Abdominal obesity: The cholesterol of the 21st century?

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J-P Després, BJ Arsenault, M Côté, A Cartier, I Lemieux.
Abdominal obesity: The cholesterol of the 21st century? *Can J Cardiol* 2008;24(Suppl D):7D-12D.

Cardiovascular disease (CVD) is a leading cause of morbidity and death in many countries worldwide. With the help of epidemiological, metabolic and clinical studies conducted over the past decades, the key factors contributing to the development of CVD have been identified. In this regard, several modifiable (hypertension, smoking, elevated cholesterol or low-density lipoprotein-cholesterol concentrations, reduced levels of high-density lipoprotein-cholesterol, type 2 diabetes) and nonmodifiable (age, sex, genetic predisposition) CVD risk factors have been recognized. Although better acute care and chronic pharmacological management have contributed to reduce CVD mortality, CVD morbidity remains very high. It has been proposed that this situation could be the consequence of the evolving landscape of CVD risk factors, which include, among others, poor nutritional habits and a reduction in physical activity contributing to the epidemic of obesity sweeping the world. However, obesity is heterogeneous both in terms of its etiology and its metabolic complications. Body fat distribution, especially visceral adipose tissue accumulation, has been found to be a major correlate of a cluster of diabetogenic and atherogenic abnormalities that has been described as the metabolic syndrome. The importance of abdominal obesity in association with the development of CVD and type 2 diabetes has been recognized in several studies, beyond the contribution of overall obesity. Additional evidence also suggests that the CVD risk related to the hyperglycemic state observed in subjects with the metabolic syndrome or type 2 diabetes is largely explained by the high prevalence of the metabolic complications of abdominal obesity. Although the presence of the metabolic syndrome clearly increases CVD risk, its clinical diagnosis is not sufficient to classify a patient at high risk for a cardiovascular event because attention must also be paid to the presence of traditional risk factors in the calculation of global CVD risk. The additional information provided by the metabolic syndrome to the risk attributed to traditional risk factors in the calculation of global CVD risk has been defined as global cardiometabolic risk. The fight against abdominal obesity as a major cause of CVD morbidity and mortality will require major societal changes and the involvement of dietitians, kinesiologists and behaviour modification specialists in clinical practice to reshape our physical activity and dietary habits. Finally, the early prevention of overweight/obesity/abdominal obesity in children, starting as early as conception, and the identification of key drivers of unhealthy nutritional and sedentary behaviours are the cornerstone of a successful comprehensive plan to fight CVD morbidity.

Key Words: Abdominal obesity, Cardiometabolic risk, Cardiovascular disease, Ectopic fat, Type 2 diabetes, Waist circumference

