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REVIEW ARTICLE

Glycation in diabetic nephropathy

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Abstract The kidney is an extremely complex organ with broad ranging functions in the body, including but not restricted to waste excretion, ion and water balance, maintenance of blood pressure, glucose homeostasis, generation of erythropoietin and activation of vitamin D. With diabetes, many of these integral processes are interrupted via a combination of haemodynamic and metabolic changes including increases in the accumulation of proteins modified by advanced glycation, known as advanced glycation end products (AGEs). Indeed, hyperglycaemia and the redox imbalances seen with diabetes are each independent accelerants for the production of AGEs, which synergistically combine in this disorder. In addition, as kidney function declines, characterised by a loss of glomerular filtration, the excretion of AGEs is decreased, possibly exacerbating renal injury by further elevating the body's tissue and circulating AGE pool. Therefore, it has become apparent that decreasing the accumulation of AGEs or interrupting their downstream effects on the kidney, are desirable therapeutic targets for the treatment of diabetic renal disease.

Keywords Diabetic nephropathy · Advanced glycation · Haemodynamic · Renal

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Introduction

Diabetes is at epidemic proportions in developed and developing nations. Although the deleterious effects of the disease itself are significant, it is the resultant vascular complications found in up to 40% of diabetic individuals, which are a major burden on health care systems and on individual quality of life. The microvascular complications include kidney disease, arguably the most important predictor for both subsequent cardiovascular disease and all-cause mortality (Groop et al. 2009; Matsushita et al. 2010). It is well accepted in diabetic kidney disease that there is an excess accumulation and exposure of the kidney to advanced glycation end products (AGEs) (Soulisliparota et al. 1995; Suzuki et al. 1999). Although AGEs such as carboxymethyllysine (CML) and MG-H1 are elevated within the circulation with diabetes (Kilhovd et al. 2003; Makita et al. 1991), there is some controversy over whether these specific AGEs are relevant circulating biomarkers of progressive renal injury. Recently, we have identified that most of the AGE modified proteins present in the circulation of diabetic patients are large protein complexes often containing other ligands for the receptor for AGEs (RAGE) such as HMGB1 (Penfold et al. 2010). There is some suggestion that urinary concentrations of AGEs may be more useful in determining the degree of kidney disease in diabetic individuals (Friess et al. 2003). However, the predominant evidence linking AGEs to diabetic renal disease comes primarily from studies in rodents, which have clearly shown the efficacy of AGE lowering therapies such as pyridoxamine (Degenhardt et al. 2002), thiamine (Babaei-Jadidi et al. 2003), alagebrium chloride (Forbes et al. 2003b), OPB-9195 (Nakamura et al. 1997) and lowering AGE dietary intake (Zheng et al. 2002) in preventing and retarding experimental diabetic nephropathy. Aminoguanidine, is

another AGE lowering therapy with other actions including inhibition of nitric oxide synthase. This agent was extremely effective in animal models (Soulis-Liparota et al. 1991) and did show potential benefits in human clinical trials (Appel et al. 1999), however, this agent with similarities to hydralazine, was associated with the presence of unique circulating immune complexes in humans, which deposited in kidneys worsening renal impairment in certain type 2 diabetic subjects. In Phase II studies in type 1 and type 2 individuals with diabetes, pyridoxamine has shown significant improvements in serum creatinine, however as per aminoguanidine, there are number of adverse events reported in this study (Williams et al. 2007). Interestingly, both benfotiamine (Alkhalaf et al. 2010) and thiamine (House et al. 2010), although seemingly well tolerated, have shown no improvements above renin–angiotensin system (RAS) blockade in diabetic patients.

Advanced glycation in the kidney

The specific effects of AGE formation in the kidney can be broadly divided into three main pathways. Firstly, extracellularly formed AGEs can alter either matrix–matrix, cell–cell or matrix–cell interactions. Indeed, it is likely that AGE formation may be physiologically required for the stabilisation of connective tissue. Under pathological conditions, excessive AGE cross-linking may lead to increased stiffening within the extracellular matrix. In addition, AGE modification of type IV collagen, a basement membrane glycoprotein, decreases endothelial cell adhesion and alters charge, which may also affect physiological protein interactions (Charonis et al. 1990; Krishnamurti et al. 1997; Tarsio et al. 1985).

