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ABOUT COVER

Peer Review of *World Journal of Diabetes*, Da-Feng Liu, MD, Doctor, Professor, The First Ward of Internal Medicine, Public Health Clinical Centre of Chengdu, Chengdu 610061, Sichuan Province, China. ldf312@126.com

AIMS AND SCOPE

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EDITORIAL

Nε-carboxymethyl-lysine and inflammatory cytokines, markers and mediators of coronary artery disease progression in diabetes

Sonia Eiras

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Abstract

This editorial refers to the article "Comparative analysis of Nε-carboxymethyl-lysine and inflammatory markers in diabetic and non-diabetic coronary artery disease patients", published in the recent issue of the *World Journal of Diabetes* 2023 is based on glucose metabolism, advanced glycation end products (AGEs), inflammation and adiposity on diabetes and coronary artery disease (CAD). This study has included CAD patients who were stratified according to glycosylated hemoglobin higher than 6.5 and sex-matched. A higher prevalence of hypertension, dyslipidemia, and non-vegetarian diet were found in the diabetic group. These risk factors might influence body weight and adiposity and explain the increment of the left atrium. Although this data was not supported by the study. The diet can also explain the non-enzymatic reactions on lipids, proteins, or nucleic acids and consequently an increment of AGEs. These molecules can emit fluorescence. However, one of the non-fluorescent and most abundant AGEs is Nε-carboxymethyl-lysine (CML). Its association with coronary artery stenosis and severity in the diabetic group might suggest its role as a player in CAD progression. Thus, CML, after binding with its receptor (RAGE), can induce calcification cascade through reactive oxygen species and mitogen-activated protein kinase. Moreover, this interaction AGE-RAGE can cause activation of the transcription nuclear factor-kb and induce inflammatory cytokines. It might explain the relationship between CML and pro-inflammatory cytokines in diabetic and CAD patients. Although this is a population from one center, the determination of CML and inflammatory cytokines might improve the diagnosis of severe and progressive CAD. Future and comparative studies among glycosylated hemoglobin, CML, and other AGE levels according to diagnosis and prognosis value might modify the clinical practice. Although these molecules are irreversible, they can act through a specific receptor inducing a signal transduction that might be modulated by inhibitors, antibodies, or siRNA. Further mechanistic studies might improve the development of future preventive therapies for diabetic patients.

Key Words: Nε-carboxymethyl-lysine; Inflammatory cytokines; Adiposity; Diabetes; Coronary artery disease

Core Tip: Coronary artery disease (CAD) is associated with 17.8 million deaths annually and nearly 30% have diabetes with insulin resistance. This metabolic disorder increases the circulating glucose levels that allow the non-enzymatic modifications of proteins, lipids, nucleic acids, *etc*. and form advanced glycation end products (AGEs). Glycosylated hemoglobin is considered a diagnostic marker for diabetes and a risk factor for CAD. However, AGEs through its receptor (RAGE) might increase signal transduction and consequently, inflammatory cytokines, and endothelial dysfunction and be markers and mediators of CAD.

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INTRODUCTION

Cardiovascular disease and obesity and type 2 diabetes mellitus

Cardiovascular disease (CVD) is the major cause of mortality and affects 32% of patients with type 2 diabetes mellitus (T2DM)[1]. This disorder is linked to obesity and a reduction of insulin signaling in cells[2]. Obesity is associated with an increment of stored energy on adipocytes that develop hypertrophy[3] and increase the inflammatory cells' attraction.

Dysfunctional epicardial fat

Computerized tomography (CT) of coronary arteries with suspected coronary artery disease (CAD) determined an accumulation of adipose tissue around them[4]. However, in patients with diabetes type 1 or 2, this association was not so clear[5]. Recently, artificial intelligence allowed us to find improved predictive models for CAD based on multi-variables (clinical, image, biochemical, *etc*.) such as epicardial fat quantity, measured by CT, and diabetes. Both factors are CAD risk factors[6]. However, this fat tissue also expresses or releases differential molecules in patients with diabetes[7,8]. The failure of the adipocyte's function enhances circulating glucose levels that modify and reduce proteins, lipids, or nucleic acids in a non-enzymatic reaction[9].

Advanced glycation end products and CAD

The name of these products is advanced glycation end products (AGEs) and Nε-carboxymethyl-lysine (CML), Nε-carboxyethyl-lysine, pyrraline, crossline, pentosidine, imidazolium cross-link derived from glyoxal and lysine-lysine, and imidazolium cross-link derived from methylglyoxal and lysine-lysine are some of them[10]. CML is one of the most common AGEs and can be processed from food, such as milk, bakery products, and coffee[11]. The study CORDIOPREV showed higher CML levels in those patients with established endothelial dysfunction in comparison with new T2DM [12]. But also circulating levels of AGE were associated with coronary artery calcification[13]. The preclinical atherosclerosis murine models showed that CML might increase the calcification of the plaques through muscle cell effects[14]. The AGE-RAGE signaling can activate secondary messengers (protein kinase C, mitogen-activated protein kinase, and nuclear factor kappa b)[15]. All of them are involved in proliferation or inflammation pathways. But, CML through CD36 can also enhance the macrophage-derived foam cells[16]. These findings suggested that CML can also be a mediator of CAD in patients. The results showed by Shrivastav *et al*[17] showed the association between CML and inflammatory cytokines in patients with and without diabetes. Thus, the peptides that block the RAGE pathways might be a therapeutic alternative against the proliferation and inflammation effects of CML[18]. Its quantification on patients with high risk for CAD might improve personalized medicine. The knowledge of how adiposity and non-vegetarian diet contribute to CML levels might help us to modify primary preventive strategies with consequences on CAD events.

