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Diabetes Mellitus and Associated Hypertension: Vascular Aging in Diabetes Mellitus and Chronic Kidney Disease

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Abstract

Because considerable important information has been published since our previous review, this update concentrates on new findings with regard to cardiovascular and renal risk factors contributing to the striking morbidity and mortality of these coexisting diseases. For example, a large body of investigative data has recently emerged suggesting or delineating a pathogenic role for hyperglycemic related glycosylation and oxidation of lipoproteins and vascular and renal tissues. Great strides have recently been made in the understanding of platelet, coagulation, lipoprotein and endothelial abnormalities in the pathogenesis of cardiovascular and renal disease associated with diabetes mellitus and hypertension. Major progress has been made in clarifying the pathophysiology of glomerulosclerosis and other processes involved in the progression of diabetic nephropathy. Furthermore, accumulating data surveyed in this review address new and promising pharmacological interventions that specifically address these pathophysiological mechanisms.

Keywords: Glycosylation; Cardiovascular; Pathogenesis; Nephropathy; Endothelia

Introduction

Cardiovascular Diseases (CVD), such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death, are leading causes of morbidity and mortality in patients with Chronic Kidney Disease (CKD) [1]. In contrast, major cardiac events are presumed to represent almost 50% of the causes of death in CKD patients. Kidney disease significantly affects global health as a direct cause of global morbidity and mortality and as a significant risk factor for cardiovascular disease [2]. A meta-analysis of observational studies estimating the prevalence of CKD suggests that approximately 13.4% of the world's population has CKD. The leading causes of CKD vary by setting, with hypertension and diabetes being the most common causes. Therefore, treating diabetes and hypertension and reaching the target results can improve renal and cardiovascular outcomes and slow or prevent progression to ESKD [3]. In particular, reasonable glycemic control and anti-hypertensive and hypolipidemic therapy are the cornerstones of the effective treatment of CKD and CVD. In chronic kidney disease, the retention of uremic toxins plays a role in the development of cardiovascular disease and death [4]. Therefore, preserving kidney function can improve outcomes and reduce CVD and CVD related mortality. This can be achieved through non-drug strategies e.g. dietary and lifestyle changes or pharmacological interventions for chronic kidney disease [5]. Based on international guidelines, this paper adopted chronic kidney disease staging based on the estimated glomerular filtration rate; we used kidney disease outcomes quality initiative CKD staging. However, progressive CKD confers escalating healthcare costs commensurate with cardiovascular morbidity and mortality [6].

Literature Review

Cardiovascular mortality in chronic kidney disease

The increased risk of cardiovascular mortality parallels the deterioration of kidney function and that cardiovascular risk is particularly evident in CKD patients with stages G 3b-4 and in those undergoing renal replacement therapy RRT. Even mild to moderate kidney damage is associated with significantly higher mortality compared to the healthy population. Parallel to the deterioration of kidney function, many pathological biochemical processes emerge, which contribute to the development of cardiovascular diseases. Such processes include chronic inflammation, insulin resistance, hyperhomocysteinemia, lipid dysmetabolism and the gradual accumulation of several toxins. In addition to the various toxicants that accumulate, there are specific metabolites and biomarkers that contribute to cardiovascular disease associated with chronic kidney disease, such as asymmetric dimethylarginine, C-reactive protein, homocysteine, ischemia modified albumin,natriuretic peptides, serum amyloid A, troponin and type I fibrinolytic zymogen activator inhibitors. Furthermore, despite regular dialysis treatment with chronic hemodialysis or peritoneal dialysis, the expected incomplete removal of organic waste compounds results in the accumulation of uremic toxins, which play a crucial role in the progression of CKD and CVD. The possible markers for CVD in CKD are intensively investigated and can also predict coronary artery disease. The levels of matrix Gla protein, neutrophil-lymphocyte ratio, and interleukin 6 were found to correlate with CVD in CKD. It seems that NLR and IL-6 are associated with the increased risk for CVD and higher matrix Gla protein levels represent a protective factor.

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Magnesium homeostasis

Magnesium is the most abundant intracellular divalent cation. Magnesium homeostasis has been discussed in detail in numerous publications, so we will focus on only the most important ones. It is essential for maintaining normal cellular physiology and metabolism, acting as a cofactor of multiple enzymes, regulating ion channels and energy generation. Magnesium also regulates vascular tone, atherogenesis and thrombosis, vascular calcification and the proliferation and migration of endothelial and vascular smooth muscle cells. As such, magnesium can potentially significantly influence the pathogenesis of cardiovascular disease. For example, various conditions could lead to hypomagnesemia. In addition, magnesium homeostasis is primarily a factor between intestinal absorption and the kidneys' regulation of magnesium excretion. Thus, kidney disorders can potentially lead to both magnesium depletion and overload and, as such, increase the risk of cardiovascular disease.

Discussion

Hypomagnesemia and cardiovascular mortality: It is well known that the genetic mutation at 17q12 is related to renal magnesium wasting with comorbid extensive coronary and vascular calcifications. The first hypomagnesemia induced vascular calcification was described in an animal model in 1988 by SG Chrysant, et al. They concluded that dietary induced hypomagnesemia aggravated hypertension and caused widespread tissue calcification in rats through calcium mediated systemic vasoconstriction and increased arterial pressure. Several years later, Mingxin Wei, et al., documented in the literature review the existence of a significant negative correlation between serum magnesium and intact parathyroid hormone, as well as a negative correlation between serum magnesium and vascular calcification in ESKD patients. This finding is true for Hemodialysis (HD) and Peritoneal Dialysis (PD) patients. They also foresee that vascular calcification could be reduced with an inexpensive magnesium containing oral phosphate binder. Ishimura, et al., demonstrated in a cohort that hypomagnesemia is significantly associated with the vascular calcification of the hand arteries; this association remained independent of calcium and phosphate levels. These authors also theorized that higher serum magnesium levels might have a crucial role in preventing vascular calcification in patients on dialysis. David M Spiegel also discussed the role of magnesium in chronic kidney failure. He believed that magnesium administered externally may serve as a phosphate binder and may have cardioprotective effects that are associated with vascular and cardiac calcification. To demonstrate these hypotheses, randomized clinical trials are necessary. Angel LM de Francisco, et al., concluded that moderate hypermagnesemia seems beneficial for vascular calcification and mortality rates in CKD patients. At the same time, magnesium deficiency increases the risk for several diseases, such as type 2 diabetes mellitus, hypertension and atherosclerosis.

Conclusion

Based on the cited reports, a reduced serum magnesium level is closely related to the risk of developing vascular calcification, type 2 diabetes and increased cardiovascular mortality. Current medical therapies utilized in the context of CKD are increasing the likelihood of hypomagnesemia, including in those in need of renal replacement therapy. All these results question the validity of 'normal' *vs.* 'ideal' serum magnesium levels to mitigate calcification and premature vascular aging. Our review specifically focused on hypomagnesemia and vascular calcification as the underlying factors of cardiovascular diseases. We can clearly state that vascular calcification is the starting point for both diabetes complications and cardiovascular diseases, including the cardiovascular complications of chronic kidney disease and aging. While it is evident that hypomagnesemia is deleterious, the question remains if the replacement of magnesium can mitigate the undesirable hard endpoints. Prospective studies are recommended to verify the conclusions that can be drawn from the results so far and to verify the risk reduction achieved with oral magnesium supplementation. By applying all this knowledge, the easily measured magnesium concentration in serum is essential in making further therapeutic decisions.

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