



The Nutrition Society Winter Meeting was held at the Royal Society of Medicine, London, on 4–5 December 2018

Conference on ‘Optimal diet and lifestyle strategies for the management of cardio-metabolic risk’ Plenary Lecture

From syndrome X to cardiometabolic risk: clinical and public health implications

Jean-Pierre Després^{1,2,3} 

¹Centre de recherche sur les soins et les services de première ligne–Université Laval, Québec, QC, Canada

²Centre de recherche de l’Institut universitaire de cardiologie et de pneumologie de Québec–Université Laval, Québec, QC, Canada

³Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, QC, Canada

Although the first description of a syndrome defined by the co-existence of atherogenic and diabetogenic metabolic abnormalities is debated in the literature, it was Gerald Reaven who proposed, in his landmark 1988 Banting award lecture, that a significant proportion of individuals (with diabetes or not) were characterised by insulin resistance causing prejudice to cardiovascular health. However, Reaven was influenced by seminal observations made more than 50 years earlier by Himsworth who proposed that there were two forms of diabetes (insulin resistant *v.* insulin sensitive). Reaven went further in proposing the theory that insulin resistance was the most prevalent cause of CVD associated with metabolic abnormalities that he named syndrome X. Because there was a syndrome X documented in cardiology, the term evolved to insulin resistance syndrome. As Reaven could also find insulin-resistant individuals in non-obese subjects, he did not include obesity as a feature of syndrome X. Imaging studies then revealed that excess adipose tissue in the abdominal cavity, a condition described as visceral obesity, was the form of overweight/obesity associated with insulin resistance and its related abnormalities. As obesity risk assessment and management remain largely based on body weight (BMI) and weight loss, it is proposed that our clinical approaches and public health messages should be revisited. First, patients should be educated about the importance of monitoring their waistline as a crude index of abdominal adiposity. Secondly, public health approaches focussing on ‘lifestyle vital signs’ including achieving healthy waistlines rather than healthy body weights should be developed.

Healthy lifestyle: Insulin resistance: Metabolic syndrome: Visceral adipose tissue

We are undoubtedly going through an epidemic of chronic lifestyle diseases. For instance, the prevalence of obesity keeps increasing all over the world and is closely related to chronic metabolic diseases such as type 2 diabetes, hypertension and CVD^(1–3). Recent data suggest that in a few years, half a billion people worldwide will have to live with type 2 diabetes⁽²⁾. Clearly, our lifestyle habits have radically changed over the past century as sedentary behaviours now kill more people than smoking⁽⁴⁾. Accordingly, overall nutritional quality has deteriorated

with overconsumption of processed foods with added sugar, salt and refined carbohydrates^(5,6). Thus, although sophisticated healthcare systems of many affluent countries can provide a decent life expectancy to their citizens, life expectancy being healthy and free from chronic diseases has not followed⁽⁷⁾, leading to prohibitive costs associated with medical treatments and procedures to keep these patients alive⁽⁸⁾. Consequently, an expanding proportion of our population lives longer while nevertheless carrying the burden of being afflicted by costly chronic diseases.

Abbreviations: SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Corresponding author: Jean-Pierre Després, email Jean-Pierre.Despres.ciusscn@sss.gouv.qc.ca



Pioneers in the field of endocrinology and metabolism have generated concepts and hypotheses that remain very relevant to the afore-mentioned issues. For instance, in 1988, while giving his famous Banting award lecture, Reaven was the first to propose that the most prevalent cause of CVD was not an elevated cholesterol concentration but rather a constellation of abnormalities related to a reduced responsiveness to insulin⁽⁹⁾. Reaven proposed that insulin resistance, which can be assessed or estimated by various techniques *in vivo* was (1) a prevalent condition in the population (about 25 %); (2) associated with a typical dyslipidaemic state (high TAG and low HDL-cholesterol concentrations) as well as with elevated blood pressure and fasting hyperinsulinaemia and (3) a central component of an atherogenic cluster of metabolic abnormalities which was a common cause of CVD^(9,10). It is also appropriate to point out that Harold Himsworth was a major influence in the Reaven proposal as the former was the first to suggest, in the 1930s, that there were two forms of patients with diabetes (those who were insulin sensitive and those who were insulin resistant)⁽¹¹⁾. Reaven extended that notion and proposed that insulin resistance could also be found in the non-diabetic population.

