Microvascular disease and its role in the brain and cardiovascular system: a potential role for uric acid as a cardiorenal toxin

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Abstract
Arteriolosclerosis (microvascular disease) may have a key role not only in driving salt-sensitive hypertension but also in mediating the development of chronic kidney disease, vascular dementia, stroke and coronary heart disease. In this paper, we review the evidence that these latter conditions result from the altered autoregulation that occurs when arterioles become diseased. We also discuss the increasing evidence that dietary intake of sugars rich in fructose may be driving the development of microvascular disease as a consequence of raising intracellular uric acid. We hypothesize that the treatment of microvascular disease may require a multifaceted approach by utilizing agents which aim at blocking of the renin-angiotensin system, reducing oxidative stress, stimulating endothelial nitric oxide production and lowering uric acid levels. Paradoxically, agents that only stimulate nitric oxide, such as oestrogens, may increase the risk of poor outcomes if microvascular disease is not reversed.

Keywords: arteriolosclerosis; autoregulation; chronic kidney disease; fructose; uric acid

Introduction
Cardiovascular and renal disease can be separated, to some extent, by whether the disease process is driven by large vessel disease (atherosclerosis), small vessel disease (arteriolosclerosis) or a combination of both. Typically, atherosclerosis involves the presence of cholesterol-laden plaques with infiltrating macrophages in large vessels, and the disease manifests when the vessel reaches a critical degree of narrowing that causes distal ischaemia, when there is embolic phenomenon or when local coagulation occurs resulting in vascular occlusion. In contrast, arteriolosclerosis usually involves proliferation and matrix deposition in small arterioles, often with luminal narrowing, and the disease manifests either from the consequence of distal ischaemia, or because of impaired autoregulation that can result in markedly altered flows and pressures to the distal vascular bed. In general, small vessel disease is what is observed with primary hypertension, in many individuals with stroke, and in hypertensive renal disease. In contrast, atherosclerosis may manifest as coronary artery disease, carotid artery disease, abdominal aneurysms and renal artery stenosis. Major risk factors for atherosclerosis include hypercholesterolaemia, smoking and family history; in contrast, major risk factors for arteriolosclerosis appear to be hyperuricaemia,
metabolic syndrome, fetal programming and possibly diet. In this review, we will focus on the role of arteriolosclerosis (microvascular disease) in the pathogenesis of chronic kidney disease (CKD). We will also focus to a lesser degree on the role of arteriolosclerosis in the pathogenesis of stroke and myocardial infarction.

The pathogenesis of microvascular disease

Arteriolosclerosis has been associated with hypertension, chronic kidney disease and left ventricular hypertrophy since the late 1800s [1,2]. While arteriolosclerosis can involve multiple organs, it is strongly associated with hypertension once the lesions are present in the kidney [3]. Here, the lesions typically involve the afferent arteriole and interlobular artery, and can be characterized by intimal thickening, vascular smooth muscle cell proliferation, and extracellular matrix deposition, resulting in an increase in the media-to-lumen ratio, and later by the replacement of the vascular smooth muscle cells by areas of fibrosis and cell loss.

Historically, most authorities have assumed that arteriolosclerosis represents the vascular response to hypertension. The original evidence supporting this hypothesis was provided by Perera, who noted that subjects with either more severe or longer duration hypertension also displayed more severe renal microvascular disease [4]. Rats made hypertensive by the administration of a high-salt diet and the corticosteroid, DOCA, also developed progressive microvascular disease [5]. In cell culture, increased pressure transduction can stimulate proliferation and activation of vascular smooth muscle cells [6] and endothelial cells [7]. In the kidney, the afferent arteriole and interlobular artery represent the site where vasoconstriction occurs in response to a rise in blood pressure; hence, this autoregulatory response results in these locations being the site for pressure-induced vascular injury.

