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Joint symposium on “Sugar-sweetened drinks and cardiometabolic risk” organized by the International Chair on cardiometabolic risk and the UK Association for the Study of Obesity, [www.aso.org.uk](http://www.aso.org.uk)
The current obesity epidemic is the topic of numerous reports and articles not only from the scientific and medical community but also from the lay press. Every week, our national newspapers cover this topic. Despite this media attention, the plethora of basic science discoveries and clinical trials on obesity and numerous comprehensive reviews and reports from consensus groups [1-2], there is no evidence that the prevalence of overweight/obesity across the globe will soon plateau.

Ultimately obesity is simply the consequence of a positive energy balance: more energy consumed and less energy expended. However, behind this simple equation are numerous determinants (biological, psychological, socioeconomic, etc.) of energy intake and likewise, the drivers of physical activity are complex. As an example, it would be difficult to promote a physically active lifestyle in a low income suburb where it is dangerous to ride a bike because urban planners have designed the area to accommodate vehicles and not human beings. Such environments may also not be suited for safe child play or for a brisk walk in the evening. How can we promote an active lifestyle if these important environmental barriers remain and are not dealt with?

These simple examples just highlight the difficulties of identifying easy targets to combat the current obesity epidemic. Nevertheless, as recently emphasized by the U.S. Surgeon General, the underlying behaviours, not obesity, may represent better targets than excess adiposity per se [3]. For instance,
available evidence indicates that improved eating habits and a physically active lifestyle have a very significant impact on cardiometabolic health, irrespective of their effects on body weight. If so, some initial actions should be considered. First, we should consider “side-lining” the words “dieting” and “obesity” and instead, emphasize healthy eating habits using a food-based approach rather than a technical discussion on the macronutrient content of the diet which is difficult to communicate in meaningful terms to the lay public [4]. Fewer processed, energy-dense foods with a high-fat/refined sugar content and more whole fruits and vegetables are simple recommendations to convey to the public. This implies that we need to make sure there is equitable access to healthy, unprocessed foods and encourage a preference for such foods. One opportunity is to improve the quality of the food and drink provided in schools. This may look simple but has logistical and cost challenges.

Another simple target is to globally increase the energy expenditure of our children through increased physical activity. Our children should be physically active at least an hour per day. Again, although simple at first sight, this recommendation also has very significant practical implications. Our children live in a “toxic” sedentary world with a plethora of options which encourage screen-time and squeeze out active play. Changing family lifestyles is critical and local communities can act as the “epicentre” to raise awareness and begin to shift social and cultural norms around food and activity. This community participatory approach has been successfully implemented in France (EPODE project, www.epode.org) and is now exported in several countries.

If we need comprehensive solution, why focus on sugar-sweetened beverages (SSBs)? Data discussed at this joint meeting provides robust evidence that an overconsumption of SSBs is associated with obesity, hypertension, type 2 diabetes and cardiovascular disease. This issue of the CMReJournal summarizes three lectures addressing this topic given by three experts, Professors Nick Finer, Frank Hu and Luc Tappy who presented at a meeting jointly organized by the Association for the Study of Obesity and the International Chair on Cardiometabolic Risk in London (UK) on November 2, 2010. Obviously, there are numerous other factors contributing to the current obesity epidemic. However, as there appears to be only limited compensatory reduction in the energy intake from solid food when SSBs are consumed [5-6], and there are credible alternatives, limiting their intake represents a simple dietary recommendation to constrain energy intake. This may particularly be relevant to the segment of the population who are very high consumers of SSBs.

