Cardiometabolic disease: the new challenge?

Reaven's hypothesis

The pathophysiology of type 2 diabetes and its relationship with cardiovascular disease remains incompletely understood, and controversial! In his 1988 Banting lecture Gerry Reaven drew together pathophysiological and epidemiological observations on the possible role of insulin resistance.[1] He noted that resistance to insulin-mediated glucose uptake was present in the majority of people with impaired glucose tolerance and type 2 diabetes, as well as one-quarter of non-obese individuals with normal glucose tolerance. He suggested that deterioration of glucose tolerance could only be prevented if the beta cell was able to increase insulin secretion and maintain chronic hyperinsulinaemia, and when this could not be achieved gross decompensation of glucose tolerance occurs, i.e. type 2 diabetes. He specifically suggested that the relationship between insulin resistance, plasma insulin level and glucose tolerance was mediated by changes in free fatty acid concentrations, which normally can be surpassed by small increments in insulin concentration, and that if hyperinsulinaemia cannot be maintained increased free fatty acids would lead to increased hepatic glucose production. This in turn would cause hyperglycaemia because of peripheral resistance to insulin-stimulated glucose uptake.[1]

Furthermore, he suggested that the 'compensatory' hyperinsulinaemia may lead to hypertension, and the relationship between hypertension, insulin resistance and hyperinsulinaemia might be causal.[1] He raised the possibility that insulin resistance and hyperinsulinaemia were involved in the aetiology and clinical course of type 2 diabetes, hypertension and coronary heart disease. As epidemiological support for this pathophysiological hypothesis he observed that there was often clustering of risk factors for coronary heart disease in the one individual, including insulin resistance, glucose intolerance, hyperinsulinaemia, increased plasma triglycerides, decreased HDL cholesterol and hypertension. He termed the cluster 'Syndrome X', later called 'Reaven's syndrome' by others. Interestingly, obesity was not a part of the cluster, probably reflecting the time when these observations were made.

Definitions of the metabolic syndrome

The following two decades have seen an explosion in research into both the pathophysiology and epidemiology of what has subsequently been called 'the insulin resistance syndrome' or 'the metabolic syndrome', depending on whether insulin resistance or central adiposity is believed to be the main abnormality. Several other risk factors, including measures of obesity, have been added, and various expert bodies have tried to put numerical values on these factors to enable standardisation between studies and comparisons between populations. The WHO definition, a by-product of the committee that met to define and classify diabetes, combined factors that were thought would give useful pathophysiological and epidemiological data.[2]

In the US, the National Cholesterol Education Program Expert Panel (ATPIII) met to decide which patients should be treated with lipid lowering therapy. This was predominantly to give advice to family doctors on the use of statins and other lipid lowering therapies.[3] They offered the metabolic syndrome as a secondary target after the primary target of lowering of LDL cholesterol. The management of the metabolic syndrome was given two objectives: to reduce the causes (obesity and lack of physical activity) and to treat associated non-lipid and lipid factors. They defined the metabolic syndrome pragmatically using factors that would be easy to measure in an office practice, including abdominal obesity. As the ATPIII definition of the metabolic syndrome was easier to apply in clinical practice than the WHO definition it was also widely used in clinical research. Additionally, several studies compared the utility of the different definitions in different geographical populations.

Reflecting advances in the understanding of the pathophysiology the International Diabetes Federation (IDF) convened an expert panel that placed central obesity (race-specific) as a key component along with two out of four other factors,[4] leading to a host of publications from various centres throughout the world comparing this new IDF definition with WHO and/or ATPIII criteria in different populations. Shortly afterwards, another expert panel, convened by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), dropped the bombshell that was summarised in an editorial in *Diabetologia* as 'the myth of the metabolic syndrome'.[5]

The myth of the metabolic syndrome?

This joint statement from the ADA and EASD, published in both *Diabetes Care* and *Diabetologia*, takes a critical look at the 'metabolic syndrome' and concludes that it should not be designated as a syndrome.[6,7] It is a thorough, if one-sided, review of the literature and concludes that clinicians should evaluate and treat all cardiovascular disease (CVD) risk factors without regard as to whether the patient meets the criteria for the diagnosis of the metabolic syndrome.[8] It is extraordinary that this has been put out on behalf of these two organisations without any chance for the opposing position to be put that there is indeed clinical usefulness for the concept of the metabolic syndrome.

The continuing need for the concept of the metabolic syndrome has been robustly defended, in journals and on-line, by Paul Zimmet and George Alberti.[9,10] They point out that the concept of the metabolic syndrome has attracted much interest in the cardiovascular field, and the cardiologists have recognised that the clustering of risk factors is a pattern of risk increasingly observed in persons exhibiting CVD. In my opinion the stance adopted by the ADA and EASD may be scientifically correct but is politically naïve, and in effect it has handed over the concept of the metabolic syndrome and all of the research funding that goes along with it to the cardiology community.