While hypertension itself can cause arteriolosclerosis, there is mounting evidence that the lesions can also be induced by a variety of other substances that act to cause vasoconstriction. For example, the infusion of angiotensin II can induce microvascular lesions in various vascular beds in the rat that resemble arteriolosclerosis [8,9]. Blocking nitric oxide synthesis can also induce renal microvascular disease [10,11]. Some drugs, such as cyclosporine, can also induce afferent arteriolar disease [12]. Certain foods, such as fructose, the main ingredient in table sugar (sucrose) and high-fructose corn syrup, can also induce renal vasoconstriction and microvascular disease [13]. In addition to vasoconstrictive agents, renal disease itself can result in the development of renal microvascular disease. For example, the remnant kidney model in rats, in which one- and two-thirds of the kidneys are removed, will result in the spontaneous development of afferent arteriolar thickening [14]. Models of low nephron number, such as induced by maternal malnutrition, can also be associated with the development of arteriolosclerosis-like lesions in the kidney (Matt Vehaskari, personal communication).

Recent studies suggest that one of the more potent stimuli for arteriolosclerosis is uric acid. Uric acid is a product of purine metabolism that circulates in the plasma at concentrations that can vary from 2 to 10 mg/dL or higher. For many years, it was thought that having elevated uric acid levels was only a risk for the development of gout or nephrolithiasis. In fact, the observation that uric acid can function as an antioxidant led many experts to consider an elevated uric acid as a beneficial host response, with possible protection from the oxidant stresses associated with ageing, cancer and cardiovascular disease [15–17]. However, more recent studies have shown that uric acid can induce vascular smooth muscle cell proliferation in vitro, with the production of pro-inflammatory, pro-oxidative and vasoconstrictive substances [18–21]. Uric acid also inhibits endothelial cell function and migration [20,22,23]. More importantly, increasing serum uric acid in rats with a uricase inhibitor was found to induce hypertension, renal vasoconstriction and the development of afferent arteriolar disease [24]. Additional studies showed that these vascular lesions were mediated by angiotensin II, a reduction in endothelial nitric oxide, and increased oxidative stress. Furthermore, there is some evidence that uric acid may have a contributory role in the arteriolar lesions that are observed in rats administered cyclosporine [25] and fructose [13] (both of which raise uric acid levels).

One possible mechanism for uric acid effects on the vasculature may be inhibition of active vitamin D synthesis. Previous studies have shown that uric acid could inhibit 1,25-(OH)2 vitamin D in vivo [26], and reduction of serum uric acid levels via allopurinol administration increased serum 1,25-(OH)2 vitamin D levels [27]. Our laboratory is currently undertaking a study to clarify the interaction between uric acid and vitamin D metabolism.

It remains unclear whether the arteriolosclerotic lesions that are observed in vivo can occur in the absence of hypertension. Certain agents such as angiotensin II and uric acid can induce vascular smooth muscle cell proliferation in vitro. In addition, reducing blood pressure with hydralazine in angiotensin II-infused rats [28] and reducing blood pressure in hyperuricaemic rats with thiazide diuretics [29] were both reported not to prevent the development of the microvascular disease. This suggests that it may be possible to induce microvascular disease in the absence of hypertension. However, the latter two studies employed tail-cuff blood pressure which may not accurately reflect the blood pressure over a 24-h period. Indeed, Mori et al. performed an elegant study in rats with angiotensin II-induced hypertension in which one kidney was maintained with normal blood pressure by using a servocontrol apparatus. Interestingly, this kidney showed minimal vascular injury despite being bathed in the same concentration of angiotensin II as the opposite hypertensive kidney [30].

A schema for the development of microvascular disease is shown in Figure 1. While a variety of mechanisms may be involved, it appears that the best milieu for inducing microvascular disease is when there is a combination of elevated pressure associated with high angiotensin II or a lack of nitric oxide.
Microvascular disease as a cause of hypertension