While exploring factors associated with insulin resistance, Reaven also noted that he could observe individuals with obesity who were nevertheless insulin sensitive whereas he could find insulin resistance in non-obese subjects; this is why he did not include obesity as one of his features of syndrome X. Imaging studies providing more sophisticated and accurate measurements of body composition initiated more than 30 years ago have since shed some light on this issue.

For instance, in 1983, Matsuzawa and co-workers in Japan were the first to report, using images generated by computed tomography, that there were remarkable differences in the way people would store abdominal fat (abdominal computed tomography images showing that some individuals had a large accumulation of subcutaneous adipose tissue (SAT) whereas others had considerable amount of intra-abdominal or visceral adipose tissue (VAT) with little subcutaneous fat)⁽¹²⁾. Inspired by these results, we began, in the mid-80s, to systematically scan abdomens of asymptomatic men and women with the use of computed tomography. At that time, we quickly reached the conclusion that there were indeed substantial individual variations in VAT *v.* SAT accumulation. On average, men were found to have twice the amount of VAT compared to premenopausal women, whereas middle-aged men and women had more VAT than young adults^(13,14). Reviewing our early work on the topic would be beyond the scope of the present paper and the reader is referred to previous review papers on the topic^(15–19). Fig. 1 summarises the constellation of metabolic abnormalities that we found to be associated with excess VAT and not with SAT. Thus, our early findings have contributed to explain why Reaven could not find an association between obesity and features of his syndrome X: excess VAT, not excess BMI *per se*, was the main driver of the dysmetabolic state of syndrome X. Subcutaneous obesity, in the

absence of excess VAT, was not found to be associated with substantial deteriorations in insulin resistance and related metabolic abnormalities. Many imaging studies (using computed tomography or MRI) have since confirmed that excess VAT is a key correlate of the features of Reaven syndrome X^(17,20–24). There is also evidence that lower body or gluteofemoral fat is negatively associated with the risk of CVD among individuals with obesity in the Dallas Heart Study⁽²⁵⁾. These results suggest that subcutaneous fat, particularly lower body subcutaneous fat, may not cause any prejudice to cardiometabolic health and may even be protective against the development of cardiometabolic outcomes. Such notion is fully consistent with the findings of a study by Klein *et al.*⁽²⁶⁾ conducted more than 15 years ago in a sample of women with obesity reporting that liposuction of a substantial amount of SAT was not associated with improvements in the cardiometabolic risk profile.

Because there is a syndrome X in cardiology (clinical symptoms of CHD without evidence of CHD from angiographic investigations)^(27,28), the term insulin resistance syndrome has also been used to describe the constellation of metabolic abnormalities first described by Reaven. Furthermore, as measuring insulin resistance cannot be performed in primary care, Grundy and co-workers then proposed at the beginning of the millennium the use of some simple clinical tools to identify individuals who would be very likely to be characterised by the abnormalities of insulin resistance: the metabolic syndrome was born (National Cholesterol Education Program Adult Treatment Panel III)⁽²⁹⁾. Because insulin resistance is frequently found among individuals with abdominal obesity and because we had previously proposed that a large waistline combined with elevated plasma TAG concentrations was predictive of visceral obesity⁽³⁰⁾, the committee proposed that simple variables such as waist circumference, TAG, HDL-cholesterol, blood pressure and glucose level could be used to discriminate individuals likely to be insulin resistant. Countless studies that have since compared individuals showing at least three out of these five clinical criteria *v.* those not meeting these criteria, the vast majority of them confirming that a clinical diagnosis of the metabolic syndrome was predictive of an increased risk of CVD^(31,32). Thus, although its clinical relevance has been questioned^(33,34), a clinical diagnosis of the metabolic syndrome is useful to at least identify the subgroup of overweight or obese individuals more likely to be characterised by an excess of VAT and related metabolic abnormalities^(17,35,36).

