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RESEARCH HIGHLIGHT

The role of oxidative stress in renal injury related to obesity

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The mechanisms linking obesity to kidney damage are unknown. AGEs are responsible for renal damage in obese individuals. The receptor AGEs (RAGE) contributes to nuclear transcription factors that result in the production of proinflammatory cytokines and this seems to contribute to the development of renal disease. Thus, intervention with antioxidant can have an important effect in the prevention and treatment of pro-oxidant and pro-inflammatory state in the kidneys resulting from obesity.

Keywords: Obesity; kidney; oxidative stress; AGEs; RAGE; inflammatory markers

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Introduction

Obesity is a chronic disease that increases the risk of mortality and reduced life expectancy, especially for presenting various comorbidities such as type 2 diabetes, dyslipidemia, insulin resistance and hypertension. Kidney is also a target organ of obesity, which can be damaged resulting in dysfunction of this organ even in the absence of hypertension or diabetes [1-3], suggesting that different pathogenic mechanisms are at work in diabetic nephropathy.

Renal changes may occur early and are associated with increased inflammatory activity with production of cytokines, oxidative stress, lipotoxicity and hemodynamic factors [4]. The different mechanisms of renal injury due to an increase in pro-inflammatory cytokines, oxidative stress and hyperfiltration can cause dysfunction of the glomerular capillary endothelium cells, mesangial cells or podocytes, and tubular interstitial cells.

The increase in free fatty acids, the result of a high calorie diet, increases the generation of free radicals, leading to endothelial dysfunction, albuminuria and inadequate response to vasodilators. The action of these mediators may affect the kidney podocytes, which are visceral epithelial cells of the kidneys, a major component of the glomerular filtration barrier. They are responsible for restricting the passage of proteins from blood to the urinary space However, these abnormalities are reversible with weight loss [5]. Positive correlation between albuminuria and body weight and body mass index has been found in diabetics as well as in non-diabetic subjects [6-8].

Oxidative stress as a mechanism of kidney damage

One contributor to the development of renal complications is an excess of nutrients, which causes oxidation and generates reactive species. In physiological conditions, there is a balance between pro-oxidants and antioxidants; the oxidative stress occurs when the production of pro-oxidants exceeds antioxidant defense [9]. Thus, lipid (lipoxidation) and glucose (glycation) oxidation generate compounds like malondialdehyde, glyoxal, acrolein, 4-hydroxy-nonenal (HNE) (products of lipoxidation) and methyl glyoxal and glyoxal (glycation products). These substances are highly reactive and exhibit high affinity with the amino acids, producing advanced glycation end products (AGEs) [10]. Because of their abundance in the circulation these products end up in up several organs, including the kidney. This exposure may be a significant factor in damaging kidney tissue [11].

In addition to these products causing damage, there is another mechanism that results in injury to the kidney. AGEs can bind to specific receptors called receptors of glycation end products (RAGE) that are expressed in different tissues [12], among them the kidney [13].

The binding of AGEs to RAGE initiates a signal transduction cascade of events involving kinases, which culminates in the activation of Ikkβ/NFkB, nuclear factors responsible for production of pro-inflammatory cytokines [14]. In addition, this binding stimulates the glomerular mesangial cell to synthesize matrix components of type IV collagen, resulting in thickening of the basal glomerular membrane and loss of function [15-17].

Initially, the relation of the RAGE receptor to renal dysfunction was associated with the presence of diabetes (12), as these patients showed an increased expression of this receptor in podocytes. Furthermore, in an experimental study with RAGE knockout rats treated with alagebrium, which reduces advanced glycation end products, a decrease in migration factor for monocytes-1 (MCP-1) and superoxide was observed, besides the reduction in albuminuria and improvements in renal function, the inflammatory profile and oxidative stress [18]. This shows that RAGE are also involved with renal dysfunction related to obesity independent of elevated blood glucose.

However we can infer that the AGE/RAGE interaction triggers inflammation in tissues expressing this receptor, and may represent the interface between oxidative stress and the inflammatory state.

Antioxidants as therapy

Since oxidative stress is a key component in the pathogenesis of the complications of obesity and its comorbidities, new treatment with antioxidants have been tested in order to alleviate the oxidative stress [19]. Several observational epidemiological studies have shown that diets rich in antioxidants from fruits and vegetables are beneficial in reducing the risk of chronic disease [20, 21]. Thus, it is likely that antioxidant nutrients found in these foods can prevent damage caused by free radicals.

Several experimental and human studies involving supplementation of antioxidants to prevent oxidative and systemic inflammatory action in the obese have also been conducted [10, 14, 22-25], but there are few studies regarding the beneficial effect of antioxidants in improving renal dysfunction in obesity. Orsolic and colleagues [26] studied the effect of propolis and epigalocatequinagalato, a component of green tea, in diabetic rats and found that these compounds reduced malondialdehyde levels in the kidneys of the animals. Another study evaluating the antioxidant effect of a herb "Oenanthe javanica" originating in Asia found that its use increased the amount of antioxidant enzymes in the kidney of rats, suggesting that the use of a systemic antioxidant could be a strategy to reduce renal oxidative stress [27]. They further showed the protective effect of quercetin on the nephrotoxicity attributed to valproic acid, an anticonvulsant drug [28]. Urios and colleagues [29] reported an inhibition of the formation of AGEs, with consequent decrease in albuminuria, with supplementation of flavonoids in diabetic rats.

A study conducted by our group tested the effect of supplementation with lycopene on inflammatory and oxidative changes in obese rat kidneys. The animals in this study were at an early stage of obesity, as yet without comorbidities, and had biochemical variables, hemodynamic and renal function similar to the controls. Treatment with lycopene decreased systemic lipid peroxidation and renal expression of the receptor for AGEs (RAGE). The anti-inflammatory action was reflected in decreased renal TNF-alpha [30].

The increase in obesity worldwide demands therapeutic actions in order to prevent or attenuate its pro-oxidant and pro-inflammatory effects. Based on this review we found that the use of antioxidants to inhibit the oxidative stress has been used in the prevention of diseases and complications of obesity, showing the ability to reduce albuminuria and modulate inflammatory markers expressed in the kidney, helping to improve renal dysfunction. Although clinical studies are required to investigate the potential use of antioxidants in obesity to alleviate oxidative stress and inflammation in the kidney and whether this may contribute to reducing dysfunction in this organ, to date, encouraging lifestyle changes that contribute to reducing body fat and strict control of comorbidities are still the most common recommendations.

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Conflicts of interest

The authors have declared that no competing interests exist.

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