L'obésité abdominale : le cholestérol du 21^{ème} siècle

Les maladies cardiovasculaires (MCV) représentent toujours la première cause de morbidité et mortalité dans plusieurs pays. Les nombreuses études épidémiologiques, métaboliques et cliniques réalisées au cours des dernières années ont permis l'identification des principaux facteurs de risque des MCV. À cet effet, plusieurs facteurs de risque modifiables (hypertension, tabagisme, concentrations élevées de cholestérol ou LDL-cholestérol, niveaux faibles de HDL-cholestérol, diabète de type 2) et non-modifiables (âge, sexe, prédisposition génétique) des MCV ont été identifiés. Bien que la prise en charge par des soins aigus efficaces et de meilleurs traitements pharmacologiques aient contribué à réduire la mortalité cardiovasculaire, la morbidité cardiovasculaire demeure très élevée. Cette situation pourrait être la conséquence d'un changement des facteurs de risque des MCV, incluant, entre autres, de mauvaises habitudes nutritionnelles et une diminution de l'activité physique quotidienne, contribuant ainsi à l'épidémie mondiale d'obésité. Toutefois, l'obésité est une condition hétérogène tant dans son étiologie que ses complications. La distribution du tissu adipeux, particulièrement la présence d'une accumulation importante de tissu adipeux viscéral, a été associée à un ensemble de complications athérogènes et diabéto-gènes qui a été défini sous le terme syndrome métabolique. La relation entre l'obésité abdominale et le développement des MCV et du diabète de type 2 est maintenant bien reconnue, bien au-delà de la contribution de l'adiposité totale. De plus, des évidences suggèrent que le risque cardiovasculaire relié à l'hyperglycémie observée chez les individus avec le syndrome métabolique ou le diabète de type 2 serait largement expliqué par la prévalence élevée de complications métaboliques retrouvées en présence d'obésité abdominale. Bien que la présence du syndrome métabolique augmente le risque de MCV, son diagnostic clinique n'est pas suffisant pour identifier un patient à haut risque de MCV, puisqu'il est également important de tenir compte de la présence des facteurs de risque traditionnels dans l'évaluation du risque global de MCV. L'information fournie à la fois par le syndrome métabolique et par les facteurs de risque traditionnels permet le calcul du risque global de MCV, qui est également décrit en tant que risque cardiométabolique global. La lutte contre l'obésité abdominale en tant que cause principale de morbidité et mortalité cardiovasculaires impliquera des changements sociétaux majeurs de même que l'engagement de nutritionnistes, kinésiologues et de spécialistes en changement du comportement humain afin de reconfigurer nos habitudes d'activités physiques et nutritionnelles. Finalement, la prévention du surpoids/de l'obésité/de l'obésité abdominale chez les enfants, et ce, dès la conception ainsi que l'identification des facteurs clés associés à une mauvaise alimentation et à la sédentarité, constituent la pierre angulaire d'une lutte ambitieuse et efficace contre la morbidité cardiovasculaire.

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Received for publication February 25, 2008. Accepted March 22, 2008

Epidemiological, metabolic and experimental studies conducted over more than half a century have permitted the identification of the major risk factors for cardiovascular disease (CVD) (1-5). Some of them are nonmodifiable and include age, sex and genetic susceptibility to CVD but many reflect our lifestyle habits, such as smoking, blood pressure, plasma lipid/lipoprotein and glucose levels, diabetes, poor diet, lack of physical activity/exercise, overweight and obesity (particularly abdominal obesity), and psychosocial factors (4). The modifiable CVD risk factors are such important drivers of risk that very few CVD events are observed among individuals who do not have them (6,7). Therefore, at least from a theoretical standpoint, if we could successfully manage modifiable risk factors, we could have a tremendous favourable impact on incidence of CVD in Canada.

MODIFIABLE CVD RISK FACTORS: AN EVOLVING MOSAIC

To a certain extent, some progress has been made in our fight against some major modifiable CVD risk factors. For instance, the prevalence of smoking has decreased over the past few decades (8). In addition, hypertension is now aggressively detected and managed with a comprehensive pharmacological arsenal and treatment is associated with clinical benefits (9). Furthermore, the availability of statins in clinical practice has been a revolution because physicians now have powerful tools to substantially lower low-density lipoprotein (LDL)-cholesterol concentrations, thereby reducing CVD events and related mortality (10,11). In addition, although smoking remains prevalent in some subgroups and sometimes is used as a means for body weight control in teenage girls, public policies and laws now in place have contributed to create an environment not permissive to, and certainly not comfortable for, smokers (8,12), which has had a very significant impact on the prevalence of smoking in Canada. Thus, the prevalence of smoking and of untreated elevated LDL-cholesterol and hypertension has decreased markedly over the past two decades. Although mortality from CVD appears to have decreased, CVD morbidity remains high (13,14). This suggests that improved procedures and medical therapy may keep CVD patients alive (15) but the overall cardiovascular health of patients with risk factors has not substantially improved, thus continuing the deleterious impact on quality of life.