More recently, although diabetic nephropathy was not traditionally considered to be an inflammatory condition, there is a growing body of evidence in recent times highlighting the central role of inflammation in its development and progression. Indeed, both hemodynamic and metabolic factors involved in the development of diabetic complications such as nephropathy activate common downstream targets, including cytokines and growth factors (Cooper 1998) which contribute to extracellular accumulation in the context of AGE accumulation as previously reviewed (Sourris et al. 2009). In particular, AGE induced production of monocyte chemoattractant protein (MCP-1), transforming growth FACTOR-β1 (TGF-β1), connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) have all been implicated in both experimental and human studies to be involved in the development and progression of diabetic nephropathy. These factors are important, but are not elaborated upon here since they have been previously extensively reviewed (Forbes et al. 2003a; Sourris et al. 2009; Turgut and Bolton 2010).

Secondly, intracellular formation of AGEs can directly alter protein function, trafficking and breakdown since they are likely generated much more rapidly within cells, in particular proximal tubular cells which have an extremely high reducing sugar flux. Although it is widely appreciated that increased glucose uptake is the reason for the increased rate of intracellular AGE formation, any metabolic imbalance which alters cell metabolism including those which produce excess glycolytic intermediates or reactive oxygen species can result in the generation of AGEs.

Thirdly, pathological effects induced by AGEs may also be mediated by interaction with cellular receptors. Though there are a number of AGE receptors, the most well studied in the development of nephropathy is the RAGE. There are numerous protein splice variants of RAGE, the most predominant of which are full length membrane associated RAGE and circulating soluble RAGE, commonly known as esRAGE (Yonekura et al. 2003). The capacity of circulating proteins such as the soluble form of RAGE to interrupt the binding of ligands to cell bound RAGE also appears to be important in the development of diabetic nephropathy. In diabetic individuals with nephropathy, studies have shown variable findings, with both a loss (Forbes et al. 2005; Basta et al. 2006) or conversely an increase (Humpert et al. 2007) in circulating soluble RAGE concentrations reported. In rodent models, administration of soluble RAGE (Wendt et al. 2003) or RAGE neutralising antibodies (Flyvbjerg et al. 2004) protect against renal injury in diabetes, a finding also seen in mice with a genetic deficiency in RAGE (Coughlan et al. 2009; Tan et al. 2010; Wendt et al. 2003). Conversely, diabetic mice which overexpress RAGE develop more advanced renal lesions than control mice (Yamamoto et al. 2001). Taken together, it is clear that the accumulation of AGEs and their modulation of specific receptors such as RAGE play important, but likely diverse roles in the development and progression of diabetic nephropathy.

Haemodynamics and blood pressure

Diabetic nephropathy is characterised by a number of specific changes. Haemodynamically, there is a significant increase in intraglomerular pressure thought to be the result of activation of vasoactive hormones including those associated with the local renal RAS. Indeed, the most successful approaches used clinically to combat diabetic kidney disease involve blockade of the generation of the main effector peptide of the RAS, angiotensin II (AngII), namely angiotensin converting enzyme (ACE) inhibitors or

the interruption of the interaction of AngII with the major receptor responsible for vasoconstriction, the angiotensin II type 1 receptor (AT1 receptor), termed AT1 receptor antagonists. ACE inhibitors (Uk prospective diabetes study group 1998; Lewis et al. 1993) and AT1 receptor antagonists (Brenner et al. 2001) have each been shown to inhibit the production of AGEs even under ex vivo conditions. Furthermore, the infusion of AGEs produces changes in the renal RAS which are reminiscent of those seen in the diabetic kidney (Thomas et al. 2005). Interestingly, infusion of AGEs into healthy rodents also increases the glomerular filtration rate (Thomas et al. 2005). Other authors have also shown that other RAGE ligands such as S100B calgranulins can augment AngII activation of JAK–STAT signalling pathways, inducing proliferation in vascular smooth muscle cells (Shaw et al. 2003).

Most of the pressor actions attributed to AngII, including vasocontriction and activation of the sympathetic nervous system, appear to be mediated via ligation to the AT1 receptor. Renal concentrations of AngII also have effects on sodium and water resorption from the proximal tubules, which directly inhibit renin secretion from granular cells of the juxtaglomerular apparatus via the AT1 receptor. Increases in AGEs (Thomas et al. 2005) and activation of the receptor RAGE (Fukami et al. 2004) have each been shown to influence the expression of the AT1 receptor, activating known pathways implicated in a number of chronic kidney diseases including diabetic nephropathy.

