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EDITORIAL

BODY SHAPE, INSULIN RESISTANCE AND INFLAMMATION: BRIDGING DIABETOLOGY AND CARDIOLOGY?

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In this issue of the **CMR**eJournal, two pioneers who have both made landmark contributions to the areas of diabetology and cardiology address two clinically important questions. First, Dr. Wilfred Fujimoto, from the University of Washington, reviews the key findings of a series of important studies conducted by his group which led them to conclude that body fat topography, especially intra-abdominal (visceral) adipose tissue accumulation, was a crucial factor associated with insulin resistance and the risk of developing type 2 diabetes in Japanese Americans [1-3]. Because his research group was among the first teams to show that intra-abdominal adiposity measured by an imaging technique, computed tomography, was a key form of overweight/obesity associated with the risk of type 2 diabetes, Dr. Fujimoto received the Jean Vague/Per Björntorp award recognizing him as one of the early pioneers of the study of regional adipose tissue distribution. Through a series of elegant studies, Dr. Fujimoto and his team have shown why there was a higher prevalence of type 2 diabetes in Japanese individuals living in Seattle than in Tokyo [4]. From astute interpretation of early results, Dr. Fujimoto was able to nicely show that intra-abdominal, but not subcutaneous adiposity, was a key predictor of insulin resistance and of the risk of developing type 2 diabetes [2, 3]. Thus, Dr. Fujimoto was truly a pioneer of the intra-abdominal adiposity concept and results of the studies conducted by his group have confirmed that the clinical observations of Vague reported in the mid-forties and the work of Björntorp published in the early eighties were important and that their theory was valid.

Since then, many groups around the world have followed the path of these investigators. Although the issue of a causal relationship between visceral adiposity and metabolic abnormalities remains uncertain and under debate, it has become clear that excess intra-abdominal adiposity is at least an excellent marker of ectopic fat deposition (including excess liver fat) and of related cardiometabolic abnormalities [5]. In addition, Dr. Fujimoto's group has also performed intervention studies to show that the intra-abdominal adipose depot can be readily mobilized with a lifestyle modification program despite moderate weight loss [6, 7], another concept which is also supported by other lifestyle intervention studies [8-10].

In the second paper of the Journal, one of the executive board members of the International Chair on Cardiometabolic Risk, Prof. Peter Libby, an academic cardiologist from Harvard University with an international recognition, briefly discusses the importance of inflammation in cardiovascular disease (CVD) and his early work on inflammation affecting processes modulating atherosclerotic plaque stability. Dr. Libby has been extremely active in this area and has published numerous seminal research observations as well as highly cited "classical" review papers on the topic in the very best medical and scientific journals [11-14]. He has pioneered the notion that a state of chronic inflammation may eventually lead to the development of an inflammatory milieu contributing to an increased degradation rate of the atherosclerotic plaque collagen matrix, making it more prone to rupture and to have a thrombotic event. Dr. Libby also makes the point that although it is clear that atherosclerosis/CVD has an inflammatory component, the triggers of this inflammatory process are not completely understood. However, with our current affluent lifestyle characterized by the overconsumption of highly processed foods of high energy density and our sedentary behaviour, Dr. Libby makes the point that there is an emerging new cause of chronic inflammation which needs to be dealt with: obesity, particularly abdominal obesity [11].

In that context, he therefore proposes that an exciting development in our understanding of factors contributing to chronic inflammatory states is the new role of adipose tissue which is now recognized to be much more than an organ solely specialized in triglyceride storage/mobilization. Indeed, available evidence clearly shows that adipose tissue, particularly the intra-abdominal adipose depot, is "inflamed" when expanded in excess, becoming an important source of production of inflammatory cytokines, referred to as adipokines [11]. Dr. Libby reviews interesting work from his group [15] and cites additional evidence [16-18] that there is an adaptive immune response in the expanded adipose tissue. Because of the number of possible mediators and of the complex cross-talk between some of these adipokines and other proinflammatory mediators, this topic will remain a very fertile area of investigation for years to come. Meanwhile, history will show that Prof. Libby clearly documented the link between inflammation and atherothrombosis and foresaw the important mediating role of obesity, particularly of intra-abdominal obesity, as a key driver of this inflammation-mediated atherothrombosis.

Finally, the last paper of the **CMReJournal** was produced by a young scientist, Dr. Amélie Cartier, who has explored the interactions between adipose tissue mass and distribution and some markers of inflammation which have been linked to excess total/intra-abdominal adiposity. Dr. Cartier also emphasizes the notion that the proinflammatory molecules produced by the hypertrophied adipose tissue are largely, but not entirely produced by infiltrated macrophages. She explores the differential relationships between adiposity/body fat distribution and two key inflammatory cytokines, tumour necrosis factor (TNF)-α and interleukin (IL)-6 [19]. Furthermore, she presents evidence that two other markers of adipokine production/levels, namely soluble TNF receptor type 2 (sTNFR2) and IL-1 receptor antagonist (IL-1Ra) could be relevant to consider when exploring the cardiometabolic consequences of excess abdominal fat deposition [20, 21]. Finally, she also deals with an understudied question: the gender difference in plasma C-reactive protein (CRP) concentrations, showing that the

higher levels observed in women than men are largely explained by the fact that women have more subcutaneous fat than men [22]. Therefore, although relative coronary heart disease risk is increased to essentially the same extent as a function of increasing CRP levels in both men and women, the absolute risk related to a given CRP concentration is likely to be lower in women than in men. Indeed, the increased CRP levels in women than in men are explained by their increased subcutaneous adiposity which is less detrimental to cardiometabolic risk than excess intra-abdominal adiposity [23, 24].

The area of regional adipose tissue distribution has been neglected by the obesity community for decades. Due to the work of pioneers like Jean Vague, Per Björntorp, Wil Fujimoto and others and because of the mounting evidence that body fat distribution is also related to inflammation and CVD, abdominal obesity is now an important issue not only for the field of obesity but also for diabetology and cardiology, making this topic an excellent substrate for cross-fertilisation between the two disciplines.

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