In parallel to the improvements in the pharmacological treatment of hypertension and dyslipidemia, we have observed in Canada, as well as in most affluent and growing economies, a constant increase in the prevalence of overweight and obesity (16-18). Unfortunately, there is also evidence that the fastest growth in the prevalence of obesity has been in the youngest age group (17). Because obesity is overall associated with hypertension, dyslipidemia and type 2 diabetes, it is anticipated that the coming generation of Canadians may not enjoy the same life expectancy as the preceding one, as the longer 'incubation time' associated with their early obesity should promote an earlier progression of coronary atherosclerosis with eventually a deleterious impact on their health. Evidence from the Bogalusa Heart Study (19) has clearly shown that obesity in children is associated with early atherosclerosis.

OBESITY: A PUZZLING CVD RISK FACTOR

Although it is widely recognized that obesity presents challenges to good health, physicians have always been puzzled by the heterogeneity of CVD risk factors among obese patients. For instance, it is now well documented that some massively obese patients are rather free from major metabolic abnormalities (20,21), whereas some other barely overweight individuals may be characterized by a whole constellation of diabetogenic and atherogenic metabolic abnormalities (22,23). Studies conducted over the past 25 years have shed light on the reasons for such individual variation in the CVD risk factor profile of overweight/obese patients. Such work has highlighted the remarkable seminal work of Jean Vague from the University of Marseille, who, in 1947, was the first to suggest that the regional distribution of

body fat was a more important correlate of the complications of obesity than excess fatness (24). His initial theory, reported in a French medical journal in 1947 (24) and then published for the first time in the English literature in 1956 (25), was first received with curiosity but with considerable skepticism by the scientific/medical community. Although some reports published in the 1960s had suggested that Vague could be right (26,27), it is really in the early 1980s that Björntorp and Kissebah simultaneously reported convincing metabolic and epidemiological data that confirmed the notion that the proportion of abdominal fat was a key correlate of diabetogenic and atherogenic metabolic abnormalities (28-31). For instance, the Gothenburg prospective study of middle-aged men and women showed that irrespective of the body mass index (BMI) (an anthropometric index of total adiposity), an increased ratio of waist-to-hip circumferences (as a crude index of relative abdominal fat deposition) was predictive of an increased risk of ischemic heart disease and of type 2 diabetes (29-31). Since this seminal work, which has spurred considerable interest, numerous studies published the past 25 years have confirmed the notion that a high proportion of abdominal fat predicts cardiovascular events beyond the risk associated with excess body fatness.

Recently, two large epidemiological studies (32,33) provided robust additional evidence that it is important to assess abdominal adiposity with the use of the waist circumference measurement as an anthropometric index of abdominal fat deposition. The first study, the International Day for the Evaluation of Abdominal obesity (IDEA) (32), was a very large cross-sectional evaluation of approximately 170,000 patients seen by primary care physicians in 63 countries. The 6400 physicians who participated in the study were asked to measure weight and height, and were also instructed on how to measure the waistline of their patients. Then, they simply reported on the clinical status of their patients. Results of IDEA clearly showed that primary care physicians can learn how to properly measure waist circumference when they are trained how to do it. Furthermore, IDEA provided more evidence that waist circumference predicted CVD and diabetes at any BMI level. Although the IDEA study was very large in size and confirmed the clinical relevance of measuring waist circumference, it had a cross-sectional design and only assessed the prevalence of diabetes and CVD associated with abdominal obesity.

Recently, investigators of the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study reported the respective relationships of waist and hip circumferences to incidence of coronary artery disease (CAD) (33). EPIC-Norfolk is a large prospective study of a population-based sample of 24,508 men and women 45 to 79 years of age, who were followed for 9.1 years for incidence of CAD. The study had considerable statistical power because 1708 men and 892 women developed CAD over the course of follow-up. The authors reported that an increased waist circumference was associated with an elevated CAD risk, whereas a large hip girth appeared to protect against CAD after adjustment for BMI, age, systolic blood pressure, cholesterol, cigarette smoking, physical activity and alcohol intake.

