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Diabetic nephropathy—What are the unmet needs?

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ABSTRACT

In this pandemic of diabetes and obesity, Asia will have the highest number of affected people with the greatest increase in the young-to-middle aged group. Asian patients have increased risk for diabetic kidney disease which may be compounded by low grade infection, obesity and genetic factors. In these subjects, the onset of albuminuria and diabetic kidney disease causes further perturbation of metabolic milieu with increased oxidative stress, anaemia and vascular calcification which interact to markedly increase the risk of cardiovascular disease. Despite receiving optimal care to control blood pressure and metabolic risk factors as well as inhibition of the renin–angiotensin system in a clinical trial setting, there is a considerable residual risk for cardio-renal complications in patients with diabetic kidney disease. Control of obesity and low grade inflammation as well as correction of anaemia may represent areas where novel strategies can be developed and tested to curb this rising global burden of cardio-renal complications.

1. Introduction

Diabetes and its devastating complications greatly reduce life expectancy and adversely affect quality of life amongst those affected, thus, posing immense challenges to many societal sectors [1]. The upsurge in the prevalence of diabetes from 171 million in 2000 to 366 million by 2030 as projected by the World Health Organization threatens to overwhelm the economic and healthcare system globally [2]. Obesity, which is the driving force for escalating diabetes prevalence is a growing problem now witnessed in both developed and developing countries. In addition to an aging population, rapid urbanization, adoption of unhealthy lifestyle and possibly increased psychosocial stress have led to a shift towards younger age of disease onset, especially in areas undergoing rapid transitions from an energy-scarce, physically active to an energy-abundant and sedentary way of living [2]. In this respect, more than two-third of the diabetic population will reside in Asia with China ranking second to India which are still developing economically with relatively few resources to cope with these complications requiring expensive interventions [3].

2. Multifaceted nature of diabetes

Diabetes is frequently accompanied by a host of other metabolic disorders including obesity, hypertension and dyslipidaemia [4]. Since its introduction by Reaven in 1998 [5], the concept of metabolic syndrome has drawn much attention, initially for its association with cardiovascular diseases [6,7], and more recently, an array of other conditions such as non-alcoholic steatohepatitis [8], obstructive sleep apnoea [9], polycystic

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ovarian syndrome [10] and chronic kidney disease [11]. Insulin resistance generated by visceral obesity and associated chronic inflammation is posited to underlie the downstream clustering of metabolic aberrations [4].

3. Diabetic kidney disease in Asia

Diabetes-related deaths amounted to almost 3 million, equivalent to 5% of world all-cause mortality in 2000. In Asia, the excess death is most prominent in the age group between 50 and 60 years, which translates to a reduction in life expectancy of more than a decade. In Caucasians, cardiovascular diseases account for a substantial proportion of deaths in diabetic patients [12]. Conversely, Asian diabetic patients succumb to non-cardiovascular conditions including end stage renal disease (ESRD), malignancy and respiratory diseases in comparable proportion to cardiovascular events [13] (Table 1).

An important predictor for cardiovascular diseases is chronic kidney disease which often co-exist [14]. Based on the Hong Kong Diabetes Registry established in 1995, we have developed a series of risk equations to predict different clinical outcomes. While there is considerable heterogeneity in terms of predictors for heart failure [15], coronary heart disease [16], end stage renal disease [17], stroke [18], malignancy [19] and all-cause death [20], albuminuria and glomerular filtration rate are the most prominent risk factors shared by all these endpoints. To this end, diabetic kidney disease can be viewed as the renal expression of systemic vascular dysfunction sharing common risk factors including oxidative stress, chronic inflammation, increased fibrogenic activity and cellular activation including the podocytes, endothelium and mesangium [21].

Diabetes is now the leading cause for ESRD worldwide, accounting for approximately 40% of patients receiving renal replacement therapy each year [22]. End stage renal disease and dialysis treatment incur substantial cost in health, social and financial terms. Its prevalence is rising in parallel to that of diabetes. The predilection of Asian diabetic population to develop renal complications is now well recognized [23]. In cross-sectional surveys, up to 60% of Asian diabetic patients have micro- or macroalbuminuria compared to 30–40% reported in Western diabetic population [24]. One explanation for this ethnic disparity in renal risk is competing mortality. Longer survival in Asians as a result of lower frequency of large vessel atherosclerotic diseases provides greater opportunity for the evolution of renal complication [25]. Furthermore, familial aggregation of diabetic renal disease indicates that genetic factor is an important determinant of renal outcome. Recently, several polymorphisms have been discovered to independently predict diabetic nephropathy in Chinese patients [26,27] although major genes for diabetic kidney disease, replicable in multiple populations, remain to be found.