Because measurement of insulin resistance is not included as a criterion of the metabolic syndrome, Reaven had also expressed concerns about the metabolic syndrome as a useful concept in clinical practice^(37–39). However, as the key point to be made is that insulin resistance is a central abnormality associated with an atherogenic and diabetogenic cluster of metabolic abnormalities, we have also suggested that such constellation should be called the Reaven syndrome⁽¹⁷⁾. Hopefully, history will fix this issue and make sure that the seminal work of this pioneer is recognised⁽⁴⁰⁾.

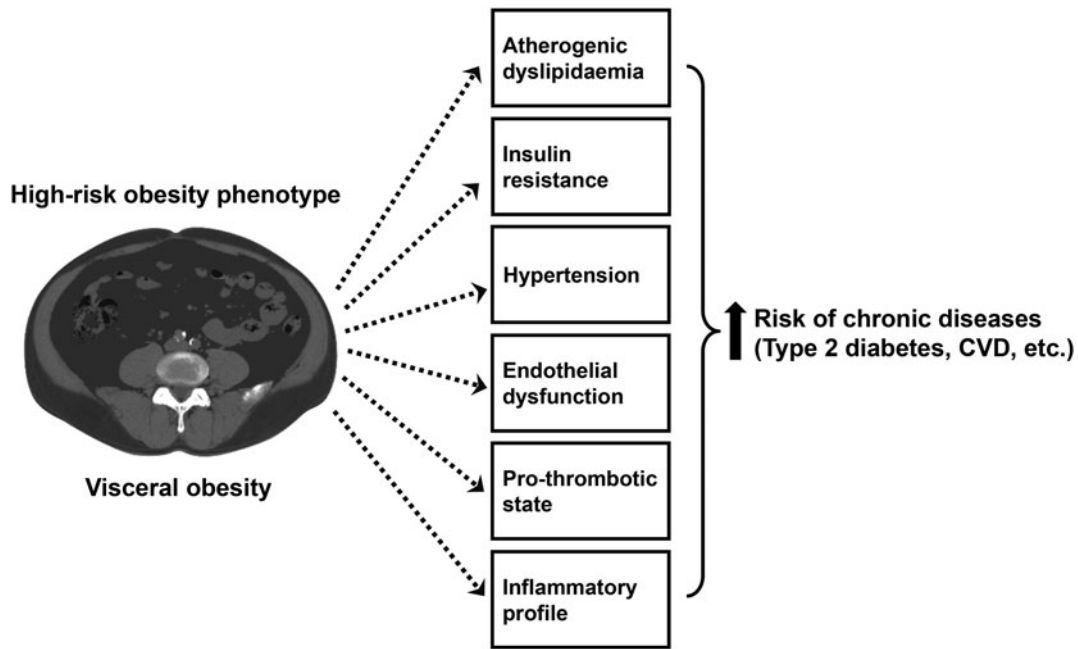


Fig. 1. Simple overview of atherogenic and diabetogenic complications associated with an excess amount of visceral adipose tissue (identified in dark grey within the abdominal muscle wall) increasing the risk of developing type 2 diabetes and CVD (CVD).