The finding that waist circumference was a predictor of CAD incidence was fully concordant with previous studies (32,34,35) that had shown that an increase in waist circumference increases CAD risk at any BMI level. In another landmark epidemiological study, INTERHEART (36), which compared myocardial infarction patients with asymptomatic controls, it was also reported that an increased proportion of abdominal fat, as reflected by a high waist-to-hip circumference ratio, was associated with a significant increase in the odds ratio for myocardial infarction.

In EPIC-Norfolk, the investigators also performed a regression analysis of waist circumference values against CAD risk and they estimated that a 5 cm reduction in waist circumference could decrease CAD risk by 11% in men and 15% in women (33). Interestingly, it has generally been considered that a weight loss of 1 kg is associated with a reduction in waist circumference of approximately 1 cm (33). Thus, a weight loss of only 5 kg would therefore be enough to produce

the reduction in CAD risk estimated by the EPIC-Norfolk investigators from a relatively small reduction in waist circumference. Of course, intervention studies will be required to confirm these estimates, but they are consistent with the well documented beneficial effect of a 5% weight loss on the metabolic risk profile (37).

ABDOMINAL ADIPOSITY AS A CVD RISK FACTOR: SUBCUTANEOUS OR VISCERAL FAT?

It has been suggested that the CVD risk resulting from an elevated waist circumference may be a consequence of excess visceral adiposity, which is predictive of insulin resistance and of a proatherogenic, thrombotic and inflammatory profile (22,23,38-43) (Figure 1). In addition to the hyperlipolytic state of hypertrophied visceral adipocytes, there is now evidence that suggests that the expanded visceral fat depot could act as a large 'endocrine gland' that becomes inflamed, releasing cytokines (adipokines) that contribute to produce an insulin resistant/proinflammatory state that increases CAD risk (44,45). However, an original and relevant finding of EPIC-Norfolk is that peripheral fat (after adjustment for BMI) was cardioprotective (33). This finding is fully consistent with the notion that lower body subcutaneous fat may act as a protective metabolic sink that could buffer excess energy through storage, thereby protecting other organs and coronary arteries against harmful lipid deposition (46). More than 15 years ago, we published results showing that the lipoprotein lipase activity of femoral fat was positively correlated with high-density lipoprotein (HDL)-cholesterol levels in women (47). Thus, women, with selective deposition of femoral fat and a high femoral adipose tissue lipoprotein lipase activity had increased levels of cardioprotective HDL because of an efficient pathway clearing triglyceride-rich lipoproteins from the circulation. Therefore, when individuals are exposed to a surplus of calories, those who accumulate excess energy in subcutaneous fat (preferably lower body) may be at lower risk of CAD, while those who cannot efficiently clear and store the energy in peripheral depots build up their visceral fat stores and increase their ectopic fat, a process leading to atherogenic metabolic disturbances that increase CAD risk (46).

Under this model, visceral obesity, which is the form of abdominal obesity with a large accumulation of intra-abdominal fat, could be a marker of the inability of the body to store excess energy in the protective subcutaneous metabolic sink (Figure 1). We have proposed that excess visceral fat deposition could be a marker of 'dysfunctional' adipose tissue associated with ectopic fat deposition with fat stored at undesired sites such as the liver, the heart, the skeletal muscle and the pancreas (46). Because this ectopic fat deposition associated with visceral obesity cannot be assessed by indices of total body fat, such as the BMI (Figure 1), there was a need to develop a simple clinical approach to identify viscerally obese patients with such dysfunctional adipose tissue. On the basis of a series of observations that we have published and reviewed in a previous issue of *The Canadian Journal of Cardiology* (48), we have proposed that the simultaneous presence of an elevated waist circumference combined with an elevated concentration of a simple metabolic marker (plasma triglycerides), a phenotype that we have described as 'hypertriglyceridemic waist', could be useful for the early identification of individuals who are likely to be viscerally obese and often characterized by a constellation of atherothrombotic inflammatory abnormalities increasing the risk of CAD and type 2 diabetes. The literature available on 'hypertriglyceridemic waist' has been recently discussed in a previous issue of this journal and its review is beyond the scope of the present paper (48).