Zimmet and Alberti also comment that the nomenclature has posed a problem, and identify several other terms that have been used to describe the syndrome, including the deadly quartet – dysmetabolic syndrome, hypertriglyceridaemic waist, cardiometabolic syndrome and cardiometabolic risk.[9]

What is cardiometabolic disease?

'Cardiometabolic disease' is a term initially used by Pescatello in exercise physiology literature, and is essentially a simplification and modernisation of Reaven's hypothesis.[11] She described a clustering of disorders (abdominal adiposity, hypertension, dyslipidaemia, hyperinsulinaemia and glucose intolerance) that together lead to CVD and type 2 diabetes. She observed that there had been a sudden increase in overweight and obesity but only a slight increase in food intake, suggesting that physical activity was more important than calorie intake in causing obesity. She hypothesised that increases in low to moderate physical activity may result in significant health gains, including the prevention of CVD and the prevention of diabetes, without preventing overweight or obesity, and that this might be a more realistic public health target than unrealistic reductions in energy intake. This provocative view of the problem from an exercise physiology perspective may well upset dietitians but will please the food industry!

More recently, the term 'cardiometabolic disease' has been extended to describe the interface between cardiology and diabetes, and to describe pharmacological interventions that would reduce cardiovascular and metabolic endpoints.

What is the ideal cardiometabolic intervention?

The ideal cardiometabolic intervention would reduce weight and abdominal adiposity, lower LDL cholesterol and triglycerides, increase HDL cholesterol, lower blood pressure, reduce insulin resistance and improve glucose tolerance. The gold standard would be proven reduction of cardiovascular events in a double-blind, placebo controlled trial, proven reduction in the development of diabetes and/or sustained reduction in HbA_{1c}. For maximum applicability it should have no side effects or contraindications.

Of currently available medications metformin has been proven to reduce myocardial infarctions in an open study (UKPDS)[12] and to reduce the development of diabetes in a double-blind study (DPP),[13] although the effects were not as prominent as changes in lifestyle, and side effects were common. In STOP-NIDDM, acarbose reduced the development of diabetes[14] and reduced the development of a composite cardiovascular outcome,[15] but again side effects were common and tolerability a problem. Pioglitazone has been shown to reduce cardiovascular outcomes in the PROactive study,[16] and to reduce the development of diabetes in the PIPOD study.[17] At present, however, its licence is for the treatment of patients with type 2 diabetes, and it is not yet approved for cardiovascular risk reduction or the prevention of diabetes.

How effective should an intervention be?

Pioglitazone and metformin each reduce HbA_{1c} by around 1%, and drugs that reduce the HbA_{1c} by a lesser amount would generally be deemed ineffective as treatments for type 2 diabetes by the licensing authorities. Pioglitazone has modest effects in reducing systolic and diastolic blood pressure, but would not be considered as a treatment for hypertension. Several new agents have beneficial effects on multiple components of the metabolic syndrome. Rimonabant is a selective CB_1 blocker that reduces weight, waist circumference and triglycerides, with increases in HDL cholesterol.[18] Data for patients with diabetes were presented at the ADA last year and showed a 0.6% drop in HbA_{1c} in addition to the above beneficial effects. Drug licensing authorities will have a difficult decision to define the exact clinical place for these novel therapies.

Cardiometabolic risk assessment

A recent sophistication has been the concept of extending routine systematic assessment from cardiovascular risk to cardiometabolic risk, i.e. the risk of developing CVD and/or diabetes. Previous risk assessment tools concentrated on coronary heart disease risk, and more recent risk tools have expanded to include total cardiovascular risk. This is estimated by factoring in the recognised cardiovascular risk factors into a risk engine, e.g. based on the Framingham equation. Yet the risk of developing diabetes is currently estimated in clinical practice using a single estimation – blood glucose. Vasudevan and Ballantyne suggest that the components of the metabolic syndrome could be used to assess the absolute risk for the development of diabetes with a similar equation or risk algorithm, and that this could be used to identify individuals at the highest risk of developing diabetes who might most benefit from expensive lifestyle modification programmes and/or pharmacotherapy.[19]

Conclusions

While arguments rage on the existence of the metabolic syndrome, clinicians will continue to treat multiple cardiometabolic risk factors. The extended benefits or disbenefits of the treatment on other aspects of risk will be considered when making treatment choices, e.g. beta blockers will be less used for the treatment of hypertension because of the increased risk of developing diabetes. Lifestyle changes and new drugs will have a role in improving multiple cardiometabolic risk factors.

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