Critiques of the metabolic syndrome

Another critique addressed to the metabolic syndrome has been to question its added value in clinical practice^(33,34). For instance, a clinical diagnosis of the metabolic syndrome (presence) does not provide information about its severity⁽³⁵⁾. In addition, although many studies including meta-analyses have shown that patients with the metabolic syndrome are at increased risk of CVD compared to those without the metabolic syndrome^(31,32), to what extent its diagnosis provides further information about absolute risk after consideration for traditional risk factors is uncertain⁽²⁰⁾. For instance, HDL-cholesterol, blood pressure and glucose (or diabetes) are already considered in global risk assessment algorithms^(41–43). On that basis, we have proposed that the presence of the metabolic syndrome most often predicts an increase in relative CVD risk and that its presence combined with classical CVD risk factors should be considered in the evaluation of global cardiometabolic risk (Fig. 2)⁽²⁰⁾. The reader is referred to previous reviews for a more complete discussion of this issue^(17,20,44).

Visceral adiposity: a key feature in the Reaven syndrome

Why does an excess of VAT cause prejudice to health? Currently, three non-mutually exclusive scenarios have been proposed^(17,19,20). First, VAT has a peculiar metabolism compared to subcutaneous fat. It becomes hypertrophic when enlarged, exposing the liver through the portal circulation to high concentrations of glycerol and NEFA. Secondly, when enlarged, VAT become infiltrated with inflammatory macrophages which contribute

to the pro-inflammatory state of visceral obesity. Thirdly, and most importantly, evidence also suggests that excess VAT is a marker of the relative inability of SAT to act as a protective ‘metabolic sink’ when facing an energy surplus. Under this scenario, when the capacity of SAT becomes saturated, the overflow of lipids leads to their accumulation elsewhere, not only in VAT but also in the liver, the heart, the skeletal muscle, the kidney, the pancreas, etc., a phenomenon referred to as ectopic fat deposition^(18,19,23,45–47). Under this model, excess VAT can be considered as an excellent marker and a consequence of dysfunctional adipose tissue, explaining why it is often accompanied by ectopic fat deposition.

In this regard, studies that have focused on liver fat have also shown that non-alcoholic fatty liver disease has become a prevalent condition and a source of major concern, being the most common cause of liver failure and transplant^(48,49). Excess liver fat (which can now be non-invasively measured by magnetic resonance spectroscopy) has also been associated with the features of the insulin resistance syndrome^(48,50,51). We have therefore been interested in deciphering the contributions of VAT *v.* liver fat in modulating cardiometabolic risk. Results obtained from a large cardiometabolic imaging study (The International Study of Prediction of Intra-abdominal adiposity and its Relationships with Cardiometabolic risk/Intra-abdominal Adiposity) have first confirmed that both VAT and liver fat were independently associated with type 2 diabetes⁽⁵²⁾. However, results from this cohort have also revealed that the most prevalent form of excess fatty liver was found among subjects with excess VAT whereas elevated liver fat in the absence of excess VAT was a much less prevalent condition⁽⁵³⁾. Therefore, from a clinical standpoint,

