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DIABETES AND RENAL ISCHAEMIA/REPERFUSION INJURY - REVIEW

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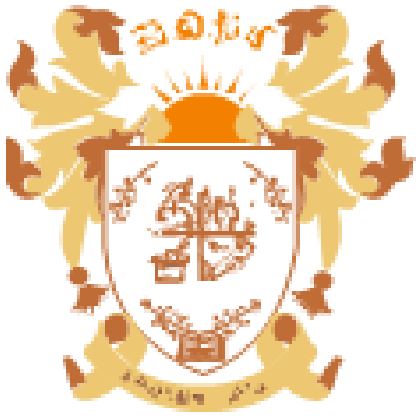

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Introduction

Acute renal failure (ARF) is a syndrome characterized by an abrupt and reversible kidney dysfunction. The spectrum of inciting factors is broad: from ischemic and nephrotoxic agents to a variety of endotoxemic states and syndrome of multiple organ failure. The pathophysiology of ARF includes vascular, glomerular and tubular dysfunction which, depending on the actual offending stimulus, varies in the severity and time of appearance. Hemodynamic compromise prevails in cases when noxious stimuli are related to hypotension and septicemia, leading to renal hypoperfusion with secondary tubular changes. Nephrotoxic offenders usually result in primary tubular epithelial cell injury, though endothelial cell dysfunction can also occur, leading to the eventual cessation of glomerular filtration. This latter effect is a consequence of the combined action of tubular obstruction and activation of tubuloglomerular feedback mechanism. In the following pages we shall review the existing concepts on the phenomenology of ARF including the mechanisms of decreased renal perfusion and failure of glomerular filtration, vasoconstriction of renal arterioles, how formed elements gain access to the renal parenchyma, and what the sequelae are of such an invasion by primed leukocytes.

Hyperglycaemia is most probably a contributing factor in the development of ischaemic acute renal failure (ARF) in many patients. Both clinical and experimental data suggest that hyperglycaemia increases the risk of ARF (1–3). Hyperglycaemia also worsens the outcome in renal transplantation (4, 5). Conversely, ischaemia–reperfusion (I/R) combined with hyperglycaemia could also be important in the development of diabetic nephropathy. Studies in our laboratory show that a brief renal ischaemia results in a progressive injury leading to end-stage renal failure in diabetic animals (6, 7). The mechanisms behind this increased sensitivity to renal I/R during hyperglycaemia are still poorly understood.

EXPERIMENTAL FINDINGS

An increased susceptibility to renal I/R injury in diabetic rats has been shown in several studies (1, 3, 6–9). Furthermore, non-diabetic rats and dogs are more vulnerable to I/R injury, when the blood glucose is elevated by intraperitoneal glucose injection or dextrose infusion (10, 11). We found that a unilateral renal ischaemia of 30 min caused a progressive, irreversible injury in the kidneys of diabetic rats, whereas kidneys in non-diabetic rats recovered almost completely (6). The injury was characterized by tubular atrophy and dilatation of the remaining tubules, infiltration of inflammatory cells, and fibrosis. The inflammatory cells were mostly T-lymphocytes, macrophages and monocytes. An increased accumulation of hyaluronan in the renal cortex and outer medulla has also been observed (unpublished observations). Insulin treatment before, but not after, renal ischaemia almost abolished the increased susceptibility to I/R in the kidneys of diabetic animals (7).

CLINICAL OBSERVATIONS

Critically ill patients

Strict metabolic control by continuous insulin infusion improves the prognosis for surgical intensivecare patients (2). Intensive insulin therapy keeping the blood glucose between 4.4 and 6.1 mmolul using a continuous insulin infusion was compared with conventional therapy where the blood glucose was kept between 10.0 and 11.1 mmolul and insulin only given if the blood glucose was above 11.9 mmolul. The overall mortality and the rate of ARF were reduced by ;40% with the intensive insulin treatment (2). The same protocol was followed whether or not the patient had a history of diabetes in this study. As pointed out by the authors, the study was performed in a setting of mostly surgical patients, whereas patients with medical diseases may respond differently (2). One possible confounding factor in this study is the high proportion of patients who had undergone cardiac surgery. It has been proposed that infusion of insulin, glucose and potassium have a positive effect on heart function after cardiac surgery (12). It could not be excluded that the infusion of glucose and insulin protected the kidneys by improved renal perfusion from better cardiac function.