Accordingly, as we have a food pyramid compatible with cardiometabolic health, it may be useful to consider an inverted hydration pyramid with SSBs at the bottom, to be consumed in very small amounts, and water at the top to be the main source of hydration. Certainly we now have enough evidence to suggest that unlimited consumption of SSBs is not part of a healthy diet and that it is only prudent to recommend that they are consumed with great moderation.
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The events that lead to the development of atherosclerosis and cardiovascular disease are progressive, with antecedents that commence early in life – even in the immediate pre- and post-natal periods. They result from genetic susceptibilities and environmental “hazards” that eventually culminate in clinical events. The earlier, more frequent and more severe development of obesity has already been shown to produce metabolic disorders such as type 2 diabetes at an earlier age than hitherto, and now commonly affects adolescents and even younger children; it can be expected that similar trends in cardiovascular disease will be seen. A clear relationship between adiposity (measured by body mass index [BMI]), intra-abdominal (visceral) fat, plasma leptin and hypertension and dyslipidemia is already apparent at age 9-11 years [1].

A recent report on a cohort of 4,857 American Indian children without diabetes (mean age, 11.3 years; 12,659 examinations) born between 1945 and 1984, found that after a mean follow-up of 23.9 years, there were 166 deaths from “endogenous” causes. Among children in the highest quartile of glucose intolerance, death rates were increased by 73% compared to the lowest quartile; the presence of hypertension in childhood increased the risk of premature death by 55% [2]. These risks have been characterized as “early vascular ageing” [3] and can be further defined by the presence of arterial stiffening related to the state of low level but chronic inflammation that exists in obesity (Table).
Further data attest to the impact of early childhood adiposity and later cardiovascular and metabolic risk [4] with relative risks of 4.8-5.8 in boys and girls respectively for later metabolic syndrome (20-year follow-up) by highest to lowest quartile for waist circumference at age 7-15. A number of studies have shown that the young already have evidence for atherosclerosis [5], 1 in 6 teenager donors for heart transplant had significant coronary artery lesions [6]. Evidence from the Bogalusa Heart Study showed that as the number of cardiovascular risk factors increased so did the severity of asymptomatic coronary and aortic atherosclerosis [7]. A systematic review found the presence of type 1 diabetes, dyslipidemia, hypertension and renal failure in childhood consistent disease risks for increased carotid intima-media thickness. In terms of incident cardiovascular events before the age of 60, a 1-unit increase in BMI raised the risks by 3-7% at age 7, and 12-15% by age 13 [8].

The development of noninvasive methods of examining the structure and function of the vasculature has expanded our knowledge of cardiovascular disease and its risk factors in children. Arterial stiffness can be measured ultrasonically to derive values for pulse wave velocity, brachial distensibility, and for augmentation pressure and index. The methods are reliable and reproducible if performed by well-trained technicians and according to well-defined protocols [9]. In one small survey of young people aged 10-23 years, those with type 2 diabetes had worse measures of arterial stiffness that correlated with intra-abdominal fat assessed by waist circumference, and blood pressure [10]. Another technique used to assess vascular function is flow-mediated dilatation (FMD) – the response of arterial calibre in response to brief ischemia – which in adults has been shown to be an independent and significant predictor for later cardiovascular death and stroke. Its validity in the young is not well established. The presence of low-grade inflammation as evidenced by elevated high-sensitive C-reactive protein levels was however associated with impaired FMD in otherwise healthy children [11].
Another factor that increases cardiovascular risk burden is the presence of obstructive sleep apnea. Although obstructive sleep apnea is much less common in children and adolescents compared with adults, its risk increases by 12% for each unit of BMI increase [12]; when present the risk for metabolic syndrome in adolescents was increased 6-fold [13].

While many of these measures represent endothelial and vascular damage, another component, namely endothelial repair, is seen to be of perhaps equal importance and driving the concept that damage occurs when the endothelium’s repair capacity is exceeded (Figure).

Hill et al. [14] concluded from a study in 2003 that in healthy men, levels of endothelial progenitor cells may be a surrogate biologic marker for vascular function and cumulative cardiovascular risk suggesting that endothelial injury in the absence of sufficient circulating progenitor cells may affect the progression of cardiovascular disease. Preliminary work from our laboratory suggests similar impairment of repair mechanisms in obese children.

