EDITORIAL

Diabetic nephropathy: a global and growing threat

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) in developed countries, as type 2 diabetes mellitus has already reached epidemic proportions by the beginning of this millennium.[1] Worldwide, DN is the primary diagnosis in 25 to 50% of people starting renal replacement therapy for ESRD. In the United States, 44% of all new patients starting dialysis in 2009 had underlying DN. In Australia, new type 2 diabetes patients starting dialysis increased 5-fold between 1993 and 2007.[2] In Japan, there was a 7-fold increase in this rate (from 6% in 1983 to the current figure of 40%).[3] In Hong Kong, the situation is no different. The incidence soared from 25% in 1996 to 46% in 2009, according to Renal Registry data from the Central Renal Committee of the Hong Kong Hospital Authority.[4] Thus in this decade, a major proportion of the predicted US$1.1 trillion medical costs of providing dialysis worldwide will stem from a single disease entity—DN.[5]

The global and growing threat of DN due to type 2 diabetes has long caught the attention of the renal community. The International Society of Nephrology (ISN, http://www.isn-online.org/isn/society/about/index.html)—founded in 1960 with the mission to pursue the worldwide advancement of education, science and patient care in nephrology—launched the annual World Kidney Day (WKD) initiative (http://www.worldkidneyday.org) in collaboration with the International Federation of Kidney Foundations in 2006. Its objective was to raise awareness of the importance of our kidneys to our overall health and to reduce the frequency and impact of kidney disease and its associated health problems worldwide. The 2010 WKD, held on 11 March in numerous countries, focused on DN with the slogan "*Protect your kidneys, Control diabetes*". In Hong Kong, this campaign took place on 14 March, and for the first time, the Hong Kong Society of Nephrology (HKSN) hosted a WKD online Chinese version (http://wkd.hksn.org/zh_tw/) to increase public awareness of diabetic kidney disease within the Chinese community. Why have we nephrologists allowed DN to grow to such a threatening magnitude over the past 2 decades? There are a number of astounding reasons.

First, there is the relentless increase in the prevalence of type 2 diabetes as a result of the metabolic syndrome. Despite an emphasis on the need for lifestyle changes—such as weight loss, diet control, and increased physical exercise—the obesity and diabetes epidemic continues to escalate. Lamentably, the number of persons with diabetes, currently estimated at 150 million, is predicted to double by 2025. This epidemic is chiefly of type 2 diabetes. Moreover, the risk of diabetes increases with age, which is particularly worrisome given the increasingly ageing population worldwide.

Second, the risk factors and pathophysiology of DN are not entirely understood. This is reflected by the observation that modern diabetes management including avid blockade of the renin-angiotensin-aldosterone system, and stringent control of glycaemia, blood pressure, and lipid levels, have only achieved limited success in preventing DN and retarding its progression to ESRD. For example, although DN is traditionally viewed as a primarily glomerular disease, emerging evidence indicates that tubular activation and injury plays an important role in its pathogenesis and progression.[6] Reducing sugars may react non-enzymatically with amino groups in proteins or lipids, resulting in oxidative and non-oxidative molecular rearrangements termed the Maillard reactions. In this context, the formation of stable covalent adducts known as advanced glycation end-products (AGEs) appear to be important.[7] In humans, irreversible advanced glycation is a part of the ageing process, which is markedly accelerated in diabetes due to hyperglycaemia. Indeed, both high glucose and AGEs appear to induce tubular inflammation and fibrosis that are intermediate processes ultimately leading to loss of renal function.[8,9] Apart from factors intrinsic to the diabetic status, genetic predisposition also plays a critical role in multiple ethnic groups.[10] Among type 2 diabetics in Hong Kong Chinese, for instance, a variant located in the acetyl-coenzyme A carboxylase beta gene (*ACACB*) is linked to an increased risk for DN.[11]

In terms of renoprotective strategies in patients with DN, there is a long way to go. Clearly, use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is now standard therapy for patients with DN. These agents reduce the progression from normoalbuminuria to micro-albuminuria,[12] from microalbuminuria to macro-albuminuria,[13] and slow the progression to ESRD.[14] Antagonising aldosterone action[15] and resorting to the direct renin inhibitor[16] have shown some promise in recent clinical trials.[17] However, the use of all these agents is often hampered by the development of hyperkalaemia, particularly in patients with advanced disease and those with renovascular disease (a not-an-uncommon vasculopathy in diabetes). Although the glitazones or the peroxisome proliferator-activated receptor (PPAR)-γ agonists may have renoprotective effects in animals,[18] there are mounting concerns that rosiglitazone (Avandia; GlaxoSmithKline, Herts, UK) causes fluid retention. A recent re-appraisal of its clinical utility by the RECORD investigators[19] confirmed that the addition of rosiglitazone to glucose-lowering therapy in type 2 diabetics increased the risk of heart

failure and certain fractures, mainly in women. More alarmingly, two further reports[20,21] encompassing over 260 000 patients associated rosiglitazone use with an increased risk of myocardial infarction, heart failure, stroke, or death. It becomes clear at present that it may be unethical to prescribe Avandia or continue clinical trials using Avandia, particularly in patients at risk of cardiovascular disease. Therefore, the quest for a safe and effective protocol or agent to control DN must continue.

Where do we go from here? At the primary care level, via education, drugs and diet, we need to adequately control all the known reversible risk factors, including: blood sugar, blood pressure, lipid levels, and body weight. We must also ensure smoking cessation, compliance/concordance with drug treatment, and avoidance of nephrotoxins (non-steroidal anti-inflammatory drugs, contrast media, unknown herbal medicines, dietary supplements, and over-the-counter drugs). Renin-angiotensin-aldosterone system blockade needs to be administered where appropriate. Complication screening protocols including those directed at early diabetic kidney disease need to be adhered to. We must also come to terms with the reality that, with our limited knowledge and treatment armamentarium, in some patients renal progression will be inevitable and eventually require referral for specialist care. Finally, we must be alert to recognising non-diabetic renal disease among diabetics, and manage their renal disorder accordingly. At the tertiary care level, basic research and clinical trials must search for a new understanding and novel therapies (agents to reduce renal fibrosis or blockade of AGE formation and downstream signalling pathways). The problem of DN is global and growing, and yet the challenge is undoubtedly local and entails health care provision from primary to tertiary levels.

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