Kidney transplantation

In kidney transplantation, hyperglycaemia is associated with an increased number of complications (4, 5). Diabetic patients with good glycaemic control in the peri-operative period had fewer episodes of acute rejection and infection than patients with good metabolic control (4). Also, non-diabetic patients with moderate hyperglycaemia, that is a blood glucose above 8 mmolul, had more acute rejections than patients with lower blood glucose levels (5).

Diabetes and radiocontrast media

Decreased renal function is the main risk factor for ARF induced by radiocontrast media (RCM) [13], and earlier claims that diabetic patients with normal renal function also had an increased risk of ARF due to RCM [14], have not been confirmed [13]. To our knowledge, no clinical study specifically addressing the issue of hyperglycaemia and nephrotoxicity of RCM has been performed. Hyperglycaemia has, however, been reported to be a risk factor for contrast-mediainduced renal failure in rats in one study [15], but not in another [16]. During percutaneous renal-artery angioplasty, radiocontrast nephrotoxicity is combined with temporarily impaired renal circulation, i.e. I/R, and in this setting, blood glucose could be of special importance.

PATHOPHYSIOLOGY

Several mechanisms have been suggested to explain why hyperglycaemia anduor diabetes increases I/R injury. Intracellular oxidative stress, due to an increased production of superoxide by the electrontransport chain in the mitochondria, has been proposed as a unifying explanation for most metabolic alterations in diabetes (17). I/R is also a state where oxidative stress has been implied (18). It could be speculated that the combined oxidative stress from these two sources could be particularly harmful. The increased inflammatory response after I/R in diabetes may play a role (19), and disturbances in production and response to NO have also been suggested to contribute to the increased sensitivity to I/R in diabetes (3). Wald et al. (1) explored whether dehydration was involved in the increased sensitivity to renal I/R seen in diabetic rats by infusing saline during ischaemia. They found that this treatment did not have any protective effect. Hyperglycaemia is probably not harmful in all types of ARF; on the contrary,

hyperglycaemia actually protects against the nephrotoxicity of some substances such as gentamicin and mercuric chloride in rats (1, 20, 21). Interestingly, this protective effect was abolished by insulin treatment (22). The pathophysiology of contrast-media-induced ARF remains to be established.

Several theories have been proposed. Contrast-media infusion may result in vasoconstriction of renal vessels, thereby causing hypoxia, and direct toxic effects on tubular cells have also been suggested (13). Considering the possibility that hyperglycaemia could increase ischaemic ARF, but protect against toxic ARF, it is not surprising that clinical studies concerning ARF due to RCM have yielded conflicting results. The increased sensitivity to I/R in kidneys during hyperglycaemia corresponds to similar findings in other organs. Hyperglycaemia increases the damage to the brain after stroke, regardless of whether the patient had diabetes or not (23). The blood glucose concentration on hospital admission is a predictor of the outcome after myocardial infarction (24).

The severe reduction in glomerular filtration rate (GFR) associated with established ischemic or toxic renal injury is due to the combined effects of alterations in intrarenal hemodynamics and tubular injury. The hemodynamic alterations associated with ARF include afferent arteriolar constriction and mesangial contraction, both of which directly reduce GFR. Tubular injury reduces GFR by causing tubular obstruction and by allowing backleak of glomerular filtrate. Abnormalities in tubular reabsorption of solute may contribute to intrarenal vasoconstriction by activating the tubuloglomerular (TG) feedback system.

