Small Vessel Disease in CKD, Diabetes, Obesity and Hypertension

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Clinical Case Scenario

78 year old moderately obese previously smoking gentleman is referred to the renal clinic for progressive deterioration in renal function. Over the past five year his eGFR has declined from 45 to 30mls/min/1.73 m^2. His past medical is remarkable for type 2 diabetes which is quite well managed with a HbA1C of 62 mmol/mol, while his hypertension is poorly controlled despite 4 antihypertensive drugs. His blood pressure is 174/76 mmHg and he has microalbuminuria (35 mg/mmol).

In the Western world diabetes and hypertension are the most common causes of renal disease and the consequent need for renal replacement therapy. Obesity has emerged as one of the major healthcare challenges afflicting the populations of developed and developing countries alike. In the clinic setting, obesity is seldom seen in isolation; rather it is often encountered together with diabetes mellitus, or impaired glucose homeostasis, and hypertension, a constellation of diseases defined as the metabolic syndrome. The disease entities under the umbrella of the metabolic syndrome each contribute to small vessel changes that ultimately lead to end organ damage including renal failure.

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What Has Occurred in This gentleman's Kidneys over the Antecedent Years, and How Could This Have Been Prevented?

It is estimated that somewhere between 1 and 5 % of patients with hypertension, depending on BP cut-offs and co-morbidity, go on to develop end-stage renal disease (ESRD) [1, 2]. This clearly suggests that there are different responses to hypertension which may be in part due to both genetic and concurrent environmental factors [3]. The presence of diabetes is of paramount importance given that in combination with hypertension, it has a particularly deleterious effect. A unique and important characteristic of the kidney is the ability to maintain a steady glomerular filtration rate over a wide range of perfusing pressures, this auto-regulatory response is essential in preserving normal renal function. The ability of the glomerulus to protect itself from systemic hypertension has been largely attributed to the degree to which the afferent arteriole can auto-regulate in response to a high systemic BP load [4, 5]. The mechanisms underlying this are incompletely understood, however there are at least two, the fast myogenic response and the slower tubuloglomerular feedback [6, 7]. When these systems are overloaded there is progressive glomerulosclerosis with ischaemic loss of functional nephrons [8].

Renal blood flow and the integrity of the glomerular membrane barrier are the main determinants of glomerular filtration rate (GFR) and albuminuria. Under normal circumstances, renal autoregulation allows for a stable renal GFR despite large fluctuations in renal blood flow which occur as a consequence of changes in blood pressure during the normal cardiac cycle. Caution should be applied when using GFR as a surrogate marker for assessment of renal function in diabetes. In early diabetic nephropathy, dysfunctional autoregulation is observed in the form of hyperfiltration which is present in up to 66 % of individuals with type1 diabetes and precedes albuminuria. Hyperfiltration can compensate for reduced number of nephrons or a dysfunctional membrane barrier and result in a normal GFR in a clearly diseased setting [9, 10].

D. Goldsmith et al. (eds.), *Cardio-Renal Clinical Challenges*,
DOI 10.1007/978-3-319-09162-4_2,

Small Artery Function and Dysfunction: Remodelling, Myogenic Tone and the Endothelium

In uncomplicated hypertension, the increase in intraluminal pressure leads to eutrophic inward remodelling. There is no change in the number of smooth muscle cells in the arterial wall, nor is there a contribution in the form of hypertrophy. The re-orientation of vessel wall constituents means that the vessel cross-sectional area remains the same; however there is an increased number of smooth cell layers and a decreased internal diameter of the vessel [9].

A key player in the autoregulation of renal blood flow is myogenic tone. This is the ability of small vessels (internal diameter <300 μm) to constrict in response to a range of physiological pressures independently of neurohormonal interference. The renal afferent arteriole vasoconstricts in response to increased luminal pressure with a stepwise increase in myogenic response [11, 12]. The myogenic response occurs in three phases: (1) Calcium influx through the L-type voltage gated calcium channels results in a large increase in intra-cellular calcium and attendant changes to membrane potential; (2) Myogenic reactivity: there is no change in intracellular concentrations of calcium, however the mechanical apparatus within the cell becomes more sensitive to calcium resulting in a further constriction in response to an increase in intraluminal pressure; (3) Forced dilatation: the arterial wall is unable to maintain a constriction against increasing pressures resulting in vessel dilatation. In the presence of an intact myogenic reflex, raised blood pressure results in eutrophic remodelling of the vessels and has a protective effect on the downstream organs including the kidneys by limiting the transmission of the raised pressures. In pathological states, when the myogenic response breaks down, there is a shift away from eutrophic towards hypertrophic remodelling where there is also an increase in wall thickness but there is no reduction in lumen diameter and the elevated central pressure will be transferred directly to the microcirculation resulting in pressure-related damage to organs such as the glomeruli [9, 10].