It appears that risk factors only previously identified in adult populations exist in children and adolescents, and that the growing prevalence of obesity with its metabolic sequelae are driving the appearance of cardiovascular risk from disorder function and form of the vasculature at an ever earlier age.
References

SUGAR-SWEETENED BEVERAGES AS A MAJOR MODIFIABLE RISK FACTOR FOR TYPE 2 DIABETES

By Frank B. Hu, MD, PhD

Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA, USA
Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

frank.hu@channing.harvard.edu

Sugar-sweetened beverages (SSBs) include the full spectrum of soft drinks (soda), fruit drinks, and energy and vitamin water drinks. Consumption of SSBs has been rising rapidly in the US. Between the late 1970’s and 2001 the percentage of total calories consumed from SSBs increased from 3.9% to 9.2% [1]. SSBs have become the primary source of added sugars in the US diet and a major source of excess calories. There is convincing epidemiologic evidence that higher consumption of SSB intake is associated with significantly elevated risk of weight gain and obesity in children and adults [2-3]. SSBs lead to positive energy balance and weight gain due to decreased satiety and an incomplete compensatory reduction in energy intake at subsequent meals following intake of liquid calories. On average, one 12-oz serving of SSB contains about 140-150 calories. If these calories are added to the typical US diet without reducing calories from other sources, one SSB per day could lead to a substantial weight gain (up to 7 kg or 15 lbs) over the course of one year [3].

There is mounting evidence that higher consumption of SSBs increases the risk of type 2 diabetes mellitus (T2DM), even after taking into account their effects on body weight. We recently conducted a meta-analysis of prospective cohort studies of SSB consumption and risk of T2DM [4], including 310,819 participants and 15,043 cases of T2DM. In this meta-analysis, we found that individuals in the highest quantile of SSB intake (most often 1-2 servings/day) had a 26% greater risk of developing T2DM than those in the lowest quantile (none or <1 serving/month) (relative risk [RR]= 1.26, 95% CI: 1.12-1.41) (Figure 1).

Key Points

- An increased consumption of sugar-sweetened beverages (SSBs) is associated with a higher risk of developing obesity in children and adults.
- An elevated consumption of SSBs increases the risk of developing type 2 diabetes beyond its deleterious impact on body weight.
- A higher intake of SSBs has also been associated with a greater risk of developing cardiovascular disease.
The largest cohort study published so far is the Nurses’ Health Study II (NHS II). In the NHS II, a cohort of over 50,000 women, those who consumed ≥1 SSB/day had an 83% greater risk of developing T2DM over the course of 8 years compared to those who consumed <1 SSB/month after adjusting for potential confounders (RR=1.85, 95% CI: 1.42-2.36, p<0.001 for trend) [5]. After further adjustment for body mass index (BMI), the RR comparing extreme categories of intake decreased to 1.41 (95% CI: 1.09-1.83, p<0.001 for trend), but was still statistically significant, suggesting that the excess risk was not completely explained by BMI. Similar results were reported in the Black Women’s Health Study. Among over 40,000 women followed for 10 years, those who consumed ≥2 SSBs/day had a 24% greater risk of developing T2DM compared to those who consumed <1 SSB/month (RR=1.24, 95% CI: 1.06-1.45, p=0.002 for trend) [6]. In both cohort studies, increasing consumption of SSBs was associated with significantly greater weight gain, even after adjustment for other dietary and lifestyle factors.

In the NHS, we found that a higher level of SSB intake was associated with increased risk of developing coronary heart disease (CHD) [7]. In over 88,000 women followed for 24 years, those who consumed ≥2 SSBs/day had a 35% greater risk of CHD compared to infrequent consumers, after adjusting for other unhealthy lifestyle factors (RR=1.35, 95% CI: 1.1-1.7, p<0.01 for trend). Additional adjustment for potential mediating factors including BMI, total energy intake and incident T2DM attenuated the associations but they remained statistically significant, suggesting that the effect of SSBs is not entirely mediated by these factors.
The adverse effects of SSBs on cardiometabolic risk may be explained by several mechanisms. In addition to weight gain, the large quantities of rapidly absorbable carbohydrates such as sucrose or high-fructose corn syrups that are used to flavour these beverages, may also contribute to the risk of T2DM and CHD (Figure 2). SSBs contribute to high dietary glycemic load, which lead to rapid increases in blood glucose and insulin levels following consumption. A high glycemic load diet has also been implicated in the increased risk of T2DM and cardiovascular disease [1].

