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].
The Road Less Traveled\(^1\)

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, adipose-free segments, which are atherosclerosis-resistant [5-6]. However, the removal

\[\text{Table: A selected list of adipose-derived mediators, as related to cardiometabolic risk.}\]

\(1\) 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*¹, 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**


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.