While arteriolosclerosis-like lesions can be induced by hypertension, there is also growing evidence to the contrary stating that renal microvascular disease can cause hypertension. This hypothesis was first championed by Harry Goldblatt in the 1930s [31]. Subsequently, our group and others have shown that the development of afferent arteriolopathy and peritubular capillary rarefaction can result in renal ischaemia with an interstitial infiltration of T cells and macrophages. This inflammatory cell infiltration then leads to intrarenal oxidative stress with activation of the local renin–angiotensin system that exacerbates renal vasoconstriction and mediates salt-sensitive hypertension. Furthermore, blocking the vascular changes, or inhibiting the interstitial inflammation, could ameliorate the development of hypertension [32–37]. Similarly, we have also shown that acutely elevating uric acid could induce hypertension by acutely stimulating renin and oxidative stress and by inhibiting endothelial nitric oxide [29,38,39], but once renal microvascular disease occurs, the hypertension becomes salt-sensitive, renal-dependent and uric acid-independent [40]. These studies suggest that the pathogenesis of primary hypertension may be initiated by various stimuli that acutely cause renal vasoconstriction or hypertension, but with time, the development of renal microvascular disease results in persistent salt-sensitive and volume-dependent hypertension. These data are in fact consistent with the observation that prevalence of renal microvascular disease and salt-sensitive hypertension increases with age [41].

In this regard, we have previously suggested that uric acid may have had a significant role in mediating the marked rise in hypertension prevalence that has occurred worldwide [42]. Over the last century, there has been a dramatic increase in the ingestion of added sugars which contain fructose, and the increased consumption of added sugars correlates both with higher serum uric acid levels and with elevated blood pressure [43,44]. Administering high doses of fructose to humans raises uric acid levels and blood pressure, and preventing the rise in uric acid with allopurinol prevents the increase in blood pressure [45]. Diets restricting fructose also lower uric acid levels and blood pressure (M. Madero, submitted). Mean serum uric acid levels are also increasing in our population in association with the rise in fructose ingestion and increasing

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Fig. 1. A variety of insults act to cause the induction of prosclerosing factors (uric acid and angiotensin II), reduce nitric oxide bioavailability, and increase oxidative stress and blood pressure. Those stimuli contribute to endothelial cell dysfunction and apoptosis, whereas in VSMC, they have proliferative and pro-inflammatory effects which induce a phenotypic switch with increased intracellular collagen deposition and diminished contractile capacity. Thickened and stiffened microvessels have a poor autoregulatory capacity, allowing the transmission of increased blood pressure to target organs, such as the kidney and the brain.
Microvascular disease and altered autoregulation: a mechanism which increases the risk for chronic kidney disease, stroke and heart disease

The arterioles have a major role in protecting distal organs from the elevated pressure present in the central circulation. In the kidney, this autoregulatory vasoconstrictive response is critical in preventing transmission of pressure to the glomeruli and peritubular capillary bed. Bidani and Griffin have provided convincing evidence that an altered renal autoregulatory response is common present in chronic kidney disease, and that this leads to increased transmission of systemic pressure to the glomeruli [54]. An insight into the mechanism was provided by the laboratory of the late Jaime Herrera-Acosta, who showed that the development of afferent arteriolar disease resulted in impaired autoregulation and glomerular hypertension [14]. Importantly, this group showed that if the arteriolar sclerosis could be prevented and renal autoregulation remained intact, the progression of renal disease could be halted [14].

The mechanism is relatively logical, for the diseased arterioles have been shown to have an increase in collagen content [10] and hence are not expected to vasoconstrict or vasodilate as quickly or as efficiently as normal arterioles. We have suggested that the consequences of altering the autoregulatory mechanisms of the arteriolar capillary bed may be critical as a risk factor for end-organ damage, particularly by increasing the risk for progression of renal disease [14]. This concept has also been proposed for the impairment of brain function by Thompson and Hakim in a recent publication [55].

Chronic kidney disease

As mentioned, the studies by Bidani and Griffin have provided key evidence that autoregulation is impaired in subjects with chronic kidney disease, and as a consequence, there is greater transmission of pressure to the glomerulus for any given systemic pressure [56]. This likely explains why lower blood pressure targets are needed for subjects with diabetic nephropathy and proteinuric chronic kidney disease in which glomerular pressures are likely elevated. Interestingly, these studies would also suggest that lower blood pressure targets may be required for hypertensive African Americans, with ageing and with long-standing hypertension, since all of these groups often develop significant renal microvascular disease [57–59]. One might also postulate that individuals with long-standing hyperuricaemia may also have defective autoregulation and require lower blood pressure targets once kidney disease develops.