CONCLUSION

This study contributes to the knowledge of biomarkers and therapeutic targets for diabetic patients and the identification of the phenotype with a higher risk for CAD events. This is a new avenue of personalized medicine (Figure 1).

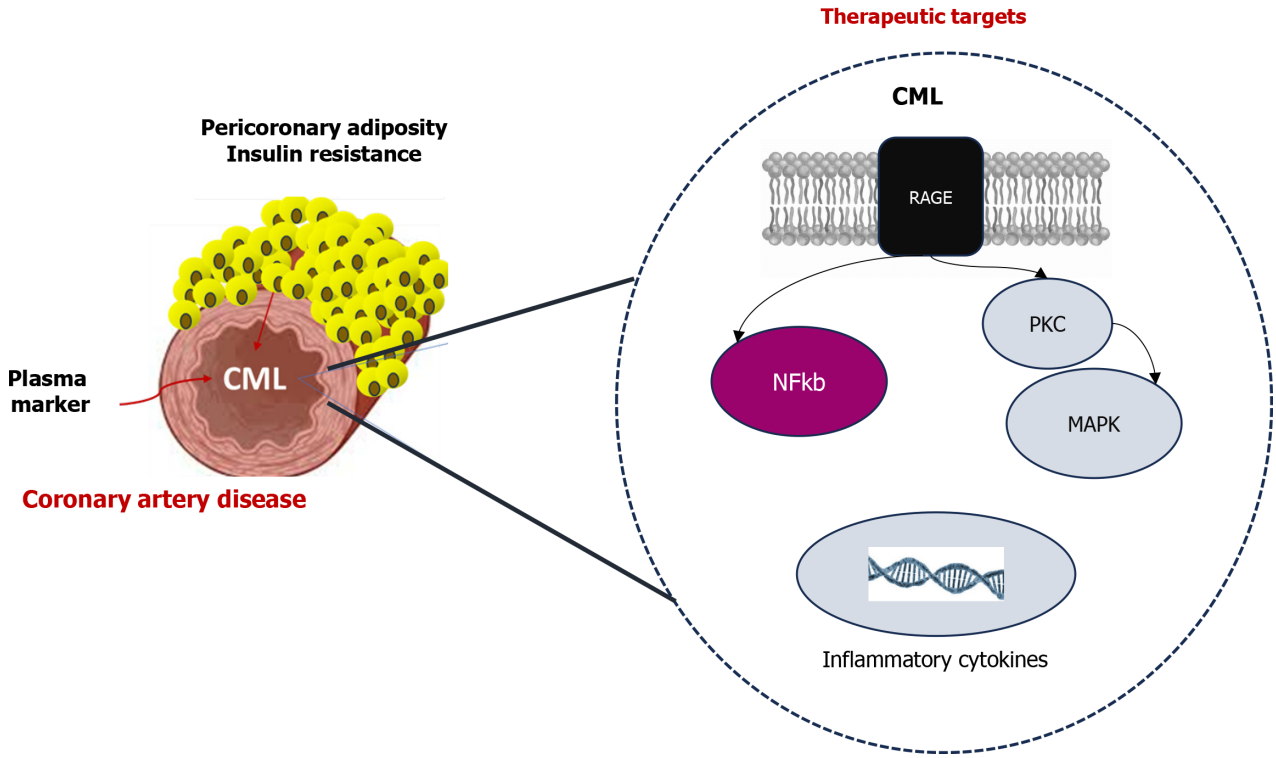

Figure 1 A summary of Nε-carboxymethyl-lysine signals transduction effects on cells. The Nε-carboxymethyl-lysine (CML) levels can be induced by an increment of adiposity, insulin resistance, and consequently, circulating glucose levels that modify molecules in a non-enzymatic way. It provokes the advanced glycation end products and CML is one of the most prevalent. But the increment of its levels might be also induced by diet. High levels of CML are markers for coronary artery disease risk. CML can also induce signal transduction and be involved in a pathological mechanism through activation of protein kinase C, mitogen-activated protein kinase, or nuclear factor kappa b, causing muscle cell proliferation or inflammatory cytokines transcription, respectively. CML can be a marker and therapeutic target. CML: Nε-carboxymethyl-lysine; PKC: Protein kinase C; MAPK: Mitogen-activated protein kinase; NFkb: Nuclear factor kappa b.

FOOTNOTES

Author contributions: Eiras S contributed to this final scientific letter.

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