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Review

Cardiorenal disease connection during post-menopause: The protective role of estrogen in uremic toxins induced microvascular dysfunction

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ABSTRACT

Female gender, post-menopause, chronic kidney disease (CKD) and (CKD linked) microvascular disease are important risk factors for developing heart failure with preserved ejection fraction (HFpEF). Enhancing our understanding of the interrelation between these risk factors could greatly benefit the identification of new drug targets for future therapy. This review discusses the evidence for the protective role of estradiol (E_2) in CKD-associated microvascular disease and related HFpEF. Elevated circulating levels of uremic toxins (UTs) during CKD may act in synergy with hormonal changes during post-menopause and could lead to coronary microvascular endothelial dysfunction in HFpEF. To elucidate the molecular mechanism involved, published transcriptome datasets of indoxyl sulfate (IS), high inorganic phosphate (HP) or E_2 treated human derived endothelial cells from the NCBI Gene Expression Omnibus database were analyzed. In total, 36 genes overlapped in both IS- and HP-activated gene sets, 188 genes were increased by UTs (HP and/or IS) and decreased by E_2, and 572 genes were decreased by UTs and increased by E_2. Based on a comprehensive in silico analysis and literature studies of collected gene sets, we conclude that CKD-accumulated UTs could negatively impact renal and cardiac endothelial homeostasis by triggering extensive inflammatory responses and initiating dysregulation of angiogenesis. E_2 may protect (myo)endothelium by inhibiting UTs-induced inflammation and ameliorating UTs-related uremic bleeding and thrombotic diathesis via restored coagulation capacity and hemostasis in injured vessels.

1. Complex interrelationship between chronic kidney disease and heart failure with preserved ejection fraction

Heart failure (HF) is a growing major public health problem that affects ~2% of the western population [1]. It has two main subtypes, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Within the HF population, more than 50% suffer from HFpEF [2]. Interestingly, chronic kidney disease (CKD) occurs in 26% to 53% of the HFpEF population and the subclinical diastolic dysfunction appears to be the most common echocardiographic feature in asymptomatic CKD patients on hemodialysis, suggesting a strong link between CKD and HFpEF [3,4]. Furthermore, clinical studies showed a linear relationship between the progression of CKD and the worsening of longitudinal function of the left ventricle in the HFpEF population [5]. The cardiac parameters in patients with CKD stage 2 and 3 already resemble early HFpEF, and the cardiac mechanics have been reported to become worse in patients with CKD stage 4 and 5. In a large cohort study on the development of heart dysfunction during 11 years of follow-up, Brouwers and colleagues demonstrated that increased urinary albumin excretion and cystatin C were more associated with the onset of HFpEF when compared to HFrEF [6]. In particular, older females with increased urinary albumin excretion or cystatin C were more vulnerable to develop HFpEF. These findings indicate a clear association between CKD and HFpEF, especially in the elderly female population.

Important findings in the field further prove that impaired renal function is a major risk for developing HFpEF [7]. Although several mechanisms underlying how CKD contribute to HF in general have been well established, including increased inflammatory responses and activated neurohormonal pathways [8], studies on the driving mechanisms on CKD-related HFpEF are limited. A recent publication by Paulus et al.

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proposed a disease mechanism in which renal dysfunction caused systemic changes in circulating factors that activated inflammation and led to microvascular disease (MVD), cardiomyocyte stiffening, and a hypertrophic response [7]. MVD often occur ubiquitously throughout the body in patients with cardiovascular disease [9]. Paulus and co-workers further proposed that identified metabolic syndrome linked cardiovascular comorbidities, such as diabetes and obesity, could act as inducers of systemic inflammation that trigger global and coronary endothelial dysfunction, leading to myocardial hypertrophy, impaired myocardial relaxation and increased myocardial stiffness [10]. In relation to cardiovascular disease in general, endothelial dysfunction is well known to be able to serve as a strong predictor of coronary artery disease onset [9]. CKD, a common cardiovascular comorbidity associated with metabolic risk factors, leads to hyperphosphatemia and accumulation of uremic toxins (UTs) that trigger inflammation and MVD, which could subsequently contribute to HFpEF onset and progression [11].

Early stage of kidney disease can already be detected by the presence of proteinuria, and a continuous retention of UTs results in a toxic circulatory environment due to the reduction of glomerular filtration rate during the progression of CKD [12]. Serum levels of some uremic toxin compounds, such as methionine sulfoxide and hydroxyproline, accumulate significantly as glomerular filtration rate declines and have been proposed as markers for detecting early stage of CKD [13]. Most UTs circulate in the bloodstream in albumin bound form, and they are not able to directly pass an intact endothelial barrier [14,15]. However, alterations in endothelial barrier do occur in response to various inflammatory mediators and atherogenic metabolic particles [16]. Many UTs, such as indoxyl sulfate and p-cresyl sulfate, have been shown to compromise the endothelial barrier function [17], which could promote protein leakage, causing direct exposure of surrounding non-vascular cells like cardiomyocytes to (protein bound) UTs. However, the exact mechanisms underlying CKD-triggered MVD and corresponding HFpEF remain to be further elucidated, especially at the molecular level.