MANAGING THE HYPERGLYCEMIA OF CAD PATIENTS WITH TYPE 2 DIABETES: ARE WE CHASING THE RIGHT TARGET?

Type 2 diabetes is considered to be a powerful risk factor for CVD (49-51). Although better glycemic control has been associated with a reduction in the risk of microvascular complications, it was found to

Figure 1 Schematic illustration of two cases of obese individuals with markedly different cardiometabolic risk. The individual on the left panel has subcutaneous obesity, has a favourable cardiometabolic profile and is at low cardiovascular disease (CVD) risk. For the same body mass index (BMI), the individual on the right panel is viscerally obese and has the atherothrombotic, inflammatory profile of the metabolic syndrome and is at higher CVD risk than the subject on the left panel. HDL High-density lipoprotein; LDL Low-density lipoprotein

have only a modest effect on atherosclerotic macrovascular disease (52,53). This could be due to the fact that the most prevalent form of type 2 diabetes is frequently accompanied by abdominal obesity, an atherogenic dyslipidemia, hypertension as well as by a constellation of metabolic abnormalities often described as the metabolic syndrome. We have recently reported that CAD in women assessed by coronary angiography was predicted by the features of the metabolic syndrome rather than by the hyperglycemic state (54). Although it is of primary importance to achieve the best possible glycemic control, it is also very important to assess and manage all CVD risk factors present in patients with type 2 diabetes. In this regard, the Steno-2 study (55) has compared the effect of a targeted, intensified, multifactorial intervention to that obtained with conventional treatment on modifiable risk factors for CVD in high-risk patients with type 2 diabetes. The investigators found that a stepwise implementation of behaviour modification combined with pharmacotherapy that targeted hyperglycemia, hypertension, dyslipidemia and microalbuminuria along with secondary CVD prevention with acetylsalicylic acid reduced the risk of cardiovascular and microvascular events by 50% over a follow-up of 7.8 years. It is therefore important to achieve the best glycemic control and to optimally manage all CVD risk factors in patients with type 2 diabetes. Results from the National Health and Nutrition Examination Survey (NHANES) have also suggested that type 2 diabetic patients with abdominal obesity and with features of the metabolic syndrome may be at greater risk of CAD than patients without the metabolic syndrome (56). Therefore, the excess abdominal fat of type 2 diabetic patients should be another relevant therapeutic target in the optimal management of their CAD risk. In this regard, a large trial (Action for Health in Diabetes; the Look AHEAD trial) (57) is currently underway to test the effect of an intensive lifestyle modification program aiming at moderate weight loss and increased physical activity on the incidence of major CVD events in 5145 individuals with type 2 diabetes. Preliminary results after one year have been published and are rather promising in showing that this program can indeed reduce body weight by 8.6% (compared with a decrease of 0.7% in the control group) and improve fitness by 20.9% compared with an increase of only 5.8% in the control group (57). These improvements were also accompanied by better glycemic control,

Figure 2) The notion of global cardiometabolic risk. This figure illustrates the notion that a diagnosis of abdominal obesity and of the features of the metabolic syndrome is not sufficient to assess global cardiovascular disease (CVD) risk, which also needs to consider traditional risk factors. The sum of the risk determined by traditional risk factors and by the metabolic consequences of abdominal obesity is defined as global cardiometabolic risk. HDL High-density lipoprotein; LDL Low-density lipoprotein

improvements in the CVD risk factor profile and by reduced use of medication. Results of Look AHEAD are very encouraging and data on long term CVD outcomes are awaited.