Table 1 – Hong Kong Diabetes Registry (1995–2005) 7583 Type 2 diabetic patients with mean follow up of 6 years (Adapted from XL Yang et al. Arch Int Med 2008, Am J Cardiol 2008, Diabetes Care 2007 and Diabetologia 2007).

Death	10.1% (768)
Coronary heart disease	6.7% (507)
Stroke	5.6% (422)
End stage renal disease	10.5% (799)
Cancer	5.4% (413)
Composite events	32.9% (2492)

4. Prevention of diabetic kidney disease

The Diabetes Control and Complications Trial [28], the United Kingdom Prospective Diabetes Study [29] and the Japanese Diabetes Intervention Study [30] have confirmed that tight glycaemic control can prevent the development of all microvascular complications including nephropathy. Once albuminuria occurs, controlling blood pressure assumes critical importance [31]. The use of renin–angiotensin blockade has been a major advance in the management of diabetic nephropathy. Major landmark studies including the Irbesartan Diabetic Nephropathy Trial [32] and RENAAL study [33] have provided compelling evidence to support the renoprotective effect of angiotensin-II receptor antagonists, independent of blood pressure lowering.

In the RENAAL study, a multi-national, multi-ethnic study of subjects with overt diabetic nephropathy and moderate renal impairment, Asian patients treated with placebo had the highest risk of developing ESRD with a 3-year cumulative incidence of over 40% compared to their Caucasian counterparts [25]. Despite this high risk, Asian patients benefited from the inhibition of the renin–angiotensin system with a 38% risk reduction for composite end point (death and ESRD) compared to 18% in the entire cohort (Fig. 1) [25,33].

Blocking the renin–angiotensin system in diabetes has pluripotent effects on modifying the systemic and glomerular haemodynamic [34] as well as attenuating the pro-inflammatory and pro-fibrotic changes in renal parenchyma [35,36]. However, despite receiving the best of therapy even in a controlled trial setting, a considerable proportion of patients

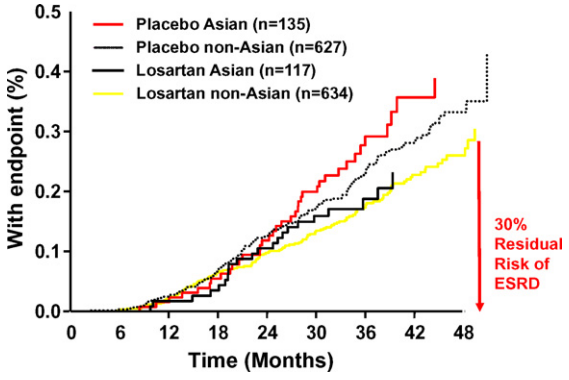

Fig. 1 – The incidence of renal endpoint (defined as doubling of serum creatinine or need of dialysis or death in 1513 type 2 diabetic patients with moderate renal impairment and clinical proteinuria enrolled in the RENAAL Study stratified by ethnicity and treatment (Adapted from Chan JCN et al. Diabetes Care 2004 and Brenner B et al. NEJM 2001).

progressed to develop irreversible ESRD. Using the RENAAL study as an example, up to 30% of patients in the treatment arm reached the combined endpoint of ESRD and death by 4 years [25,33] (Fig. 1).

5. Obesity and inflammation in diabetic kidney disease

There are now several lines of evidence implicating the importance of other metabolic factors including obesity, dyslipidaemia and inflammation in the development of diabetic kidney disease. Based on the Hong Kong Diabetes Registry, the presence of metabolic syndrome increased the risk of diabetic kidney disease by 30%, independent of conventional risk factors of albuminuria, glucose and lipid levels, disease duration, sex, age and medications. Besides, there was graded increase in risk of diabetic kidney disease with increasing number of components of metabolic syndrome, central obesity being the strongest predictor [37].

For many decades, obesity has been known to cause structural changes to the renal parenchyma, and biopsies from obese subjects consistently showed glomerulomegaly with or without focal segmental glomerulosclerosis [38]. While older studies reported obesity-related renal changes only in subjects with extreme obesity, newer data are accumulating to indicate increased risk of renal disease even in submorbid obesity [39,40].