The fructose content of SSBs may exert additional adverse metabolic effects. Fructose is preferentially metabolized to lipid in the liver, leading to increased hepatic de novo lipogenesis, dyslipidemia and insulin resistance [8]. Fructose consumption has also been shown to promote accumulation of intra-abdominal (visceral) adiposity. In a recent study comparing the 10-week effects of consuming glucose- or fructose-sweetened beverages providing 25% of energy requirements, both groups showed similar weight gain, but only the fructose group showed a significant increase in intra-abdominal adiposity [9].

In summary, there is strong epidemiologic and clinical evidence linking SSBs and increased risk of obesity and T2DM. Thus, limiting intake of SSBs is critical for prevention of these conditions. Recently, the American Heart Association released a scientific statement recommending reductions in added sugar intake to no more than 100-150 kcal/day for most American women and men respectively, as a means of reducing cardiovascular disease risk [10]. Currently, a number of public health campaigns to limit intake of SSBs are underway and strategies such as taxation are being considered as a means of reducing intake of SSBs in the general population. Although many factors contribute to a growing pandemic of obesity and T2DM, ample evidence exists to indicate that regular consumption of SSBs is an important modifiable risk factor for these conditions. Thus, reducing consumption of SSBs in place of healthy alternatives such as water should be widely recommended to reduce risk of obesity and T2DM.
References

Sucrose, fructose and glucose are caloric sweeteners. Fructose and glucose are monosaccharides present in small amounts in fruits and honey, while sucrose is found in substantial amounts in sugar cane and beets. Sucrose and fructose are not essential components of Man’s feeding, and their consumption has remained low throughout the prehistory and middle age. Sucrose consumption in Europe increased essentially during the nineteenth century, and presently represents 10-25% of total energy intake in most parts of the world. Sweetened beverages are major contributors to sugar intake, and represent up to 10% total energy in North America [1-2].

It has long been noticed that high-sugar intake may have adverse health effects. In rodents, consumption of a high-sucrose diet leads to the development of obesity, insulin resistance, diabetes, dyslipidemia, fatty liver, and high blood pressure [3]. More than 50 years ago, it had already been
suspected that consumption of refined sugar in humans may be linked to dyslipidemia and coronary heart disease [4-5].

The sucrose moiety is constituted by one molecule of glucose linked to one molecule of fructose. In the gut, sucrose is split into glucose and fructose before being absorbed into the portal blood. Fructose and glucose thereafter have a quite different metabolic fate. The initial steps of fructose metabolism do not require insulin. Due to this non-dependency upon insulin secretion, and to the fact that fructose ingestion does not markedly increase glycemia, fructose has once been thought to be a suitable sweetener for diabetic patients. After glucose ingestion, a minor (~15%) portion of the absorbed glucose is extracted by the liver through the transporter GLUT2. Once inside the cell, glucose is converted into glucose-6-phosphate by the enzyme glucokinase, the expression of which is dependent on insulin. Glucose-6-phosphate is then converted into pyruvate in the glycolysis pathway. Key glycolytic enzymes are inhibited by citrate and ATP, and hence hepatic glucose degradation is modulated according to the energy status of liver cells. After fructose ingestion, fructose, like glucose, is transported into hepatic cells by GLUT2. Once inside the cells, it is rapidly converted to fructose-1-phosphate and to glyceraldehyde-phosphate and dihydroxy-acetone-phosphate by specific enzymes (fructokinase and aldolase B). In contrast to glycolysis, these initial steps for fructose degradation are not regulated by the energy status of the cell, and hence the near total amount of fructose reaching the liver is metabolized into triose phosphates, which are secondarily converted into glucose, glycogen, lactate, and, to a smaller extent, lipids. Due to this large hepatic synthesis of triose phosphates, which are lipogenic precursors, fructose is probably the most potent lipogenic nutrient in our diet [6-7].

