Resveratrol on the Cardiovascular Health

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Cardiovascular disease (CVD) is closely related to chronic kidney disease (CKD), and patients with CKD have a high risk of CVD-related mortality. Traditional CVD risk factors cannot account for the higher cardiovascular risk of patients with CKD, and standard CVD interventions cannot reduce the mortality rates among patients with CKD. Nontraditional factors related to mineral and vitamin-D metabolic disorders provide some explanation for the increased CVD risk. Non-dialyzable toxins, indoxyl sulfate (IS) and p-cresol sulfate (PCS)—produced in the liver by colonic microorganisms—cause kidney and vascular dysfunction. Plasma trimethylamine-N-oxide (TMAO)—a gut microbe-dependent metabolite of dietary L-carnitine and choline—is elevated in CKD and related to vascular disease, resulting in poorer long-term survival. Therefore, the modulation of colonic flora can improve prospects for patients with CKD. Managing metabolic syndrome, anemia, and abnormal mineral metabolism is recommended for the prevention of CVD in patients with CKD. Considering nontraditional risk factors, the use of resveratrol (RSV), a nutraceutical, can be helpful for patients with CVD and CKD. Resveratrol is a possible therapeutic option for patients with CKD with or without CVD. In this regard, RSV can influence the traditional and nontraditional CVD risk factors and alleviate the effects of uremic toxins in patients with CKD.

resveratrol, CKD, CVD, uremic toxin

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). The strong causality between CKD and CVD risk means that preventing the progression of CKD can also prevent CVD. In patients with CKD, increased CVD risk is multifactorial, and a targeted intervention for a single traditional risk factor is inadequate. Therefore, research on innovative therapeutic strategies and CVD risk factors is essential [1]. We evaluated traditional and nontraditional risk factors of CVD in CKD and analyzed their relationship. Nutraceuticals are derived from foods and have been demonstrated to have physiological benefits, establishing them as likely the most suitable option for preventing CVD in patients with CKD.

Resveratrol (RSV), a nutraceutical, is a naturally occurring polyphenol that can be found in red wine and grapes [2]. Reports have indicated that it is beneficial for treating or preventing CVD by improving metabolic syndrome components [3][4]. Moreover, RSV reduces the amount of plasma protein-bound uremic toxins and trimethylamine-N-oxide (TMAO) levels by maintaining balance in the gut microbiota [5]. RSV has been demonstrated to be safe and tolerable in humans. This overview focuses on how RSV can influence traditional and nontraditional

cardiovascular risk factors and provide beneficial effects by attenuating the effect of uremic toxins in patients with CKD.

2. Relationship between CVD and CKD

The traditional risk factors common for CVD and CKD are advanced age, hypertension, diabetes, dyslipidemia, smoking habit, family history of CVD or CKD and male sex. Toxic metabolites produced during uremia, such as indoxyl sulfate (IS), account for most cases of CVD in patients with CKD. Changes in how these chemicals are metabolized constitute nontraditional risk factors [6][7]. Other nontraditional factors, including TMAO, accumulate in patients with CKD and aggravate CVD. In addition, dysregulation of calcium, phosphorus, PTH or vitamin D metabolism was evaluated.

Screening and testing in the early stages of CKD can aid the development of interventions that can delay disease progression. In fact, the focus of treatments and interventions should be shifted to the early stage of CKD because early identification through screening may substantially attenuate the impact of CKD and delay or even prevent its development [8].

3. Effect of Nontraditional Risk Factors (Uremic Toxins) on the Development of Cardiovascular Disease

In patients with CKD, CVD is highly prevalent and traditional risk factors cannot adequately predict cardiovascular events. In CKD, the influx of urea and other residual toxins alters the gut microbiota. The number of beneficial microbes that produce short-chain fatty acids (epithelial energy source) decreases, whereas the number of microbes that produce uremic toxins increases [9].

Indoxyl sulfate and p-cresol sulfate (PCS) accumulate in the organs of patients with CKD. The local and systemic disturbances caused by the toxins in biologic metabolism and cellular signal transduction result in uremic syndrome. Chronic kidney disease perturbs inter-organ communication through small molecules, including uremic solutes and signaling molecules [10]. Moreover, IS plays a role in regulating drug-metabolizing enzymes (DMEs) and transporters during inter-organ communication [11]. In healthy individuals, the concentration of IS is 0.1–2.39 μM in healthy individuals but exceeds 500 μM in patients with advanced CKD [12]. In addition, IS is related to the progression of CVD in patients with CKD, which may be due to increased OS in the myocardium and vasculature [13]. Barreto et al. demonstrated that IS may be related to a higher CVD mortality in patients with CKD [14].

TMAO is derived from the metabolites of the gut microbiota, dietary choline, lecithin and L-carnitine. In patients with CKD, serum TMAO levels are high, which contributes to lower survival. In a mouse model, TMAO accelerated atherosclerosis by inhibiting cholesterol transfer from tissues to the liver [15]. Studies have shown that TMAO is independently related to cardiovascular events and that a relationship between TMAO levels and ischemic cardiovascular events exists, especially in CKD Stages 3b and 4 [16]. For these reasons, selective inhibition of TMAO prevents renal damage and cardiovascular events in patients with CKD [17].