The mechanisms involved in vascular remodelling are numerous. Of note, integrins play a key role in the myogenic process and wall remodelling. Integrin $\alpha_5\beta_1$ is implicated in the initial influx of calcium necessary for basal vessel tone establishment, and integrin $\alpha\upsilon\beta_3$ mediates force maintenance via calcium sensitisation of contractile apparatus during the myogenic reactivity phase [13] and is necessary for the pressure induced inward remodelling process. Further research has highlighted the potential involvement of the epithelial sodium channel (ENaC) and related proteins such as the acid-sensing ion channel proteins [14].

In patients with type 1 or 2 diabetes mellitus and co-attendant hypertension, growth of the arterial wall occurs in an outward fashion with an increase in wall thickness and preservation of the lumen diameter (hypertrophic remodelling) [15, 16]. It is important to note that no such structural changes are observed in patients with diabetes but normal blood pressure. A 10-year follow-up study of patients with type 1 diabetes has shown that improved metabolic control leads to eutrophic remodelling and an increase in vessel distensibility, thus the patients benefit from a reduction in transmission of the elevated central blood pressures to end organs [9]. Studies have shown that in hypertensive patients with diabetes, a significant regression of vascular remodelling of small resistance arteries is achieved with drugs blocking the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) [17].

Co-attendance of obesity and diabetes confounds vascular remodelling. Similar to patients with diabetes, obese patients demonstrate an increase in media-to-lumen ratio in keeping with hypertrophic remodelling [18]. Interestingly, persistent weight loss following weight reducing surgery is able to regress these vascular changes as well as improve metabolic parameters including insulin sensitivity [19].

Endothelial Dependent Mechanisms

The endothelium is the lining of all blood vessels throughout the body and is highly specialised to each vascular bed. Even within the kidney there are different specialised endothelial beds with unique adaptations; these include the glomerular, peritubular and juxtamedullary capillaries [20].

It has long been recognised that there is widespread endothelial dysfunction found in patients with CKD [21], this applies not only to patients with significant CKD (stages 2–5) [22, 23] but may also be found in individuals with normal excretory renal function and only microalbuminuria, a potent predictor of cardiovascular disease [24] and progression of kidney disease in both the diabetic and non-diabetic population [8, 25]. Endothelial dysfunction evaluated as vasodilator response to acetylcholine has also been reported in the obese population thus confounding the pathophysiology observed in patients with the metabolic syndrome [18]. The exact mechanisms and causality remain to be fully determined; however it is clear that there is a complex interplay between low grade inflammation and endothelial activation. There is either increased production and/or accumulation of a variety of cytokines and endothelial activators, including, but not limited to, vWF, TNFa [26] and ADMA [27].

Glomerular Endothelial Changes in Diabetes

The exact nature and pathophysiology of diabetic small vessel disease is beyond the scope of this chapter; however there is a complex interplay between oxidative stress, endothelial dysfunction [28] and vessel remodelling.

An important feature of this small vessel disease within the kidney in diabetes is aberrant vasodilation of the afferent arteriole and impaired renal auto-regulation allowing greater transmission of systemic pressures to the glomerular capillaries [29]. This contributes to glomerular hyperfiltration, one of the earliest features of pre-diabetic nephropathy [30] as previously introduced.

An emerging player in the evolution of diabetic nephropathy would appear to be the glomerular endothelium with its fenestrations covered by the endothelial glycocalyx [31], a highly specialised extra-cellular matrix which covers all endothelial cells [32]. The endothelial glycocalyx, including that within the glomerulus, is an important molecular sieve, permitting selective filtration of plasma constituents from the blood into the interstitium [33]. Damage to this endothelial glycocalyx causes increased passage of proteins which may be pivotal in the development of disease, and indeed hyperglycaemia has deleterious effects on the glycocalyx causing shedding from the endothelial surface and increased macromolecule permeability [34].