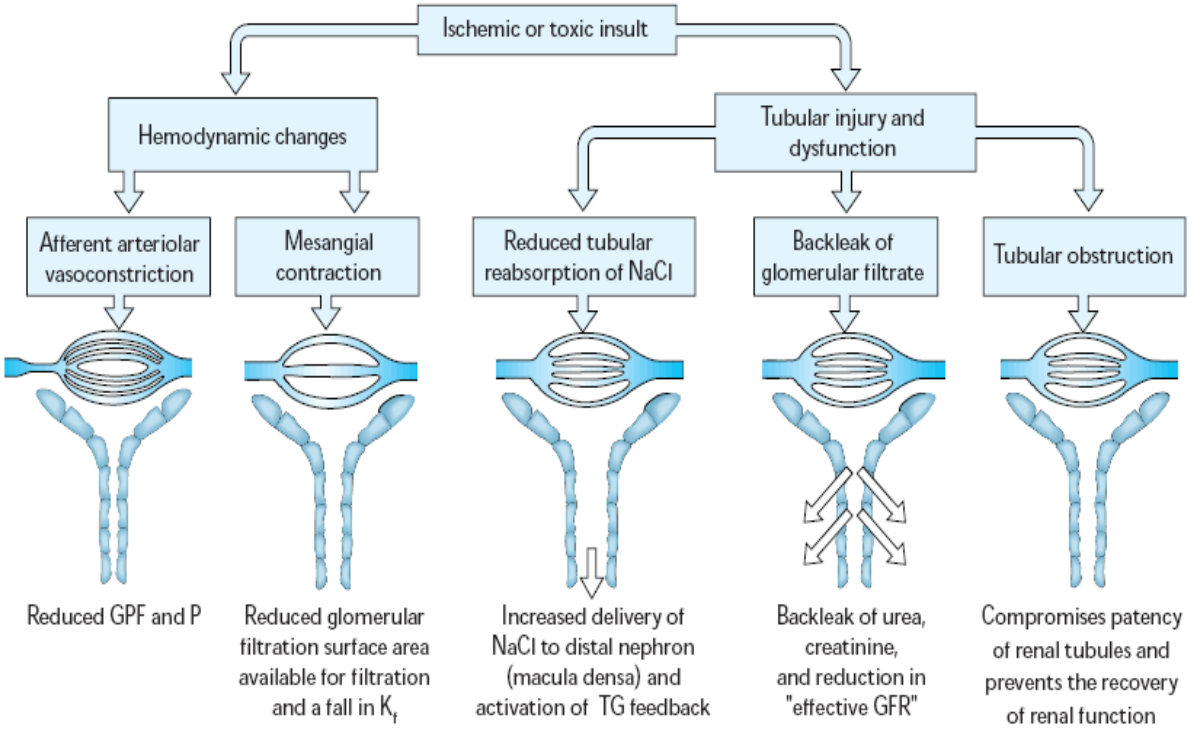

Figure 1: **Pathophysiology of ischemic and toxic acute renal failure (ARF).** GPF-glomerular plasmaflow; P-glomerular pressure; Kf-glomerular ultrafiltration coefficient.

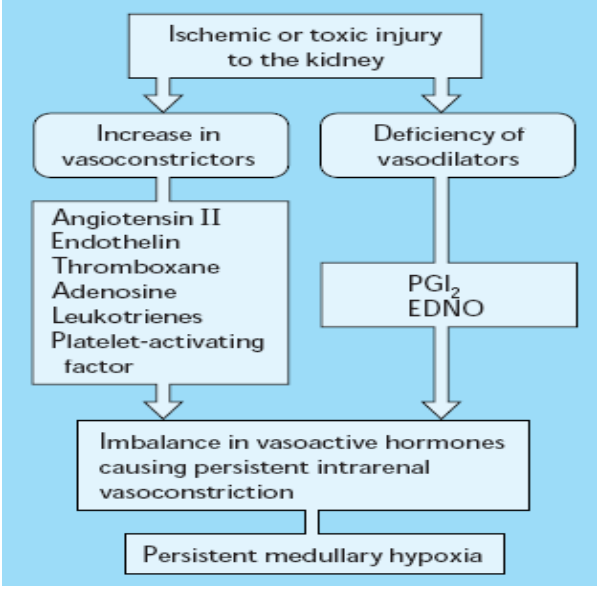

Figure 2: Vasoactive hormones that may be responsible for the hemodynamic abnormalities in acute tubule necrosis (ATN).