There is strong evidence, both in animal models and in humans, that a hyperenergetic high-sucrose diet produces adverse metabolic effects, of which an increase in plasma triglycerides is the most striking. This hyperlipemic effect appears to be even enhanced in overweight, insulin-resistant patients [8]. There is strong evidence that the fructose component of sucrose is essentially responsible for these effects. Fructose administration acutely impairs hepatic insulin actions in healthy human subjects [9]. Consumption of a hyperenergetic high-fructose diet also rapidly produces a slight, but significant increase in fasting plasma glucose and in hepatic glucose production, indicating some degree of hepatic insulin resistance [10].

An increased dietary fructose intake rapidly and consistently raises fasting plasma triglycerides. This effect is observed in both healthy, normoglycemic subjects and in patients with type 2 diabetes [11-12]. There is evidence that a stimulation of hepatic de novo lipogenesis plays an prominent role in this process since: 1) fructose markedly increases fractional hepatic de novo lipogenesis; 2) the increase in fasting plasma triglycerides correlates with the increase in hepatic de novo lipogenesis; and 3) dietary supplementation with n-3 fatty acids, which downregulate de novo lipogenesis, reduces both de novo lipogenesis and fasting plasma triglycerides [13]. Besides a significant increase in fasting plasma triglyceride concentrations, a high-fructose intake also enhances postprandial lipemia, due, at least in part, to a decreased clearance of triglyceride-rich lipoproteins [13]. In overweight subjects, dietary supplementation with fructose-sweetened drinks increased body weight, hepatic de novo lipogenesis, and intra-abdominal (visceral) fat volume, and impaired glucose tolerance. In contrast, administration
of glucose-sweetened drinks did not produce these effects. Total body weight gain was, however, similar with fructose and glucose drinks [14].

In view of the rapid effects of fructose on plasma lipids and on hepatic insulin sensitivity, it was surprising to observe that, in healthy, insulin-sensitive subjects, hyperenergetic high-fructose diets, administered for as long as 4 weeks, failed to decrease whole body insulin sensitivity, suggesting that skeletal muscle (which is the major contributor to whole body insulin sensitivity) was not directly affected by fructose.

There are, however, several mechanisms by which fructose may in the long term induce insulin resistance (Figure). Short-term fructose administration significantly increased intrahepatic and intramuscular lipid concentrations. Since ectopic lipid deposition appears to be associated to insulin resistance, this observation raises the concern that longer-term effects of fructose administration may be associated with significant lipotoxicity, and may eventually lead to more generalized insulin resistance. There is also the concern that fructose intake may contribute to the development of non-alcoholic fatty liver disease. Furthermore, a high sucrose or fructose intake, when associated with a hyperenergetic diet, is expected to increase body weight and body fat mass, which may secondarily cause insulin resistance [15-16]. Besides a stimulation of de novo lipogenesis and lipotoxicity, other mechanisms may also be involved in fructose-induced insulin resistance. Fructose administration produces an oxidative stress through the generation of reactive oxygen species, and triggers an endoplasmic reticulum stress response, which may be associated with impaired insulin signalling [17]. In addition, fructose increases uric acid production due to its rapid and complete phosphorylation to fructose-1-phosphate, which produces massive hepatic degradation of ATP to ADP and AMP. The ensuing hyperuricemia may cause an endothelial cell dysfunction, resulting in an impaired postprandial muscle vasodilation, and this phenomenon may contribute to insulin resistance [18].
There has been much debate over the past years regarding the role of dietary high-fructose corn syrup (HFCS) in the pathogenesis of obesity and of metabolic diseases at large. Since the 1960’s the corn industry developed technologies to extract starch from corn, hydrolyze it to glucose, and convert part of the glucose into fructose through enzymatic isomerisation. This resulted in the production of HFCS. HFCS can be produced using various fructose:glucose ratio, the most commonly used being HFCS-55, containing 55% fructose and 45% glucose, i.e. a fructose:glucose ratio close to the 1:1 ratio found in sucrose. Due to the high sweetening power of HFCS, together with its low production cost, HFCS utilization rapidly increased in North America over the past 50 years, and HFCS has replaced sucrose in a substantial portion of sweetened beverages. Although the increase in HFCS consumption roughly parallels the increase in obesity prevalence in the US, however to date there has been no solid evidence that the consumption of HFCS-55 produces different metabolic effects than equivalent amounts of sucrose [19]. However, this point remains unsettled, and the results of several ongoing studies are awaited.