Retinal Microvasculature and Cardiovascular Risk

The retinal microcirculation provides a non-invasive and readily accessible window to the human microvasculature and the recent advances in imaging technology using computer-based analysis of retinal photographs allow retinal vascular calibre to be quantified in a reproducible way. Changes in retinal vascular calibre are associated with demographic factors such as age and ethnicity, and more recently genetic factors have been implicated [35]. However, changes such as narrowing of retinal arteriolar calibre, enhanced arteriolar wall reflex and wider venular calibre are associated with the metabolic syndrome [36, 37] and its components such as larger waist circumference [38, 39], higher triglyceride levels [39], diabetes and hypertension [38, 40], as well as stroke [41, 42], coronary microvascular disease [43] and coronary artery disease [44]. Retinal microvascular changes can even predict subsequent vascular events following ischaemic stroke [45]. These changes are also observed in the paediatric and adolescent population [46–48]. Although fewer data are available from individuals with CKD, retinal microvascular signs such as venular dilatation are associated with CKD both in the presence and absence of diabetes, thus reinforcing the link between renal and retinal microvasculature independently of diabetes [49]. Furthermore, associations have been observed between CKD and a greater decrease in central retinal venular equivalent over time [50]. In a study of adolescents with type1 diabetes but normal albumin excretion rate and no retinopathy at baseline, higher venular length-to-diameter ratio and lower simple tortuosity independently predicted incident renal dysfunction [51]. In a further study, arteriovenous (AV) nicking and opacification were associated with lower eGFR, and a smaller fractal dimension and presence of focal arteriolar narrowing, AV nicking and opacification were associated with higher albumin/creatinine ration. Moreover, narrower retinal arterioles, smaller fractal dimensions and focal arteriolar narrowing as well as AV nicking and opacification were shown to be associated with higher likelihood of having microalbuminuria [52].

In conclusion, this non-invasive tool can be utilised to predict outcomes in diseases with cardiovascular complications and further longitudinal data are required to assess the ability of retinal studies to predict future event rates in patients with CKD.

Inflammation and Perivascular Adipose Tissue

The contribution of low grade inflammation to hypertension has been identified as a potential new pathophysiological process implicated in vascular remodelling in diseases obesity and hypertension. Studies have shown that both innate and adaptive immune systems may be play a role and T cells have been identified as important players. The balance between Th1 effector lymphocytes and Treg lymphocytes may be crucial for blood pressure elevation and consequent organ damage development. Activated Th1 cells may contribute to damage to the vasculature, kidney and perivascular fat. Tregs represent exhibit an anti-inflammatory role offering protection from blood pressure elevation and from the development of organ damage, including micro and macrovascular alterations. Inflammation results in vascular remodelling through cytokine activity, smooth muscle cell proliferation and oxidative stress [53].

For years, fat cells or adipocytes found throughout the body have been dismissed as mere energy stores; however a growing body of evidence suggests that fat cells are engine rooms producing and secreting a number of metabolically active substances with both endocrine and paracrine properties. Surrounding almost every blood vessel in the human body are white adipocytes which together with a number of other, predominantly inflammatory, cells are collectively termed perivascular adipose tissue (PVAT). It is now recognised that PVAT not only provides mechanical support for any blood vessel it surrounds but also secretes vasoactive and metabolically active cytokines known as adipokines which regulate vessel function and affect vessel tone in health and disease. The emergence of obesity as a major challenge to our healthcare systems has contributed to the growing interest in adipocyte dysfunction with a view to discovering new pharmacotherapeutic agents to help rescue damaged PVAT function and enhance its vasorelaxant effect. PVAT function has been investigated in mammals including dog, pig and rat

