The great metabolic syndrome debate

Since the original observation that glucose intolerance, visceral adiposity, hypertension and dyslipidaemia tend to cluster with a frequency that is higher than dictated by chance, the existence of a syndrome has been postulated. This metabolic syndrome encompasses a constellation of metabolic disturbances and all known cardiovascular disease (CVD) risk factors, and is a common, age-related disorder mainly driven by the increasing prevalence of obesity; it has been claimed to be a powerful predictor of CVD. However, the existence of such a syndrome has recently been challenged on the basis of uncertainty of the pathogenetic mechanism(s), too many definitions and diagnostic criteria, and doubt about any advantage as compared to existing risk calculation engines. In this issue, Dr Balkau revisits the evolution of the metabolic syndrome concept and provides a critical appraisal of its clinical relevance.

Since the original work of Reaven,[1] insulin resistance has been considered the common denominator of the many metabolic and non-metabolic abnormalities of the syndrome. In spite of the fact that insulin resistance is generally defined as the impaired ability of insulin to promote glucose utilisation in insulin-dependent tissues, recent work has provided the basis for understanding how impaired insulin-signalling activation and concomitant hyperinsulinaemia may trigger, in tissues such as the endothelium, pathways involved in the atherogenic process as well as inflammation. Nonetheless, insulin resistance is unlikely to be the unique pathogenetic mechanism, since only a certain percentage of individuals with metabolic syndrome have impaired insulin sensitivity, and not all the insulin-resistant subjects have the syndrome. This is also reflected in the frequent use of diagnostic criteria for the syndrome not necessarily including measurements of insulin action.[2,3] However, the advantage of a definition also relies in its practicability. From this point of view it appears that individuals meeting the Adult Treatment Panel (ATP) III criteria usually have other abnormalities that may contribute to increased cardiovascular risk.

To what extent the metabolic syndrome may perform better than other risk calculators remains a matter of discussion. However, it is apparent that such risk calculation would be improved by separately considering specific conditions, for instance patients with and without diabetes. Finally, when different therapeutic approaches toward one or another component of the syndrome are considered it becomes clear how difficult it is to affect the entire syndrome, strengthening the entangled interconnection of the features within the syndrome.

In spite of all these limitations, and an urgent need for further research, the suggestion of the European Association for the Study of Diabetes/American Diabetes Association joint document[4] to 'treat all cardiovascular risk factors without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome' is rationale enough. This is not because it offers a way to overcome ongoing controversy, but because it is based on intervention trials. Thus, in the Steno 2 Study, intensive treatment of hyperglycaemia, hypertension and dyslipidaemia, together with aspirin could reduce cardiovascular disease by 53%.[5] In the meantime, the positive hints generated by discussion about the metabolic syndrome should not be discarded. These precious hints can be summarised as follows:

- Although imprecisely defined, the syndrome may offer a simple public health concept and identifiable starting point for clinical intervention
- Even if there is a lack of certainty regarding its pathogenesis, insulin resistance may contribute to the clustering of several factors, if not adding to them in term of CVD risk
- There may be doubt regarding its value as a CVD risk marker, but insulin resistance and its cluster of associated abnormalities are probably as important as hypercholesterolaemia as a CVD risk factor.

Stefano Del Prato, MD
Professor of Endocrinology
University of Pisa, Italy

References

1. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1495–1507.
2. Alberti KGMM, Zimmet PZ, World Health Organization (WHO) Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
3. Grundy SM, Brewer HB, Cleeman JI, *et al.* Definition of metabolic syndrome. Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004; **109**: 433–438.
4. Kahn R, Buse J, Ferrannini E, *et al.* The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabet Care* 2005; **29**: 2289–2304.
5. Gaede P, Vedel P, Larsen N, *et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383–393.