Cerebrovascular disease and stroke

The cerebral arterioles also have a key role in protecting the brain from systemic pressures. As with the kidney, the development of cerebral microvascular disease may impair autoregulation and increase the risk of stroke and vascular dementia [60]. Lowering the blood pressure precipitously in subjects with cerebral microvascular disease may increase the risk for ischaemic stroke just as increasing the blood pressure or cerebral blood flow too rapidly may increase the risk of haemorrhagic stroke [61].

There are a number of different imaging patterns of cerebral microvascular disease comprising silent cerebral infarction, white matter hypointensities and cerebral microbleeds [62]. Interestingly, the possibility that uric acid may have a role in cerebral microvascular disease has been suggested. Schretlen and colleagues have found that subjects with elevated uric acid are at increased risk for vascular dementia and have evidence for increased cerebral microvascular disease as noted by MRI scans [63,64]. Others have linked fructose intake with the development of dementia, including in experimental animals [65]. However, another recent study showed that higher uric acid levels were associated with less dementia and a better cognitive function but only after controlling for features of the metabolic syndrome. This latter paper also did not separate vascular dementia from other causes of dementia [66]. An elevated serum uric acid is also known to increase the risk for stroke [67,68].

Interestingly, chronic kidney disease increases the risk of development of cerebral microvascular disease and, once developed, it predicts survival [69–71]. More studies are needed to determine if the link between CKD and stroke is microvascular disease induced by a common substance such as uric acid.

Cardiovascular disease

The coronary arterioles that lie distally to the coronary arteries may not have an important role in autoregulation, but
their function and patency may still be important in the long-term outcome of patients suffering from myocardial infarction. For example, in subjects who undergo thrombolytic therapy for acute coronary occlusion, the development of poor myocardial blood flow post-intervention due to diseased distal microvasculature results in poor outcomes [72]. Interestingly, we have found that the presence of impaired post-coronary intervention myocardial perfusion following thrombolytic therapy was independently associated with elevated serum uric acid levels (Kanbay et al., submitted for publication). Again, these studies suggest that uric acid, by driving microvascular disease, could act in this manner to contribute causally to coronary heart disease.

**Microvascular disease and vasodilatory agents: a potential for toxicity?**

As discussed, the presence of microvascular disease is likely to alter the ability of the arteriole to autoregulate, with the greatest risk being to the kidney and the brain. While the presence of microvascular disease suggests that lower blood pressure targets may be needed to prevent progression of renal disease or stroke, this may also be the reason that the use of vasodilators may result in enhanced perfusion of hyperperfusion syndromes. Evidence that this may be the case can be observed in a study in which L-arginine (a precursor for the synthesis of nitric oxide) was administered either to prevent or to treat hyperuricaemia-associated hypertension (Figure 2) [39]. If L-arginine was administered prophylactically (chronic treatment), it prevented the development of the arteriolopathy, reduced systemic pressure, and maintained glomerular pressure in the normal range. However, if it was administered after the microvascular lesions were induced (acute infusion), it lowered systemic pressure but paradoxically increased glomerular pressure (Figure 2).

The observation that stimulating nitric oxide paradoxically increased glomerular pressure in the setting of renal microvascular disease could account for some apparently paradoxical findings in the literature, such as studies reporting that the anti-oxidants vitamin E [10] or β-carotene [15] can increase the risk for haemorrhagic stroke. In the Women’s Health Initiative, the use of oestrogens (which increase NO) was also reported to increase the risk for stroke, especially in older women [73]. It is conceivable that this increased risk is due to the presence of underlying microvascular disease.

**Reversing microvascular disease and long-term treatments**

If microvascular disease is a true risk factor for hypertension, chronic kidney disease, stroke and vascular dementia, and coronary heart disease, then what can be done to prevent or reverse it? In this regard, the best evidence to date suggests a role for blockade of the renin–angiotensin system. Studies by Chatziantoniou et al. have shown that the afferent arteriolopathy from L-NAME infusion can be reversed by a 4-week course of ACE inhibition [74,75]. Schiffrin and Ferrario have also shown that chronic ACE inhibitor treatment can reverse microvascular disease in hypertensive humans [76–78]. Other treatment modalities, such as endothelin antagonists, may also be beneficial. In any case, some intervention is likely required, as it is known that the arteriolopathy, such as from chronic inhibition of NO synthesis, can persist for at least 10 weeks in the absence of treatment [79].