In this review we focused on the microvasculature in female CKD patients before and after menopause, which will improve our understanding on the subsequent development of HFpEF. Firstly, female gender and aging, two major risk factors of HFpEF, will be addressed. Secondly, the evidence for the role of estrogen (E_2) mediated protection mechanisms in the onset and progress of renal disease-related MVD and HFpEF will be summarized. Finally, we will further discuss the new information that we have gathered from the analysis of publicly available NCBI Gene Expression Omnibus (GEO) database sets for the transcriptome response of endothelial cells (ECs) to E_2 and CKD associated circulatory factors. Based on this, we propose putative pathways of CKD-related MVD that are susceptible to E_2 protection.

2. Postmenopausal women are at high risk of developing HFpEF

The prevalence of HFpEF increases with age and HFpEF patients are typically older than those with HFrEF [18]. In general, the average age of HFpEF patients are between 73 and 79 years old [19]. Aging has been proposed as an independent risk factor for abnormal diastolic function [20]. Age-dependent increase in left ventricular mass index has been observed in humans, and age-dependent increase in cardiomyocyte size has been observed in animals. In addition, increased interstitial fibrosis has also been noticed in aged myocardium. These changes due to aging contribute to myocardial stiffness, putatively leading to diastolic dysfunction in HFpEF. Unfortunately, clinical trial data of treatments for HF were mostly collected from the young and the middle-aged patients, leading to the lack of adequate evidence in treating the elderly, not to mention the older HFpEF patients specifically [21].

Besides the elderly population, women are consistently ~2 times more at risk than men to develop HFpEF and outnumber men by a 2:1 ratio in the HFpEF patient population [22]. Women also differ from the male HFpEF population as they show less evidence of coronary artery disease but are more vulnerable for coronary MVD, indicating a sex-based difference in the underlying pathology of HFpEF [22,23]. Left ventricular diastolic dysfunction (LVDD) can be considered as a pre-stage of HFpEF. In the female population, LVDD onset and progression into HFpEF is strongly associated to the postmenopausal period [24]. High estrogen levels appear to protect the premenopausal heart from ventricular remodeling triggered by hypertension, although the specific mechanism remains to be further defined. Therapeutic interventions for HFpEF have failed to improve the mortality rate. At the moment early detection and treatment of LVDD appear to be the only effective strategy to prevent progression into HFpEF.

Since both aging and female gender appear to be important risk factors for LVDD and HFpEF, it has been postulated that gender specific hormones and changes in hormone levels may play an important role in the higher prevalence of HFpEF in women, particularly in the postmenopausal population [25]. Studies in the early 1990s already showed the beneficial effects of menopausal hormone therapy (MHT) on preventing coronary heart disease [26]. However, subsequent randomized clinical trials failed to demonstrate that MHT prevents secondary events in ischemic heart disease, cerebrovascular events, or progression of coronary atherosclerosis in postmenopausal patients with already established coronary disease [27,28]. Recently, reevaluation of those trails and the initiation of new clinical trials have shed light on how to improve MHT. In particular, the effects of early versus late MHT intervention were evaluated, as comparison between previous MHT responsive and non-responsive groups have indicated that women who received intervention at the early postmenopause stage without pre-existing coronary disease were more likely to benefit from MHT than older patients with pre-existing coronary disease [29]. A recent retrospective single-center study showed that MHT was significantly associated with improved left ventricular relaxation indices, which is in line with the reported improvement in diastolic function following MHT in postmenopausal women, pointing towards the need for further investigation of the use of MHT in treatment of HFpEF [30]. Together, these clinical studies indicate the postmenopausal women are at high risk of developing HFpEF.

3. Postmenopausal estrogen depletion in female CKD patients and microvascular dysfunction

A limited number of studies have started to reveal the putative disease mechanisms of LVDD and HFpEF in women with CKD. An in vitro study showed that the contraction rate in uremic toxin p-cresol treated cardiomyocytes was decreased, and p-cresol impaired cardiomyocytes gap junctions by increasing the activity of protein kinase Cα [31]. UTs have also been shown to induce cardiac remodeling response via estrogen receptor dependent mitogen-activated protein kinase and nuclear factor-κB pathways, suggesting that estrogen receptor signaling could interfere with the negative effects of UTs [32].

Brunet et al. have summarized two major mechanisms of how UTs contribute to vascular dysfunction [33]: (1) UTs promote inflammation by stimulating leukocyte activation and endothelial adhesion molecule expression. Activated inflammation and immune responses increase the migration and proliferation of vascular smooth muscle cells (VSMCs). However, UTs also inhibit the proliferation of ECs and enhance the apoptosis of endothelial progenitor cells, thus impairing vascular repair. (2) UTs stimulate the transdifferentiation of VSMCs into osteoblast-like cells and reduce digestibility of collagen and other extracellular matrix proteins by forming irreversible crosslinks, which subsequently lead to an increased vessel stiffness and vascular dysfunction. Among over 150 UTs that have been listed to date, some UTs like indole-3-acetic acid strongly accumulate in the circulation of patients who are still in an early stage of CKD as compared to normal levels observed in healthy individuals [34]. The concentrations of 11 different uremic toxins have been reported to be 2.3 to 44.7 times increased in

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