4. Effect of RSV on Traditional Cardiovascular Risk Factors

4.1. Effect of RSV on Vascular Function

Angiotensin II (Ang II) acts on the angiotensin II type 1 receptor (AT1R) to induce the production of ROS and subsequent OS. By contrast, angiotensin 1–7 (Ang 1–7) acts on the Mas receptor (MasR) and provides protective effects. Previous studies have shown that RSV can prevent renal function deterioration, ameliorate proteinuria and improve renal histological findings in aged mice by downregulating Ang II/AT1R activity and promoting Ang 1–7/MasR activity [18]. Another study demonstrated that RSV inhibits Ang II and increases the effects of angiotensin-converting enzyme 2 (ACE2) to prevent arterial aging [19]. RSV promotes the synthesis of nitric oxide (NO) from endothelial cells and suppresses the production of endothelin-1, thereby reducing OS. Mounting evidence suggests that RSV treatment protects against the detrimental effects of induced vascular damage. Thus, RSV has protective effects on vascular function and blood pressure [20].

4.2. Effect of RSV on Myocardial Function

Myocardial inflammation causes cardiac damage. Increased activation of NF-κB, a nuclear transcription factor responsible for the production of proinflammatory cytokines, is involved in the immune and inflammatory response of the myocardium, thereby aggravating myocardial injury [21]. In a rat model of sepsis, RSV was reported to inhibit related inflammatory factors and the NF-κB signaling pathway and activate the PI3K/mTOR signaling pathway, thereby protecting the myocardium during sepsis [22]. RSV therapy increases the expression of the autophagy biomarkers beclin-1 and LC-3II but reduces the expression of IL-6. These findings show that RSV has protective effects in ischemia-reperfusion injury in a diabetic rat model [23].

4.3. Effect of RSV on Metabolic Syndrome Components

Metabolic syndrome increases the risk of CVD, stroke and type II diabetes. RSV acts through different mechanisms to improve the symptoms of metabolic syndrome and related disorders [24]. RSV activates SIRT-1, which activates eNOS, thereby resulting in cardioprotective, antioxidant and anti-inflammatory effects [25][26]. Tamaki et al. reported that in addition to SIRT-1, RSV activated the adenosine monophosphate-activated kinase (AMPK) signaling and Nrf2/ARE antioxidant pathways in a rat periodontitis model [27]. In addition, RSV treatment markedly reduces profibrotic protein expression and increases the expression of the ACE2/MasR axis components to increase vasodilatation and reduce blood pressure. Moreover, RSV inhibits the migration of vessel SMCs, which have important antiatherogenic and antiatherosclerotic effects [19][28].

5. Biologic Role of RSV in Atrial Fibrillation

Atrial fibrillation (AF) and CKD usually occur together, which poses a medical dilemma because of the risk of thromboembolism and bleeding episodes [29]. RSV directly affects heart function and rhythm through cardiac remodeling and ion channel activity [30]. RSV also suppresses hypertrophic heart remodeling through the activation

of SIRT-1/AMPK and the subsequent inhibition of NFAT activation, which is implicated in the evolution of AF [31], cardiac myopathy and congestive heart failure [32]. In a study investigating the therapeutic efficacy of RSV in ameliorating AF in an animal model, RSV was found to attenuate atrial fibrosis and modulate ion channels to reduce AF through the PI3K/eNOS signaling pathway [33]. Thus, the cardiovascular protective effects of RSV include reducing OS and alleviating inflammation through Nrf2 and SIRT-1 activation, upregulating the PI3K/eNOS pathway and downregulating the NF-κB pathway [34].

6. RSV with Strong Anti-Carcinogenic Effect via Cardiovascular Protective Effects

Reactive oxygen species (ROS) play a pivotal role in the pathogenesis of both heart disease and tumor progression. Any disturbances in ROS metabolism results an increase in OS which initiates subcellular changes and resultant cardiomyopathy and heart failure. A previous study indicated that exogenous antioxidant RSV is of value in preventing both the development of heart disease and cancer by acting as ROS scavenger [35]. RSV reverses multidrug resistance in cancer cells and sensitizes cancer cells to standard chemotherapeutic agents. The proposed mechanisms of RSV to prevent carcinogenesis include the inhibition of OS, inflammation and cancer-cell proliferation and the activation of tightly regulated cell-death mechanisms [36]. RSV possesses a wide range of preventive and therapeutic options against different types of cancer [37] through its proapoptotic, antiproliferative and anti-inflammatory actions [38][39]. RSV also suppresses the malignant biologic behaviors of cancer cells, including proliferation, antiapoptosis, invasion, migration, EMT progress, levels of ROS and stemness [40]. Recently, RSV is proved be chemopreventive from tumorigenesis by targeting Sirt1 and suppression of NF-κB activation [41]. In brief, RSV provides additional anti-carcinogenic effects parallel with cardioprotective effects.

7. Conclution

The findings of this study suggest that RSV is a possible therapeutic option for patients with CKD with or without CVD. In this regard, RSV can influence the traditional and nontraditional CVD risk factors and alleviate the effects of uremic toxins in patients with CKD.

One of the nontraditional risk factors for CVD is uremic toxin-related cardiovascular side effects. IS causes electrical and structural remodeling in myocardial tissue, leading to atherosclerotic vascular disease. RSV treatment restores intestinal epithelial TJ proteins to increase epithelial integrity. RSV alters the gut microbiota to reduce indole levels in the intestinal lumen. Moreover, RSV inhibits hepatic SULT to reduce the production of uremic toxins such as IS.

In addition, RSV treatment markedly reduces the expression of pro-fibrotic proteins and increases the expression of the components of the ACE2/MasR axis to cause vasodilatation and reduce blood pressure. RSV inhibits the migration of vascular SMCs, which have important antiatherogenic and antiatherosclerotic effects [19][28]. Moreover,

RSV exhibits anti-sclerotic activity in CKD by delaying disease progression. The development of RSV derivatives to reduce the occurrence of CV events in patients with CKD is warranted.

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