A persistent reduction in renal blood flow has been demonstrated in both animal models of acute renal failure (ARF) and in humans with ATN. The mechanisms responsible for the hemodynamic alterations in ARF involve an increase in the intrarenal activity of vasoconstrictors and a deficiency of important vasodilators. A number of vasoconstrictors have been implicated in the reduction in renal blood flow in ARF. The importance of individual vasoconstrictor hormones in ARF probably varies to some extent with the cause of the renal injury. A deficiency of vasodilators such as endotheliumderived nitric oxide (EDNO) and/or prostaglandin I2 (PGI2) also contributes to the renal hypoperfusion associated with ARF. This imbalance in intrarenal vasoactive hormones favoring vasoconstriction causes persistent intrarenal hypoxia, thereby exacerbating tubular injury and protracting the course of ARF.

DIABETIC NEPHROPATHY

Diabetic nephropathy, damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world.

The main job of the kidneys is to remove waste from the blood and return the cleaned blood back to the body. Kidney failure means the kidneys are no longer able to remove waste and maintain the level of fluid and salts that the body needs. One cause of kidney failure is diabetes mellitus, a condition characterised by high blood glucose (sugar) levels. Over time, the high levels of sugar in the blood damage the millions of tiny filtering units within each kidney. This eventually leads to kidney failure. Around 20 to 30 per cent of people with diabetes develop kidney disease (diabetic nephropathy), although not all of these will progress to kidney failure. A person with diabetes is susceptible to nephropathy whether they use insulin or not. The risk is related to the length of time the person has diabetes.

There is no cure for diabetic nephropathy, and treatment is lifelong. Another name for the condition is diabetic glomerulosclerosis. People with diabetes are also at risk of other kidney problems including narrowing of the arteries to the kidneys, called renal artery stenosis or renovascular disease.

The finding that hyperglycaemia increases renal I/R injury may have implications for the understanding of diabetic nephropathy as well. Ischaemia has been suggested in the development of diabetic nephropathy (25). Besides the glomerular changes, interstitial fibrosis and infiltration of inflammatory cells are important features of diabetic nephropathy (26). In fact the degree of tubulointerstitial injury is as closely related to the decline in function as are the glomerular alterations (27). The tubulointerstitial fibrosis and infiltration of inflammatory cells observed in diabetic rats after renal I/R share similarities with what is seen in diabetic nephropathy (6). Repeated minor ischaemic events, caused for instance by smoking or sympathetic activation due to stress, could clearly participate in the development of diabetic nephropathy.

It is clear that diabetes can lead to kidney disease, but just why high blood sugars should damage the glomeruli is unclear. High blood pressure (hypertension) is a known risk factor for kidney disease and people with diabetes are prone to hypertension. The renin-angiotensin system which helps regulate blood pressure - is also thought to be involved in the development of diabetic nephropathy. Other risk factors include cigarette smoking and family history. Diabetic nephropathy progresses steadily despite medical intervention. However, treatment can significantly slow the rate of damage.

PREVENTION

Clinical studies concerning diabetes and acute renal failure are few, so far. The available data are also from specific clinical settings such as surgical intensive care and renal transplantation, making it difficult to extrapolate the results to other situations. However, these studies call for an increased awareness of hyperglycaemia when renal circulation could be jeopardized, for example during intensive care, intravenous injection of RCM, or sepsis. Obviously an extremely strict metabolic control is associated with an increased risk of hypoglycaemia, but this can be avoided, especially in an ICU setting, were blood glucose can be monitored on a regular basis. However, there could be additional beneficial effects of insulin per se, besides lowering the blood glucose. For instance, anti-apoptotic effects of insulin have been shown in vitro (28, 29). Insulin treatment reduces apoptosis in the tubular cells in the renal medulla after renal I/R injury in diabetic rats, if given prior to the injury (7). This may explain in part why insulin protects renal function and morphology after renal I/R in diabetic rats. However, none of the studies published so far is able to distinguish between a direct protective effect of insulin, an effect on glycaemic control, or a combination of both.

Conclusion

Reviews are accumulating to indicate that diabetes is a contributing factor in the development of ischaemic ARF. We believe that diabetes, in situations where the kidney is subjected to poor perfusion or ischaemia, represents an underestimated clinical problem. Further research is needed to define in which settings an improved glycaemic control is beneficial, and to establish the mechanisms behind the increased sensitivity to I/R during hyperglycaemia. Also, the question whether diabetes control is important during radiocontrast infusion is not definitively solved.

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