Based on the data presently available, there is overwhelming evidence that an overconsumption of sucrose or of fructose can produce deleterious metabolic effects. Fructose can indeed increase fasting and postprandial lipemia, can produce a mild impairment of hepatic insulin sensitivity, and can increase ectopic fat depots. Hypercaloric fructose intake will also increase total body fat and intra-abdominal fat mass, which may in turn contribute to insulin resistance and metabolic disorders. Initiatives aimed at reducing sugar intake are therefore likely to reduce overweight and metabolic disorders. However, there is a number of issues which presently remain unsettled:

1) Most studies, which have addressed the potential mechanisms by which fructose may contribute to metabolic diseases, have used large fructose intake together with high energy intake. There is an urgent need evaluating the effects of sucrose and fructose intake as part of an isoenergetic diet.

2) Athletes are a special group of subjects, with very high physical activity and energy expenditure. These subjects often consume a very high amount of sugars, but are not at risk of (and even appear to some extent protected against) metabolic diseases. How physical activity modulates the effects of fructose, and whether physical activity modifies the maximal “safe” intake of sugars need to be determined.

3) The metabolic responses to fructose appear to be blunted in premenopausal women [19-20]. However, overweight women have similar risk of developing metabolic diseases such as diabetes than overweight men. More data are needed regarding the health effects of sugar according to sex.

4) A limited amount of data suggests that the deleterious effects of sugars may be enhanced in specific subgroups of individuals (offspring of patients with type 2 diabetes, overweight, insulin-resistant subjects). This may have practical implications regarding personalized dietary recommendations.

5) There is ample evidence that a hyperenergetic, high-sucrose diet produces adverse metabolic effects in humans. There is also epidemiological evidence showing that obesity
and metabolic diseases are associated with high-sugar intake and/or high sweetened beverages intake. Intervention studies are however still needed to demonstrate that a reduction of sugar intake indeed decreases cardiometabolic risk factors in patients with metabolic disorders.

References


Recently, obesity and related cardiovascular disease (CVD) are among the major physical, social and economic burdens, globally. The World Health Organization has predicted a "globesity epidemic" with more than one billion adults being overweight (body mass index [BMI] ≥25 kg/m²) and at least 400 million of these being clinically obese (BMI ≥30 kg/m²). Arguably, we have learned more about the molecular control of food intake and energy homeostasis, particularly, the role played by adipose tissue in the pathogenesis of various diseases, including CVD. Atherogenic stimuli such as inflammation, endothelial dysfunction, hemostasis, and smooth muscle cell growth are influenced by adipose tissue-secreted signalling proteins, collectively termed adipokines (Table). Cumulatively, such an adipocentric approach has integrated the traditional cardiovascular risk factors (age, sex, smoking, hypertension, dyslipidemia, homocysteinemia) and intra-abdominal (visceral) obesity and related features of the metabolic syndrome, hence, global cardiometabolic risk [1-3].