Finally, even among patients with type 2 diabetes, poor cardiorespiratory fitness has been shown to be a predictor of CVD mortality at any BMI level (58). These results emphasize further the need to not only aim at better glycemic control and management of CVD risk factors in patients with diabetes but to also promote physical activity/fitness in this population of high-risk patients. Thus, because a high proportion of patients with type 2 diabetes are abdominally obese and physically unfit, these results emphasize the importance of targeting all risk factors in these patients including their excess waistline and their sedentary behaviour.

IMPLICATIONS OF VISCERAL OBESITY FOR ASSESSMENT AND MANAGEMENT OF CVD RISK: THE NOTION OF GLOBAL CARDIOMETABOLIC RISK

Meta-analyses have shown that a clinical diagnosis of the metabolic syndrome increases risk of CAD by approximately 1.5- to 2.0-fold (59,60). Although this consequence of visceral obesity can be seen as a new modifiable CVD risk factor, it is important to point out that the metabolic syndrome cannot assess global CVD risk (46). This is one key criticism that has been addressed to the metabolic syndrome concept: it cannot be used as a global CVD risk calculator. In a recent paper (46), we introduced the notion of cardiometabolic risk as describing the global risk of CVD resulting from the well known 'classical' risk factors (age, sex, smoking, hypertension, LDL- and HDL-cholesterol, diabetes and family history of premature CAD) plus the added risk related to a new, emerging modifiable risk factor: the metabolic syndrome (Figure 2). Because the most prevalent form of the metabolic syndrome is observed among patients with an excess of abdominal/visceral fat, we have proposed that once classical risk factors have been assessed, the further risk of the metabolic syndrome could be captured by identifying individuals with a hypertriglyceridemic waist, because this phenotype has been shown to identify individuals with both visceral obesity and metabolic abnormalities (48).

MANAGEMENT OF ABDOMINAL OBESITY IN CLINICAL PRACTICE: WISHFUL THINKING?

Most physicians are convinced that diet and physical activity/exercise are at the cornerstone of therapy for the management of abdominal obesity and related cardiometabolic abnormalities. However, changing nutritional and physical activity in clinical practice may be a 'utopia' under the current health care model. Physicians have little time and

support to successfully implement a lifestyle modification program that requires, by all means, the support of a multidisciplinary team in regular contact with the patient as shown by the results of the Diabetes Prevention Program, Diabetes Prevention Study and Look AHEAD trial (57,61,62). Therefore, because the management of abdominal obesity requires the reshaping of nutritional and physical activity habits, the involvement of dietitians, kinesiologists and behaviour modification specialists must be prioritized in the health care model, otherwise, there is little chance that progress will be made in the clinical management of this powerful new risk factor for CVD. Furthermore, fundamental societal changes will have to be implemented to fight the primary drivers of poor nutritional and physical activity habits with a strong focus on children, starting as early as possible after conception. Thus, in addition to improving the clinical environment by providing more multidisciplinary support, public health policies should focus on the early prevention of overweight and obesity by creating favourable and permissive environments for healthy eating habits and more physical activity/exercise, which should be implemented early in life. For that, major and cohesive investments in prevention will have to be made with the concerted contribution of all relevant stakeholders.

ACKNOWLEDGEMENTS: The work of the authors has been supported by research grants from the Canadian Institutes of Health Research, the Canadian Diabetes Association, the Heart and Stroke Foundation and by the Foundation of the Québec Heart Institute. Dr Després is Scientific Director of the International Chair on Cardiometabolic Risk, which is supported by an unrestricted grant from Sanofi Aventis awarded to Université Laval. Benoit J Arsenault is a recipient of a training scholarship from Hôpital Laval Research Centre. Mélanie Côté is supported by a scholarship from the Fond de la recherche en santé du Québec. Amélie Cartier is supported by the training program in obesity which is funded by the Canadian Institutes of Health Research.

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