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EDITORIAL

The unhealthy fruits of insulin resistance

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Extracting energy and substrates from the environment and excreting useless or even toxic by-products is key to cellular survival. However, in the evolution from a single-cell organism to a highly complex multi-organ multi-cellular species, cells have differentiated in function, needs and in their access to the environment. Therefore, it is no surprise that the elaborate cooperative cellular system that is called the human species has concomitantly developed a highly integrative and complex metabolic system which tries to ensure that the needs of individual organs and cells are appropriately met.

This also explains why a seemingly simple disease entity called 'type 2 diabetes mellitus' (DM2) in fact encompasses a huge spectrum of differing underlying metabolic disturbances, all hallmarked by a high glucose. Moreover, as the paper by Brouwers *et al.* on familial combined hyperlipidaemia (FCHL) and subsequent risk of diabetes in this issue of our Journal nicely illustrates,[1] DM2 itself is just one part of a far wider group of metabolic disturbances that may share some features but differ in others.

For clinicians it is appealing and sometimes useful to try and classify these diseases in distinct groups based on certain clinical features. However, this approach is fraught with problems because of the clinical heterogeneity in (the presence of) symptoms, and because a simple clustering of symptoms such as the 'metabolic syndrome' does not correlate with one single and uniform pathophysiological explanation.[2]

This is also clear from the data of Brouwers *et al.* Within the syndromal diagnosis of 'FCHL' two types of dyslipidaemia may occur, either alone or in combination. However, these same dyslipidaemias may also occur in the context of other abnormalities, most notably those associated with obesity and insulin resistance. And, as the authors demonstrate, against this background of obesity and insulin resistance, DM2 is more likely to develop. Clearly the distribution of BMI was not equal between cases and controls, with about 60% of spouses in the lower BMI quartiles and 60% of cases in the higher BMI quartiles. Accordingly, the authors corrected for confounders associated with insulin resistance such as BMI, and the association they found is persistent. From their data the authors subsequently conclude that 'FCHL is a dynamic entity that may progress to DM2'.

However, what is most noteworthy in their data is that of all variables, only correcting for baseline insulin levels negated the association they found between FCHL and subsequent diabetes. Thus, it would be more appropriate to say that FCHL and DM2 are fruits of a tree firmly rooted in the myriad of metabolic effects of insulin and insulin resistance. Some (genetic) factors may eventually prove to be root causes of both diseases and one candidate is the upstream transcription factor 1 (USF1).[3] However, it is the genetic and environmental factors that are superimposed on this basis, e.g. increased apolipoprotein B production or beta-cell vulnerability, which determine whether the primary phenotype will be FCHL or DM2, and in which order these abnormalities will develop. Unfortunately, no healthy fruit grows from the tree of insulin resistance, and some branches will end up carrying both fruits at the same time.

REFERENCES

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