlation with the Gensini score, IL-6, and TNF-α, and a negative correlation with nitric oxide. Similarly, Kerkeni *et al* (2014) suggested that the serum concentrations of advanced glycation end-products (CML and pentosidine) are significantly elevated in patients with coronary artery disease. Furthermore, serum pentosidine levels are independently associated with occurrence of CAD with odds of 1.52. Additionally, the optimal cutoff value for pentosidine to predict the presence of CAD was found to be 3.2 µmol/mol [26]. Gaens *et al* (2009) suggested that CML upregulates RAGE-dependent inflammatory responses and increases serum IL-6 Level and TNF-α, which are negatively associated with serum

nitric oxide and a high BMI rate [27]. Further in logistic regression analysis we found the CML level (264.43-364.31 ng/mL) significantly increases the risk of diabetic coronary artery disease. Similarly, Semba et al. (2008), suggested that in non-diabetic subjects, serum CML was associated with anemia (OR 1.33, 95% CI 1.03-1.72, p =0.029) in a multivariate logistic regression model, adjusting for age, sex, race, smoking, coronary heart disease, heart failure, and renal insufficiency [28]. Kralev *et al* (2009)., suggested that a cut-off value of CML >9.5 AU/mg protein was associated with an odds ratio of acute myocardial infarction of 39.7 [29].

CONCLUSION

In conclusion, this study provides evidence for the association of CML and inflammatory markers with coronary artery disease in diabetic and non-diabetic patients. The results suggest that CML, IL-6, and TNF-α may be potential biomarkers for the prediction of coronary artery disease in diabetic patients, while nitric oxide may be a potential biomarker for the prediction of coronary artery disease in non-diabetic patients. These findings have significant clinical implications for the early diagnosis and management of coronary artery disease, particularly in diabetic patients who are at higher risk for developing cardiovascular complications. Further research on larger cohort is needed to validate these findings and explore the underlying mechanisms of CML and inflammatory markers in the development of coronary artery disease which may be helpful developing therapeutic interventions further.

ARTICLE HIGHLIGHTS

Research background

Coronary artery disease (CAD) is a widespread global health issue, responsible for a significant number of deaths. India, in particular, bears a substantial burden, contributing to approximately one-fifth of CAD-related fatalities. The development of CAD has been closely linked to the accumulation of Nε-carboxymethyl-lysine (CML) in

the heart muscle, a phenomenon associated with fibrosis. Understanding the role of CML in CAD development is crucial for combating this life-threatening condition.

Research motivation

This study is motivated by the need to shed light on the factors contributing to CAD, especially in the context of diabetes. CAD is a complex disease, and understanding its underlying mechanisms can help in early diagnosis and more effective management. Diabetes is a significant risk factor for CAD, and investigating the interplay between CML, inflammatory markers, and CAD in individuals with and without diabetes can provide valuable insights into its pathogenesis.

Research objectives

The primary objective of this research was to evaluate the impact of CML and inflammatory markers on the biochemical and cardiovascular characteristics of CAD patients, differentiating between diabetic and non-diabetes mellitus patents . The study aimed to identify potential links between CML, diabetes, and CAD, and to assess if these factors could serve as predictive biomarkers.

Research methods

To achieve these objectives, the research enrolled 200 consecutive CAD patients undergoing coronary angiography. The patients were categorized into two groups based on their serum HbA1c levels, with Group I having HbA1c levels of ≥6.5 and Group II with HbA1c levels <6.5. Various parameters, including lipoprotein levels, plasma HbA1c levels, CML, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and nitric oxide levels, were analyzed to assess the differences between the two groups.

Research results

The study revealed several significant findings. Group I, comprising 81 males and 19 females, had a mean age of 54.2 ± 10.2 years, with a mean diabetes duration of 4.9 ± 2.2

years. Group II, consisting of 89 males and 11 females, had a mean age of 53.2 ± 10.3 years. Group I exhibited more severe coronary artery disease, with a higher percentage of patients suffering from triple vessel disease (TVD) and more severe stenosis in the left anterior descending (LAD) coronary artery compared to Group II. Group I patients also had a larger left atrium diameter.

Significantly, Group I patients displayed higher levels of CML, TNF-α, and IL-6 and lower levels of nitric oxide compared to Group II patients. The study also demonstrated strong correlations between CML and inflammatory markers, with CML showing a significant positive correlation with IL-6 (r = 0.596, P = 0.001), TNF-α (r = 0.337, P = 0.001), and a negative correlation with nitric oxide (r=-4.16, P = 0.001).

Odds ratio analysis indicated that patients with CML in the third quartile (264.43-364.31 ng/mL) were significantly associated with diabetic coronary artery disease at both unadjusted and adjusted levels when considering various covariates.

Research conclusions

The research concludes that CML and inflammatory markers, particularly IL-6 and TNF-α, may play a significant role in the development of CAD, especially in individuals with diabetes. These findings suggest that CML and inflammatory markers can serve as potential biomarkers for predicting CAD, not only in diabetic patients but also in non-diabetic individuals. Understanding the mechanisms linking CML and inflammation to CAD provides valuable insights for improved CAD diagnosis, risk assessment, and management, which can ultimately contribute to reducing the burden of this life-threatening disease.

Research perspectives

Future studies should explore interventions targeting CML and inflammatory markers to mitigate CAD risk. Investigating therapeutic strategies and diagnostic tools based on these biomarkers can aid in early CAD detection and personalized treatment, potentially reducing CAD-related mortality rates globally.

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