The contribution of another important receptor for AngII, the AT-2 receptor, has also been suggested in diabetic renal disease (Cao et al. 2000). The AT2 receptor gene shares only 34% of sequence homology with the AT1 receptor, despite having equal binding affinity for AngII (de Gasparo et al. 1995). In adult kidneys, the AT2 receptor is localised primarily to glomeruli, but is also found at low levels in cortical tubules and interstitial cells (Ozono et al. 1997). Since the AT2 receptor is highly abundant in foetal tissues, it is believed to play an important role in nephrogenesis and therefore the development of congenital obstructive nephropathies and uropathies (Pope et al. 1998). More recently, a link between the AT2 receptor and RAGE has been established both in vitro (Ruster et al. 2009) and in vivo, where the protection against the development of diabetic renal disease afforded to mice deficient in RAGE could be attributed to activation of renal AT2 receptors (Sourris et al. 2010). Delineation of the AGE–RAGE signalling pathways which either overlap with or are unique to those seen with RAS blockade is undeniably worth further exploration. This will extend understanding of agents which inhibit advanced glycation or downstream signalling as we try to translate many of these intriguing findings to the clinical context.

Ion and water balance

Active transport is responsible for the observation that renal cells contain relatively high concentrations of potassium ions, but low concentrations of sodium ions. The mechanism responsible for this is the sodium–potassium pump, which moves these two ions in opposite directions across the plasma membrane at a ratio of 3:2, respectively. The most efficient example of this is in the S1/S2 segmental proximal tubular cells, where sodium is actively exported to allow for glucose uptake via sodium glucose transporters (SGLTs).

It is well accepted that the function of this sodium–potassium pump, the Na^+/K^+ ATPase is impaired in the diabetic kidney (Unlucerci et al. 2001). Indeed, this impairment has been associated in type 1 diabetic individuals with excess circulating concentrations of methygloxal and glyoxal (Han et al. 2007). Another recent study has shown that AGEs modulate arachidonic acid and phosphoinositide metabolism to inhibit the Na^+/K^+ ATPase via clathrin-mediated endocytosis (Gallicchio and Bach 2010). Also, other authors have shown that under hyperglycaemic conditions, glycation of membrane lipids may cause a significant change in the structure and stability of membrane proteins, which may alter membrane function and Na^+/K^+ ATPase activity (Levi et al. 2008).

It should also be mentioned here that a major functional role of the AT2 receptor is in maintaining water balance. Given that over-expression of RAGE may induce a decline in the AT-2 receptor, AGE modulation of RAGE may ultimately affect body water content. Indeed we have previously shown that mice deficient in the AT2 receptor do not adapt their water intake in response to diabetes to the same degree as seen in their wild type counterparts or RAGE KO mice (Sourris et al. 2010). Consequently, AT2 deficient mice do not respond to AngII mediated signals to increase water intake as shown by other studies (Ichiki et al. 1995; Siragy and Carey 1997). Furthermore, diabetic AT2 KO mice have lower glomerular filtration rates and less urinary output than both RAGE KO and wild type diabetic mice. This is in line with suggestions that hyperfiltration is a protective adaptation seen in early diabetes in both rodents and humans.

Interestingly, hyperfiltration is also seen in normoglycaemic rats exposed to infusion of AGEs (Thomas et al. 2005). In support of this, a recent study has shown the first evidence that childhood/adolescent obesity is characterised by lower plasma AGE levels, despite lower insulin sensitivity, enhanced-oxidative stress and microinflammation, suggesting that hyperfiltration in response to an excess AGE load may be an adaptive protective response. Indeed in that study, hyperfilration facilitated enhanced removal of AGE peptides, a renal haemodynamic feature that is characteristic of obesity (Sebekova et al. 2009). Regular moderate exercise also reduces circulating concentrations

of AGEs and ameliorates early diabetic nephropathy in obese Zucker rats (Boor et al. 2009). Indeed, regular moderate exercise could possibly represent an easy and effective non-pharmacologic approach to reduce the accumulation of AGEs in diabetic individuals, as has been previously shown in non-diabetic individuals (Boor et al. 2009). These findings demonstrating various environmental, yet non-dietary factors that affect AGE accumulation in the body, may also explain why there may be such large discrepancies reported in the concentrations of circulating AGEs in patients with diabetic renal disease.