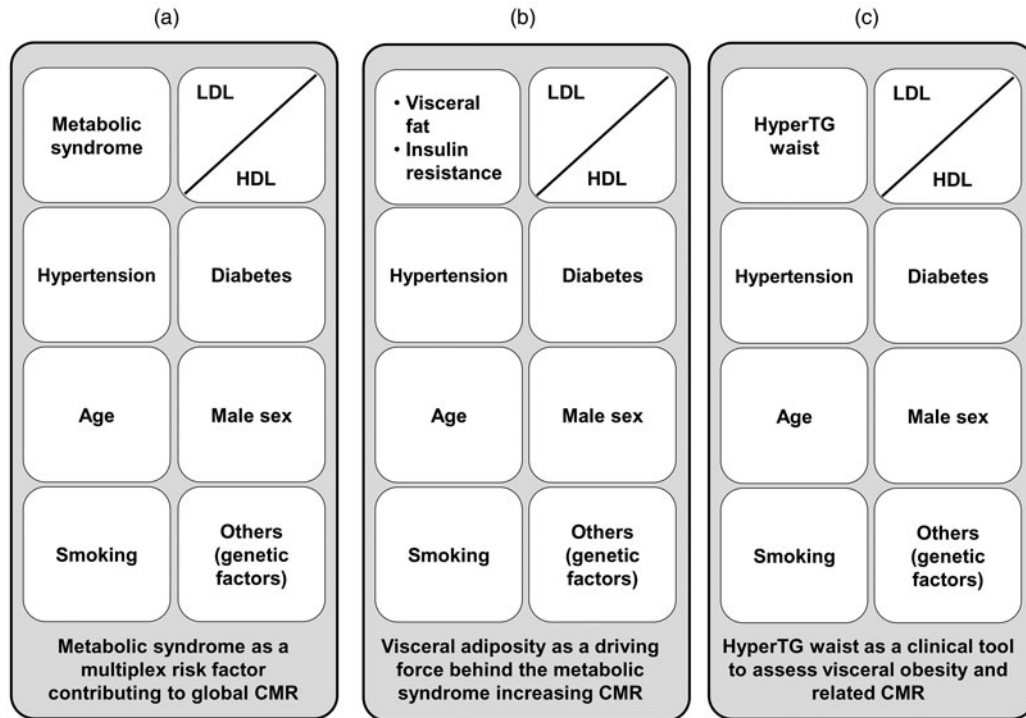


Fig. 2. Contribution of metabolic syndrome to global cardiometabolic risk (CMR). (a) Under this model, metabolic syndrome is considered as a multiplex risk factor that cannot be used as a risk calculator but rather as one component of global CMR. (b) This model shows the contribution of visceral adiposity as the driving force behind the most prevalent form of the metabolic syndrome. (c) This model shows the added value of hypertriglyceridaemic (hyperTG) waist as a simple clinical tool to identify individuals most likely to be characterised by visceral obesity. Under this model, hyperTG waist alone does not assess the global risk but is useful as its presence further increases the global risk associated with traditional CVD risk factors. Adapted from⁽²⁰⁾.

considering the increasing prevalence of non-alcoholic fatty liver disease, we believe that it is important to emphasise to clinicians that its most prevalent form is found among men and women with visceral obesity.

Along with the seminal observations of Himsworth, it is also important to point out that about 75 % of patients with type 2 diabetes are characterised by some excess of VAT/ectopic fat, whereas about 25 % of them do not show substantial VAT/ectopic fat deposition. Thus, despite their diabetes, this less prevalent subgroup of patients with almost normal levels of VAT/ectopic fat is at a lower cardiometabolic risk than patients with both diabetes and excess VAT/ectopic fat, a finding concordant with previous observations that features of the metabolic syndrome, often but not always present in patients with type 2 diabetes, contribute to exacerbating their CVD risk⁽⁵⁴⁾.

Assessment and management of visceral obesity in clinical practice: time for a paradigm shift

Traditionally, as many clinical obesity guidelines consider obesity as a disease, the rationale for its treatment has been very simple: as excess body weight/fat is bad, weight loss must be targeted and is the criterion to assess therapeutic success. From the evidence reviewed earlier,

it is proposed that a paradigm shift is necessary. First, patients who are overweight or obese are quite heterogeneous regarding their health risk and the term ‘metabolically healthy obesity’ has even been coined to describe a subgroup of patients who may be at a much lower health risk than expected from their obesity⁽⁵⁵⁾. However, to go as far as stating that they are metabolically healthy is heavily debated as it depends upon how we define ‘healthy’⁽⁵⁶⁾ but these individuals are certainly at lower risk than patients with excess VAT⁽⁵⁷⁾. These lower risk patients characterised by subcutaneous obesity are likely to benefit less from weight loss (in terms of improvement of their CVD risk factors) than individuals with an excess of VAT and liver fat. In this regard, lifestyle intervention studies involving diet and exercise have shown that a substantial loss of VAT can be achieved in patients with initially high levels of VAT and that such changes could sometime be observed in the absence of weight loss^(58–60). Under those circumstances, a given lifestyle modification programme will not only produce a loss of VAT but it may also generate an increase in muscle mass, leading to trivial changes in body weight^(60,61). On that basis, we have previously proposed that weight loss may not optimally assess the responsiveness of some overweight/obese individuals with excess VAT and that waist circumference may be more appropriate

