

Diabetes mellitus and vascular disease: targeting cardiometabolic risk

The isolation and clinical availability of insulin in the early part of the twentieth century almost inevitably focused attention on the importance of glycaemic control in the management of this condition. It became apparent fairly quickly, however, that, in what were to become known as type 1 diabetic subjects, insulin therapy frequently converted an acute metabolic disorder into a chronic vascular disease. Before long, Himsworth reported insulin-sensitive (type 1) and insulin non-sensitive (type 2) diabetes, a seminal observation on the road to better understanding of these complex metabolic disorders.

A large proportion of the next 70 years focused on the underlying causes of the micro- and macro-vascular complications of diabetes. In this edition of the journal, Barnett (page 9–14) highlights the importance of obesity and adipocyte responses in the pathogenesis of diabetes and cardiovascular risk and describes potential therapeutic approaches which may arise from that understanding. It is important to emphasise the shift from treating individual cardiovascular risk factors to developing strategies that manage multiple risk factors, for a number of reasons. First, there is strong evidence from epidemiology and clinical trials to indicate that multiple risk factor clustering increases risk of vascular outcomes and that managing multiple risks ameliorates the progression of vascular disease. Second, as argued in this review, treatments such as metformin and the glitazones have effects on multiple classical and non-classical cardiovascular risk factors, which have shown some indications of improving vascular outcomes.

Finally, there is the question of our patients themselves. Ask any audience of doctors whether they finish a course of antibiotics for an acute infection once the symptoms improve, and 30–50% will admit they do not. In the mean time, the same audience is often asking a largely asymptomatic group of patients to take up to eight different therapies a day, whilst measuring food intake and glucose levels and having any number of visits to specialist and non-specialist clinics. Clearly, the more things you ask an asymptomatic patient to do, the less likely he or she is to carry them out, and compliance is the largely undiscussed aspect of diabetes management that sits as the elephant in the corner of the room. It is not enough for us merely to ask our patients to do more, in the vain hope of achieving various guidelines: we need to develop therapeutic approaches that support our patients, and one approach is fewer treatments that target more risk.

This brings us to the adipocyte and our developing

understanding of the relationship between obesity, insulin resistance and cardiovascular disease. Once thought of as a simple storage cell, the adipocyte has been elevated to the lofty heights of an endocrine organ that, when fat-filled, secretes multiple adipokines involved in the development of insulin resistance and cardiovascular disease. Evidence indicates that the changes that occur in an adipocyte under these circumstances may be central to the development of type 2 diabetes. This provides us with another potential therapeutic target for the prevention of both type 2 diabetes and associated cardiovascular disease. Clinically, attacking obesity through a diet/exercise programme is associated with improvements in glycaemic control and vascular risk markers when significant weight loss is attained. This is generally associated with a sense of well-being and empowerment which improves quality of life as well. Unfortunately, whilst drugs which target weight loss and/or the adipocyte improve glycaemic control and vascular risk, they are not without significant side effects that limit their clinical usefulness. One view of these observations is that the complex phenotypic shift in a diabetic subject mitigates against 'one size fits all' therapeutic approaches and that we need to develop approaches that take into account individual needs, including how far a patient is willing to go to achieve optimal management. Additionally, the multiple side effects of the glitazones, a class of drugs which target adipocyte transcriptional regulation, perhaps indicate that we are approaching the core of what makes us work and that if we really want to tinker with this process, we need more information about this complex cell.

The last 20 years has seen an unprecedented growth in knowledge about this fascinating condition and its association with cardiovascular disease. We have developed an evidence base, of sorts, with clear guidelines concerning what we should be trying to achieve for our patients. At the same time, there is something vaguely dissatisfying about the whole process. Some patients now do amazingly well compared to 20 years ago, with improved glycaemic control and minimal complications after years of diabetes. However, a very large number have a less satisfying course, spiralling down towards multiple therapies and ultimately insulin treatment, with significant weight gain, vascular complications and serious reductions in quality of life. There is always a call for more research, but the seriousness of the current epidemic of obesity and diabetes calls for a further determined push to develop focused novel therapeutic approaches that improve management by increasing compliance and lessening side effects.

Conflict of interest statement

PJG has acted on Advisory Boards for GlaxoSmithKline, Takeda and Lilly.

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