Maintenance of blood pH

We are all born with a very high alkaline blood pH of 7.4. Over the years as we age, this pH level becomes more acidic. Acidosis is said to occur when arterial pH falls below 7.35. Two organ systems, the kidneys and lungs, maintain this acid–base homeostasis by regulating blood bicarbonate (HCO_3^-) concentrations. Metabolic acidosis may result from increased production of metabolic acids, disturbances in the ability to excrete acid or release of bicarbonate via the kidneys. Renal acidosis is associated with an accumulation of urea and creatinine as well as metabolic acid residues of protein catabolism. An increase in the production of other acids may also produce metabolic acidosis. Indeed, lactic acidosis may occur from a fall in the rate of oxygen diffusion from arterial blood to tissues and is suggested to occur in the diabetic kidney, particularly at the corticomedullary junction (Miyata and de Strihou 2010).

Ketoacidosis is another example of acid imbalance which occurs in diabetes. It is due to the accumulation of ketoacids (ketosis) and reflects a severe shift from glycolysis to lipolysis for energy needs, where methylgloxal is produced as the result of cytochrome P450 catalysed oxidation of acetone. High protein diets also induce ketoacidosis, in addition to significantly increasing the circulating concentrations of methylglyoxal (Beisswenger et al. 2005). Indeed, there is some evidence of a role for reducing protein intake in meta-analyses of a number of studies in type 1 diabetic patients. These analyses suggest that low-protein diets significantly slow the increase in albuminuria [relative risk, 0.56 (CI, 0.40 to 0.77); (Pedrini et al. 1996)] and it is possible that at least some of the beneficial effects of protein restriction may occur as a result of reduced systemic and renal levels of AGEs and their precursor molecules.

Glucose homeostasis

Perhaps one of the least appreciated function of the kidney is its role in the prevention of hypoglycaemia. Indeed, the proximal tubules have sodium dependent glucose transporters (SGLT), located on the apical side of the proximal tubule cell, which accumulate glucose within the cell against a concentration gradient by transporting glucose concurrently with sodium. A sodium concentration gradient is provided by the enzyme complex Na–K ATPase located on the basolateral side that pumps sodium out of the cell. Once the glucose concentration is higher in the cell than in the interstitial space, glucose is passively transported across the basolateral side of the cell via facilitative glucose transporters (GLUT 2) into the interstitium. In the early segments of the proximal tubule, the low affinity, high flux transporter SGLT2 on the apical membrane is coupled with a facilitative glucose transporter with similar characteristics on the basolateral side, GLUT2. Together these two glucose transporters reabsorb up to 90% of filtered glucose under normoglycaemic conditions. Previously oxidative stress and exposure to AGEs have been shown to inhibit Na+/glucose cotransporter activity in renal proximal tubule cells under high glucose conditions (Han et al. 2005). Conversely, aminoguanidine has no effect on diabetes-induced inactivation of kidney Na^+,K^+ ATPase in rats (Unlucerci et al. 2001). Given that selective SGLT2 inhibitors have been shown in clinical trials to induce glycosuria and reduce serum glucose levels (List et al. 2009) in diabetic individuals, the influence of AGEs on this process warrant further investigation. Indeed, both thiamine and benfotiamine prevent glucosuria without improvement in glycaemic control by increasing renal glucose uptake in models of experimental diabetes (Babaei-Jadidi et al. 2003).

Vasopressin is a peptide hormone synthesised by the hypothalamus and released by the posterior pituitary that controls the reabsorption of molecules in the tubules of the kidneys by affecting the tissue's permeability. It plays a key role in homeostasis by regulation of water, glucose, and various salts in the bloodstream. Previous studies have shown the efficacy of inhibition of the actions of vasopressin in diabetic rodents (Bardoux et al. 2003). Interestingly, vasopressin undergoes rapid glycation in the presence of reducing sugars with the formation of Schiff's bases at one or both of the two amino functional groups (Tarelli et al. 1994). Again the effects of advanced glycation of the actions of this hormone remains to be determined, however, it is feasible that these changes in vasopressin could alter its biological function, thereby influencing sodium and glucose homeostasis.