Several mechanisms have been proposed to explain obesity-related renal changes. One explanation is the greater work load imposed on the kidneys as a direct result of larger body mass, as increased tissue turnover and toxic output place additional strains on the nephrons [41]. Another hypothesis is lipotoxicity in which the exposure of renal tissues to excess free fatty acid leads to generation of oxidative stress and cytotoxic lipid products [42]. Recent attention has focused on adipose tissue being a rich source of pro-inflammatory cytokines and growth factors such as tumour necrosis factor α, interleukin-6 and leptin [43]. The plethora of circulating cytokines is believed to have direct effects on renal haemodynamics and glomerular cellularity [44] (Fig. 2).

In support of this notion, in a cross-sectional analysis of Chinese patients with Type 2 diabetes, quintiles of white cell count within normal range were positively correlated with risk of microvascular complications including nephropathy in a graded manner [45]. Along a similar vein, the Insulin Resistance Atherosclerosis Study showed that C-reactive protein and fibrinogen were related to albuminuria in diabetic population [46]. Detailed immunology studies have confirmed aberrant expression of T-cell co-stimulatory molecules, and raised pro-inflammatory cytokines and adhesion molecules in diabetic patients with established nephropathy [47,48]. Adding to this complexity are the predictive role of low grade chronic infection with hepatitis B or C for diabetic kidney disease and adverse outcomes in both Chinese and Afro–American populations [49,50]. Taken together, prevailing low grade inflammation appears to be the sentinel event that causes glomerular and tubular damage in the high glucose milieu of the diabetic kidney, this may provide the pivotal link between obesity and renal disease.

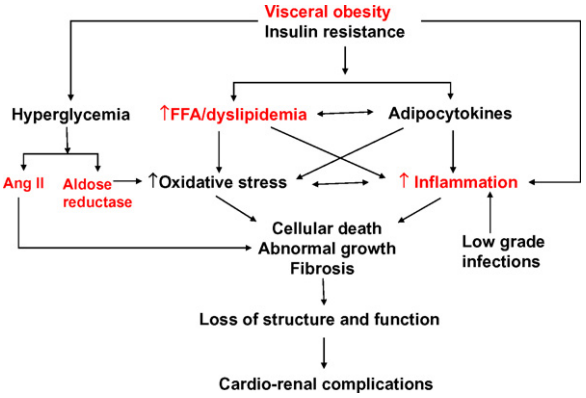

Fig. 2 – Visceral obesity can give rise to increased free fatty acids (FFA) and adipocytokines leading to insulin resistance. The latter can aggravate lipotoxicity and glucotoxcity resulting in increased oxidative stress. Low grade infection may further enhance the inflammatory responses associated with visceral adiposity. These factors can in turn be determined by genetic (e.g. risk variants of angiotensin II and aldose reductase pathways) or environmental factors (e.g. hepatitis B infection or environmental toxins). These metabolic, inflammatory and haemodynamic processes interact in a multiplicative manner resulting in loss of structure and function and multiple organ damage.

6. Anaemia and diabetic kidney disease

Anaemia is a common phenomenon in the diabetic population, with up to 20% of patients being affected [51,52]. Anaemia in patients with diabetes is not restricted to those with renal impairment, as about half have normal renal function [53]. Failure to up-regulate erythropoietin production in response to a declining haemoglobin level has been suggested to be the primary mechanism leading to chronic anaemia [53]. Accordingly, the presence of anaemia may be a distinctive marker for renal tubulointerstitial dysfunction even before overt nephropathy manifests.

Several large scale prospective studies have now shown that anaemia predicts adverse cardiovascular events in patients with diabetic kidney disease. Post hoc examination of the RENAAL study identified haemoglobin as an independent predictor for ESRD in addition to serum creatinine, albumin and proteinuria [54]. In a pooled analysis of community-based cohorts of patients with diabetes, anaemia interacted synergistically with chronic kidney disease to increase the risk of cardiovascular diseases and mortality [55]. Chronic anaemia produces deleterious consequences on the haemodynamics with peripheral vasodilatation and increased cardiac output to cumulate in maladaptive left ventricular hypertrophy. In addition, chronic myocardial hypoxia as a result of reduced oxygen delivery may further contribute to sustained myocardial damage and dysfunction. Since erythrocytes are the key cache of anti-oxidants in the blood stream, anaemia also predisposes to increased oxidative stress. Together with the ectopic vascular calcification due to abnormal bone metabolism with onset of chronic kidney disease, especially in patients with diabetes,

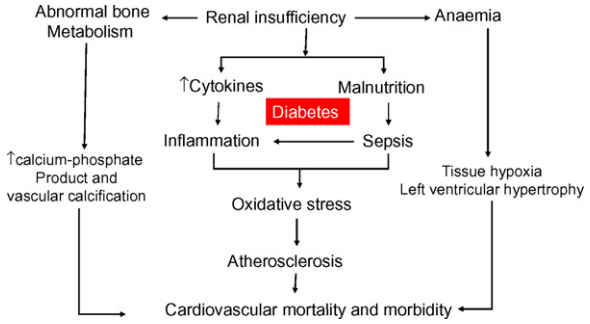

Fig. 3 – With the onset of renal insufficiency, there can be further perturbations of the metabolic environment resulting in increased inflammation, abnormal bone metabolism and anemia. These factors can further increase the risk of cardiovascular complications due to vascular calcification, left ventricular hypertrophy and tissue hypoxia (adapted from Pecoits-Filho R et al. NDT 2004).