to evaluate the loss of unhealthy body fat induced by a lifestyle modification programme⁽⁶²⁾. Thus, waist loss may be clinically more relevant than weight loss. A legitimate question to be asked is: What is the magnitude of waist reduction required to generate improvements in the indices of cardiometabolic health? Additional lifestyle intervention studies will be needed to specifically address this issue but results achieved so far are encouraging. For instance, although they did not target a reduction in their participants' waistlines as a primary endpoint, the two well-known Diabetes Prevention Study⁽⁶³⁾ and the Diabetes Prevention Program⁽⁶⁴⁾ reported average reductions in waist circumference of about 4 cm, such change being associated with a substantial reduction in the incidence of type 2 diabetes (−58 %) in the intervention arms. In a lifestyle intervention study specifically conducted in abdominally obese men, we also reported substantial improvements in the indices of cardiometabolic health associated with a reduction of waist circumference slightly >5 cm over 3 years⁽⁶⁵⁾. Lastly, the workplace health lifestyle intervention programme conducted by our laboratory and producing substantial improvements in the cardiometabolic health profile of blue- and white-collar workers also generated an average reduction of 4 cm in the waistline of participants over a period of 3 months⁽⁶⁶⁾. Although further work will be required to fully address this issue, the afore-mentioned results suggest that even a waist circumference reduction of moderate magnitude (≥4 cm) could generate substantial benefits in terms of cardiometabolic health.

Secondly, as high-risk patients with excess VAT often have a diet of low overall nutritional quality and are too often sedentary, it would be important, in addition to monitoring waist circumference changes over time, to target overall nutritional quality and level of physical activity. Discussion of results obtained in a health promotion programme conducted in our laboratory^(66–68) has shown the value of using simple field tools to rapidly and reliably measure overall nutritional quality using a food-based questionnaire and level of physical activity^(66,67) and that these two lifestyle metrics were powerful correlates of waist circumference and related cardiometabolic risk.

As cardiorespiratory fitness is currently the most powerful variable to discriminate cardiometabolic risk^(69–71), it has been proposed that we should find ways to measure it in primary care, even with the use of non-exercise equations⁽⁷¹⁾. Again, results from our workplace health programme have shown that four simple lifestyle metrics (waist circumference, cardiorespiratory fitness measured using a simple submaximal exercise test, overall nutritional quality and level of physical activity) were powerful predictors of traditional CVD risk factors measured in primary care such as cholesterol, blood pressure and HbA1c^(66–68). On that basis, we propose that the implementation of simple tools to (1) identify patients most likely to be viscerally obese; (2) assess 'lifestyle vital signs', should be tested in the context of primary care to evaluate the added value of not only focussing on excess body weight and weight loss but also of assessing key metrics related to patients health, irrespective of their body weight.

Finally, in a world where the lay public is bombarded by the media about the risk of obesity and the importance of healthy body weight, consideration should be given to (1) the stigma of considering obesity as a disease; (2) the pitfalls of considering obesity as a homogenous entity; (3) the positive message associated with empowering patients with new notions and tools where we go beyond excess weight and weight loss, while we rather emphasise the importance of key lifestyle habits that have an impact not only of their health but also on their waistline and their cardiorespiratory fitness, irrespective of the BMI. Thus, consideration should be given to aligning public health messages to recent scientific evidence.

Acknowledgements

Dr Jean-Pierre Després is the Scientific Director of the International Chair on Cardiometabolic Risk which is based at Université Laval.

Financial Support

The work of the author has been funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada, the Canadian Diabetes Association, the Fonds de recherche du Québec-Santé and the Fondation de l'Institut universitaire de cardiologie et de pneumologie de Québec.

Conflict of Interest

None.

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