models as well as some ex-vivo, in-vitro studies of human blood vessels [54, 55]. There are a number of functional and structural characteristics of PVAT which vary between species and anatomical site. Recent studies have reported that healthy human PVAT can exert a local vasorelaxant effect on adjacent blood vessels and elegant pharmacological protocols have suggested that adiponectin [56], angiotensin 1–7 [57, 58] and hydrogen sulphide [59] may all be implicated. The mechanism of action of these molecules in this context remain to be clarified, however our most recent data has highlighted the pivotal role of the large calcium sensitive potassium (BKCa) channel in facilitating the action of adiponectin as we have demonstrated that absence of BKCa leads to a loss of normal PVAT relaxing function. Furthermore, microelectrode studies of de-endothelialised rat mesenteric vessels have shown that in constricted arteries, the hyperpolarisation to exogenous adiponectin is inhibited by selective blockade of BKCa [60]. In support of this theory, there is evidence that stimulation of the $ß_3$ adrenoreceptor, which leads to a degree of lipolysis, releases a factor which indirectly activates myocyte BKCa channels. In obesity adipocytes hypertrophy and angiogenesis does not keep up with the increase in adipocyte growth, thus rendering fat cells hypoxic and inflamed [56]. There is evidence of increased macrophage numbers, higher concentrations of TNFα, heightened oxidative stress levels and loss of normal PVAT vasorelaxant activity in obesity. In support of this proposed theory, in models where there is a reduction or absence of activated macrophages PVAT anticontractile function is preserved despite induced inflammation by hypoxia protocols [61]. Intuitively, one would conclude that the abolishment of PVAT vasorelaxant effect would result in an increase in basal vessel tone, contributing to peripheral vascular resistance in obesity. Weight reducing (bariatric) surgery is associated with a restoration of normal PVAT vasorelaxant function despite patients remaining morbidly obese [62] and there is clear evidence from several laboratories that the loss of anticontractile activity can be rescued using either antioxidants such as superoxide dismutase [62], or inhibitors of the renin angiotensin system or antagonists of the angiotensin II receptor as well as aldosterone blockers. There is the possibility of the prevention of diabetes as a result of introducing agonists that can preserve PVAT vasorelaxant function and adiponectin analogues pose the greatest potential in the cohort of patients with the metabolic syndrome as this molecule can potentially treat obesity-related hypertension by helping to reduced basal vessel tone and offering anti-diabetic effects in this cohort.

"What Importance Does This Have for Our Patient in Clinic? And What Further Advice Can We Offer?"

It is known that patients who are seen in renal clinics have a slower progression of renal dysfunction and improved patient survival [63]. Lifestyle assessment and modification should form part of all outpatient consultations. The Joint British Societies [64] have published extensive guidelines regarding lifestyle advice in primary and secondary cardiovascular prevention. These also apply to patients with all forms of CKD.

Of particular note is that exercise has been demonstrated to reduce mortality and improve health-related quality of life in patients with CKD [65, 66] whether this acts solely through improvement of arterial stiffness [67] or also has beneficial effects on the microvasculature remain to be determined.

In this context it would be easy to focus on the immediate problems of improved glycaemic and blood pressure control; however, to reduce vascular dysfunction and improve survival it is important to reduce all risk factors by implementing measures such as smoking cessation, a healthier diet and increased levels of exercise. Large clinical trials (e.g. HOT and UKPDS) have recommended maintaining blood pressure below 130/80 in individuals with diabetes [30], and more recently, the European Society of Hypertension guidelines (2013) [68] state emphasise a systolic BP target of <140 mmHg in all while <130 mmHg should be considered in the presence of overt proteinuria. Individual targets should be set lower for younger high risk patients but these might not be deemed safe in the elderly population at risk of complications from a low BP.

Lowering cholesterol using statins in the at-risk population is also of paramount importance to reduce cardiovascular risk and overall morbidity and mortality. Beyond their lipid lowering effects, it is postulated that statins might have a role in treating adverse microvascular changes such as endothelial dysfunction encountered in CKD, diabetes and obesity [69]. This is partly explained by their ability to reduce caveolin-1 expression in endothelial cells thus promoting nitric oxide production [70, 71] and also via their anti-inflammatory effects by reducing superoxide generation on endothelial cells [72].

A recent systematic review and meta-analysis of statin use in CKD patients has shown a significant relative risk reduction in cardiovascular events, coronary events and cardiovascular or all-cause deaths [73].

In conclusion, microvascular disease is a major concern in CKD and metabolic syndrome and its components. A multi-faceted and holistic approach must be taken when assessing and treating patients with these disorders in order to reduce their cardiovascular risk.

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