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

AGEs, inflammation and adiposity in diabetic CAD

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Abstract

This editorial refers the article "Comparative analysis of Nε-carboxymethyl-lysine and inflammatory markers in diabetic and non-diabetic coronary artery disease patients", nº87664, 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 glycosylated hemoglobin higher than 6.5 and sex-matched. Higher prevalence of hypertension, dyslipidemia and non-vegetarian diet were found on diabetic group. These risk factors might influence on body weight and adiposity and explain the increment of 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 AGE is Nϵ -carboxymethyl-lysine (CML). Its association with coronary artery stenosis and severity on diabetic group might suggest its role as player on CAD progression. Thus, CML,

after binding with its receptor (RAGE), can induce calcification cascade through reactive oxygen species (ROS) and mitogen-activated protein kinase (MAPK). 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 on 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 AGEs levels according 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 which might be modulated by inhibitors or 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.

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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 risk factor for CAD. However, AGEs through its receptor (RAGE) might increase a signal

transduction and consequently, inflammatory cytokines, endothelial dysfunction and be markers and mediators of CAD.

INTRODUCTION

CVD and obesity and T2DM

Cardiovascular disease (CVD) is the major cause of mortality and affects to 32% of patients with type 2 diabetes mellitus (T2DM) [1].This disorder is linked to obesity and a reduction of insulin signaling on 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 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 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 failed of the adipocytes function enhances circulating glucose levels that modify and reduce proteins, lipids or nucleic acids in a non-enzymatic reaction[9].

AGEs and CAD

The name of these products is advanced glycation end products (AGEs) and Nϵ -carboxymethyl-lysine (CML), Nϵ -carboxyethyl-lysine (CEL), pyrraline, crossline, pentosidine, imidazolium cross-link derived from glyoxal and lysine-lysine (GOLD), and imidazolium cross-link derived from methylglyoxal and lysine-lysine (MOLD) are some of them[10]. CML is one of the most common AGEs and can be proceed from food, such as milk, bakery products, and coffee[11]. The study CORDIOPREV showed higher CML levels in those patients with established and endothelial dysfunction in comparison with newly type 2 diabetes mellitus (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 cells effects[14]. The AGE-RAGE signaling can activate secondary messengers (protein kinase C, MAPK and NFkb)[15]. All of them are involved on proliferation or inflammation pathways. But, CML through CD36 can also enhance the macrophages-derived foam cells [16]. These findings suggested that CML can also be a mediator of CAD. The peptides that block the RAGE pathways might be a therapeutic alternative for against proliferation and inflammation effects of CML[17]- Its quantification on patients with high risk for CAD might improve the personalized medicine. The knowledge of how adiposity and non-vegetarian diet contributes 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 identification of the phenotype with higher risk for CAD events.

This is a new avenue of personalized medicine.

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