As mentioned, lowering uric acid can prevent the development of renal microvascular disease in response to hyperuricaemia [24,29] and/or fructose [13]. The question whether established microvascular disease induced by hyperuricaemia is reversible remains unknown. Clinical studies do suggest that microvascular disease can be reversed with long-term RAS blockade [76–78]. In relation to the role of uric acid, the beneficial impact of a variety of uric acid-lowering agents on the development of cardiovascular end points has been considered in several studies. These include studies suggesting an improvement with uric acid-lowering therapies on chronic kidney disease [50,80],
unstable angina [81], insulin resistance [82] and hypertension [49,83]. Further studies are necessary to determine the effects of these therapies on microvascular structural changes.

**Conclusions**

In conclusion, there is increasing evidence that arteriolar sclerosis (microvascular disease) may have a key role in cardiorenal disease. Renal microvascular disease may be a key mechanism for inducing salt-sensitive hypertension. In addition, the development of microvascular disease results in altered autoregulatory and microvascular functions, and may increase the risk for stroke, vascular dementia, coronary heart disease and chronic kidney disease. Non-specific vasodilators may not be beneficial if microvascular disease is not actively treated with RAS blockade. In addition, the role of dietary fructose and uric acid in this process is likely but requires further study.

**References**


Organ donation, transplantation and religion

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Abstract

Religious concerns may be an important reason why patients decline listing for a renal transplant. These issues may be equally, or even more, important when live donation is discussed. There is good reason to believe that religious concerns play a significant role much more often than clinicians and transplant teams believe. The issue is certainly further compounded by the fact that a few, if any, patients come forward with their religious concerns, not least because issue of transplantation is new to them anyway and because they meet with transplant teams whom they do not know. Health professionals, on the other hand, may wish to avoid this sensitive issue altogether or may lack knowledge on religious issues pertaining to transplantation. Some may be entirely unaware. We encountered a case in clinic that revealed our remarkable lack of knowledge in this regard. Here, we aim to provide an overview on how the different religions view transplantation and organ donation, with an emphasis on practical points for health care professionals who are involved in transplant listing and organ donation, with an emphasis on practical points for health care professionals who are involved in transplant listing, organ donation and retrieval, and transplantation itself. Knowledge of these facts may provide a background to deal with these issues professionally and appropriately and to increase transplant numbers.

Keywords: organ donation; religion; transplantation

Introduction

There is good evidence that patients from indigenous and migrant ethnic minorities are more likely to develop end-stage renal failure but less likely to receive a renal transplant [1]. They are also typically less likely to receive a well-matched kidney since they are under-represented among deceased donors: in the UK, only 5.1% of deceased kidney donations during the financial year 2008/2009 were from non-white donors, although a quarter of patients on the waiting list were non-white [2]. Unfortunately, low rates of live donation among ethnic minorities have been described as well [3]. Recent studies suggest that, apart from cultural, social and educational issues and language barriers, religious concerns may also play a role in a decision against donation [4]. However, care must be taken not to equate ethnicity with religion, and detailed analysis is required to dissect the various factors. There are also striking differences between countries as to the willingness to donate (Table 1). Some of these differences may be explained by different infrastructure, law or consent system, but religious factors may play a role as well, particularly in countries with low deceased donation rates [5]. We recently encountered a case in our clinic that made us rethink our approach to this issue, particularly in the large numbers of Muslim patients we see in our catchment area in the North West of England. In this review article, we first explore the Islamic view of organ donation and transplantation. We then provide an overview on how the different religions view transplantation and organ donation. We then provide an overview on how the other major religions view this topic, starting with the two other Abrahamic faiths (Christianity and Judaism), then moving on to the two major religions in India (Hinduism and Sikhism) and then to the religions of East Asia (Buddhism, Confucianism, Shintoism and Taoism). Finally, we discuss the issue of directed donation and religion.

Case vignette

A 46-year-old Muslim female patient with IgA nephropathy was seen for an annual review on the renal transplant...