Recently, a number of alternative therapies have shown efficacy in decreasing the formation of AGEs including green tea or its extracts (Babu et al. 2008). In particular, one study demonstrated that green tea decreased glycogen storage in renal proximal tubule cells in diabetic rats, improving renal function and glycaemic control (Babu et al. 2008). Indeed, in diabetes both the liver and kidney

contribute to glucose overproduction with renal glucose uptake markedly increased. This is likely to suppression of renal FFA uptake via a glucose–fatty acid cycle, thereby partly explaining the accumulation of glycogen commonly found in the diabetic kidney and known as the Armani-Ebstein lesion (Mauer et al. 1976). Also a rise in lactate out of proportion to the level of pyruvate is also seen in diabetic individuals as well as those with chronic kidney disease even in the absence of diabetes (Heierli and Tholen 1981).

Erythropoietin and anaemia

Anaemia is often detected but is commonly overlooked in individuals with diabetes. The cause of anaemia in diabetic subjects, particularly those with renal impairment, appears to be multifaceted. Indeed, the hyperglycaemia characteristic of diabetes, can lead to hypoxia within the renal interstitium, resulting in impaired production of erythropoietin by the peritubular fibroblasts with subsequent development of anaemia (Singh et al. 2008). The anaemia in patients with diabetes has been suggested to contribute to the pathogenesis and progression of cardiovascular disease and aggravate diabetic nephropathy. Furthermore, anaemia occurs earlier in diabetic when compared with non-diabetic individuals as chronic kidney disease develops. Further complicating the anaemia seen with diabetic renal disease is the phenomenon of glycation of erythrocyte membrane proteins (Bryszewska and Szosland 1988; Singh et al. 2009). The modification of membrane proteins such as haemoglobin (Mortensen 1985), depends not only on blood glucose levels but also erythrocyte age. These studies have shown that the enhanced non-enzymatic glycosylation of proteins in diabetic subjects extends beyond haemoglobin to other proteins of the erythrocyte membrane, probably affecting other proteins that have a much slower turnover than haemoglobin that are also exposed to high concentrations of glucose as a result of diabetes.

Activation of vitamin D

Calcitriol, the activated form of vitamin D, promotes intestinal absorption of calcium and the renal reabsorption of phosphate in concert with parathyroid hormone (PTH). This vitamin increases circulating calcium concentrations [Ca^{2+}] by promoting absorption of dietary calcium from the gastrointestinal tract and increasing renal tubular reabsorption of calcium, while PTH increases the rate at which the kidneys excrete inorganic phosphate (Pi). Calcitriol also stimulates the release of calcium into the circulation from bone, by its action on specific bone cells involved in bone resorption known as osteoclasts. Recent studies have demonstrated that AGE–RAGE interactions on osteoblastic cells involved in bone formation, so called osteoblasts, are likely to diminish bone formation (Santana et al. 2003). Other studies have shown that excess AGEs enhance osteoclast induced bone resorption (Miyata et al. 1997) and thus in the context of decreased bone formation, there is a net effect of AGEs on reducing bone mass. However, since calcitriol concentrations were not measured in these studies, it is difficult to determine if these effects of AGEs were via direct or indirect modulation of calcitriol, effects on the function of PTH or both. The situation may be even more complex with the recent finding that calcitriol also blunts the deleterious impact of AGEs in renal endothelial cells (Talmor et al. 2008). Taken together, these findings suggest that improving the AGE burden that occurs in diabetic renal disease is likely to have widespread effects on the levels of various calcium regulating hormones such as calcitriol and PTH with associated downstream benefits on bone loss. Indeed, the complex effects of AGEs on bone are likely to be relevant in diabetic subjects, particularly those with progressive renal impairment.

Conclusion

As clearly demonstrated within this review, the kidney has many functions which may be altered by advanced glycation. Specifically, AGEs appear to have profound effects on glomerular filtration, glucose handling and ion/water resorption particularly as seen in the diabetic setting. Furthermore, by targeting the AGE–RAGE pathway, it is likely to lead to improvements in various processes linked to renal function. With renal impairment clearly shown to be associated with increased mortality, it is hypothesised that the interruption of the AGE–RAGE axis to optimise renoprotection, could be linked to decreased cardiovascular disease and potentially reduced all-cause mortality.

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