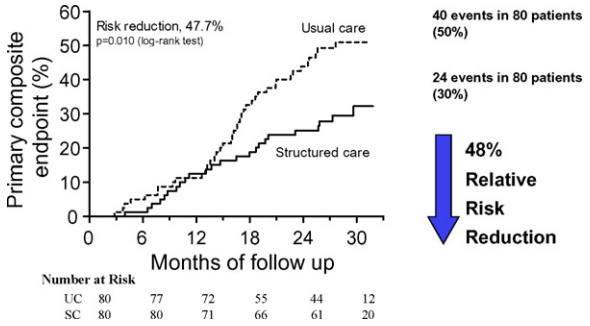

Fig. 4 – Protocol driven care delivered by a pharmacist-diabetologist team with particular emphasis on risk stratification, periodic assessments, treatment to targets and reinforcement of treatment compliance reduced death, renal failure and dialysis rate by 50% in Chinese type 2 diabetic patients with moderate renal impairment compared to usual care (Leung WYS et al. Am J Med 2005).

anaemia and low grade inflammation substantially magnify the risk of cardiovascular diseases in these subjects [21] (Fig. 3).

Despite these pronounced adverse consequences, anaemia is under-recognized and largely untreated in the diabetic population [56]. Previous studies that have examined the effects of early anaemia correction on cardiovascular outcome and mortality in pre-dialysis patients have failed to show a significant clinical benefit [57,58]. The lack of desirable outcome may be accounted for by higher blood pressures, increased blood viscosity and volume overload. There have been several reports suggesting that early erythropoietin treatment may retard the progression of renal diseases and delay the commencement of renal replacement therapy [59–61]. Correction of anaemia improves renal tissue oxygenation, reduces hypoxic damage and associated oxidative stress. However, many of these study cohorts of chronic kidney disease had heterogeneous aetiologies and that patients with diabetic kidney disease were under-represented. Whether correction of anaemia in diabetic patients who are inherently at higher risk of cardiovascular disease than patients with non-diabetic chronic kidney disease confers cardiovascular or renal protection is yet unclear.

7. Translating best evidence to best practice

International authorities have published guidelines based on clinical evidences and expert opinions on best practice and treatment targets. The recently published follow-up report of the STENO-2 study showed an impressive 20% absolute risk reduction in mortality and 30% reduction in cardiovascular events in Type 2 diabetic patients with microalbuminuria who were intensively treated to goals stipulated by the American Diabetes Association guideline [62]. In practice, intensive risk factor control is difficult to accomplish and national audits have revealed suboptimal adherence to monitoring processes, unsatisfactory treatment compliance and low rates of attainment of multiple treatment targets, which collectively explain the poor clinical outcomes. Cost constraint and lack of awareness of latest recommendations contribute to under-use of high-impact therapies such as renin–angiotensin blockade and lipid lowering agents [63–65]. Several pilot programs have shown that using a concerted multi-disciplinary approach with particular focus on aggressive risk factor control, reinforcement of drug compliance and patient's education, tailored to specific healthcare structure and culture, can substantially reduce risk of death and major clinical outcomes by 50–70% [66–68] (Fig. 4).

8. Conclusions

The past two decades have witnessed a remarkable torrent of publication on diabetes and related complications, a reflection of rapidly rising disease prevalence and profound health impact worldwide. Diabetic kidney disease and the inexorable spiral to ESRD have the most debilitating consequences among all diabetes complications. While considerable advances have been achieved in slowing the progression of diabetic nephropathy, the ultimate goal of arresting or reversing disease development remains unfulfilled. Persuasive evidences have implicated non-traditional risk factors including obesity, chronic inflammation and anaemia in the pathogenesis of diabetic kidney disease. Future research is required to study the effectiveness of early intervention of these metabolic risk factors on the progression of cardiovascular and renal diseases in high risk diabetic patients receiving optimal therapy for conventional risk factors.

Conflict of interest

There are no conflicts of interest.

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