

## Aggressively preventing diabetes

The metabolic syndrome is a known precursor for type 2 diabetes mellitus. Lifestyle changes such as weight loss, diet, and increased physical exercise are known to prevent the occurrence of diabetes. However, despite an emphasis on the need for lifestyle changes, the obesity and diabetes epidemic continues to escalate and diabetes is projected to be the number one killer worldwide in the near future. Moreover, the risk of diabetes increases with age, which is particularly worrisome given the increased aging of the worldwide population.

The metabolic syndrome and/or pre-diabetes are defined by a waistline of  $\geq 102$  cm ( $\geq 40$  inches) for men and  $\geq 89$  cm ( $\geq 35$  inches) for women, a systolic blood pressure  $> 130$  mmHg, a diastolic blood pressure  $> 85$  mmHg or current medication with antihypertensives; fasting triglyceride level  $> 1.7$  mmol/l ( $> 150$  mg/dl); HDL cholesterol level  $< 1.0$  mmol/l ( $< 40$  mg/dl) for men or  $< 1.3$  mmol/l ( $< 50$  mg/dl) for women; a fasting blood glucose level of 5.6–7.0 mmol/l (100–126 mg/dl); or insulin resistance. The association of these criteria with risk of cardiovascular morbidity and mortality increases as an increasing number of criteria are met.

In addition to lifestyle changes, other recommendations have emerged for the treatment of established diabetes mellitus. To decrease the risk of diabetic complications in at-risk patients, evidence suggests that a blood pressure goal of  $< 130/80$  mmHg rather than  $< 140/90$  mmHg is beneficial (Schrier, R. W. *et al. Kidney Int.* **61**, 1086–1097; 2002). A 2010 paper, however, demonstrated that a systolic blood pressure target of  $< 120$  mmHg did not reduce the rate of a composite outcome of fatal and non-fatal major cardiovascular events compared with a target of  $< 140$  mmHg (Cushman, W. C. *et al. N. Engl. J. Med.* doi:10.1056/NEJMoa1001286). Given the association of lipid disorders with diabetes, statin therapy is now recommended to decrease LDL cholesterol  $< 2.6$  mmol/l ( $< 100$  mg/dl). If the diabetic patient has microalbuminuria and/or decreased renal function as defined by an increased serum creatinine level, blockade of the renin-angiotensin-aldosterone system (RAAS) is recommended to decrease the risk of cardiovascular complications and progression of renal dysfunction. Although such treatments are important for patients with diabetes, can one argue that such treatments should be instituted before the horse is out of the barn and diabetes mellitus is established?

On pages 319–330 of this issue of *Nature Reviews Nephrology*, Ruggenti and colleagues discuss the benefit of early treatment in the course of diabetes to prevent renal and cardiovascular complications. To date, however, the benefit of aggressive therapy versus standard therapy for

the prevention of diabetes and cardiovascular complications in patients with the metabolic syndrome and/or pre-diabetes has not been established. A study comparing aggressive versus standard therapy for such patients should have several end points, including the prevention of diabetes and a decrease in cardiovascular complications. Attenuation of urinary albumin excretion (UAE) and of deterioration of renal function should also be assessed. An increase in UAE is a reliable index of diffuse vascular damage in organs other than the kidney, including the heart, brain and peripheral nervous system.

In such a randomized, prevention study, patients with the metabolic syndrome and/or pre-diabetes would be given recommendations for lifestyle changes in addition to receiving either aggressive (blood pressure goal of  $< 130/80$  mmHg, an LDL cholesterol goal of  $< 2.6$  mmol/l [ $< 100$  mg/dl], and RAAS blockade) or standard treatment (blood pressure goal of  $< 140/90$  mmHg, an LDL cholesterol goal of  $< 3.4$  mmol/l [ $< 130$  mg/dl], and no RAAS blockade). This type of multicenter, prospective, randomized study would need sufficient statistical power and duration to enable questions to be definitively answered. Nevertheless, there could not be a more important future focus for worldwide health.

In this regard, a 2010 study in patients with impaired glucose tolerance and either cardiovascular disease or risk factors for cardiovascular disease demonstrated that treatment with the angiotensin-receptor blocker valsartan for 5 years, together with lifestyle changes, reduced the incidence of diabetes by 14% but did not reduce the rate of cardiovascular events compared with lifestyle changes alone (Califf, R. M. *et al. N. Engl. J. Med.* doi:10.1056/NEJMoa1001121).

A prevention study using a multifaceted and aggressive treatment approach for the treatment of the metabolic syndrome and/or pre-diabetes would make it difficult to determine which intervention is most important. However, studies in patients with diabetes have demonstrated that such a multifaceted approach is more effective than any single intervention (Gaede, P. *et al. N. Engl. J. Med.* **348**, 383–393; 2003). Since millions more individuals have the metabolic syndrome and/or pre-diabetes than have diabetes mellitus, would such an aggressive therapeutic approach be formidably expensive? I believe that if the epidemic of diabetes is slowed and rates of cardiovascular complications, renal complications, amputations, adult blindness and neuropathy are decreased, the combined aggressive approach would surely be cost-effective.

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**Competing interests**  
The author declares no competing interests.