**Key Points**

- Perivascular adipose tissue (tunica adipose) is considered a novel component of global cardiometabolic risk.
- Hence, not only intima-media and epicardial/pericardial adipose tissue thickness, but also tunica adipose thickness, should be evaluated in identifying high-risk populations susceptible to cardiovascular disease and monitor vascular wall changes during follow-up studies and therapeutic trials.
The Road Less Traveled

The prevailing response-to-injury hypothesis of Russell Ross states that atherosclerosis is an inflammatory disease, leading to intimal lesions and luminal loss [4]; that is, the intimal road to atherogenesis. Accordingly, intima-media thickness became an accepted measure of structural vascular remodelling and a strong predictor of CVD. However, it is unlikely that such a road may solely travel the whole multiplex network like that of atherogenesis. An interactive approach targeting all structural components of the vascular wall was required [5-6].

Large- and medium-sized blood vessels, where usually atherosclerosis develops, are surrounded by perivascular adipose tissue (PVAT). Hence, adipokines, via a paracrine way, may contribute to different pro- and anti-atherogenic events [7-11]. Pharmacological studies aimed at modifying the production and/or receptor sensitivity of PVAT-derived adipokines are required.

Given the key role of inflammation in the development of atherosclerotic lesions, what role might PVAT play in the process of atherogenesis? For instance, it is known that the proximal segments of coronary arteries are surrounded by subepicardial adipose tissue, and these segments are atherosclerosis-prone as compared to the distal, intramyocardial, adiposa-free segments, which are atherosclerosis-resistant [5-6]. However, the removal

Table: A selected list of adipose-derived mediators, as related to cardiometabolic risk.

1 Frost R. (1874-1963) from his poem The road not taken:
...Two roads diverged in a wood, and I-
I took the one less traveled by,
And that has made all the difference.
of PVAT enhances neointima formation after injury, which is attenuated by transplantation of subcutaneous adipose tissue [9]. Likewise, high-fat feeding induces inflammation and decreases adiponectin expression in PVAT resulting in neointima formation, which is inhibited by local application of adiponectin [9].

In effect, PVAT, recently designated tunica adiposa [11], may be a novel component of global cardiometabolic risk. Therefore, not only intima-media and epicardial/pericardial adipose tissue thickness [11-14], but also, adiposa thickness should be evaluated in, for example, identifying high-risk population susceptible to CVD and monitor vascular wall changes during follow-up studies and therapeutic trials [15-16].

**Conclusion**

Traditional concept of atherogenesis focuses on the intimal road, where “inside-out” inflammatory processes and endothelial dysfunction trigger atherosclerotic plaque formation. Here we took the adipose road, which is less traveled, focusing on the possible paracrine role of PVAT in an “outside-in” signalling pathway in CVD [5-7, 9-11]; its role in insulin resistance should also be considered [8].

Until recently, physicians have looked upon obesity as accumulation of external adipose tissue. This was routinely evaluated by various anthropometric measurements including BMI and waist, hip and, recently, neck circumference. However, recent noninvasive techniques, such as echography, computed tomography, magnetic resonance imaging and positron emission tomography, reveal a new picture of adipose tissue distribution [17]. Hence, in global cardiometabolic risk, we should appreciate not only anthropometric values of external adipose tissue, but – more importantly - the “weight” of internal adipose tissue, particularly, PVAT as well as epicardial and pericardial adipose tissue [11-14]. Metabolic-cognitive association [18-19] might also be listed in global cardiometabolic risk.

**References**


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1 Frost R. (1874-1963) from his poem *The road not taken:*

...Two roads diverged in a wood, and I -
I took the one less traveled by,
And that has made all the difference.
For more information:

myhealthywaist.org

Contact Us

Jean-Claude Coubard
Executive Director

Office: +33 1 47 09 91 74
Cellular: +33 6 33 34 78 13

Mailing address and secretariat:

International Chair on Cardiometabolic Risk
Centre de recherche de l’Institut universitaire de cardiologie et de pneumologie de Québec
Pavilion Marguerite-D’Youville, 4th Floor
2725 chemin Ste-Foy
Québec QC G1V 4G5
CANADA

Tel.: 1-418-656-8711, extension 3183
E-mail: chair.cardiometabolic-risk@criucpq.ulaval.ca
Fax: 1-418-656-4953