

## Global Spotlights

# CardioMetabolic medicine, one more last step forward

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Since the concept of metabolic syndrome (MetS) was firstly formalized by Professor Reaven in 1988, insulin resistance was identified as the underlying common factor driving the associated cardiovascular (CV) risk. Ten years later the World Health Organization attempted to provide a comprehensive definition in order to identify and treat these high-risk individuals.<sup>1</sup> Some argued that a mere factional clash would then drive the evolution of this definition, swinging between the will to promote or dilute the role of insulin resistance. On the contrary, such debate led to a critical revision of MetS paradigm and paved the way for the current knowledge on CardioMetabolic risk.<sup>2</sup> Nevertheless, some shortcomings still undermine the effective consensus around this definition, so that even Reaven himself has come to wonder if MetS diagnosis is really necessary.<sup>3</sup>

1. European Society of Cardiology/American Heart Association (ESC/AHA) guideline for primary prevention of CV disease do not encompass MetS: ESC SCORE risk charts did not consider MetS in CV risk estimation and even the latest released guidelines do not include body mass index (BMI) and/or waist circumference as CV risk modifiers. AHA generally acknowledges that pooled cohort equations may underestimate CV risk in MetS—then considered as risk-enhancing factor—and claims to revise the 10-year CV risk estimation in MetS patients at borderline/intermediate risk. Nevertheless, although the sum (MetS as a whole) should be considered clinically relevant, for any risk factors treatment as per clinical guidelines is still recommended.
2. The mismatch between MetS and obesity: during the first decade of 20th century the awareness of excess body weight/obesity burden significantly grew, but far from the concept of MetS. The concept of ‘obesity paradox’ was born, keeping scientists hostage for a decade further.
3. The rationale behind MetS definition is unclear: the foresight in MetS consensus definition was to identify high waist circumference—rather than BMI—as adiposity index and essential criterion for MetS definition. However, the role of other MetS determinants is currently challenged and even the concept of syndrome might be itself questioned.

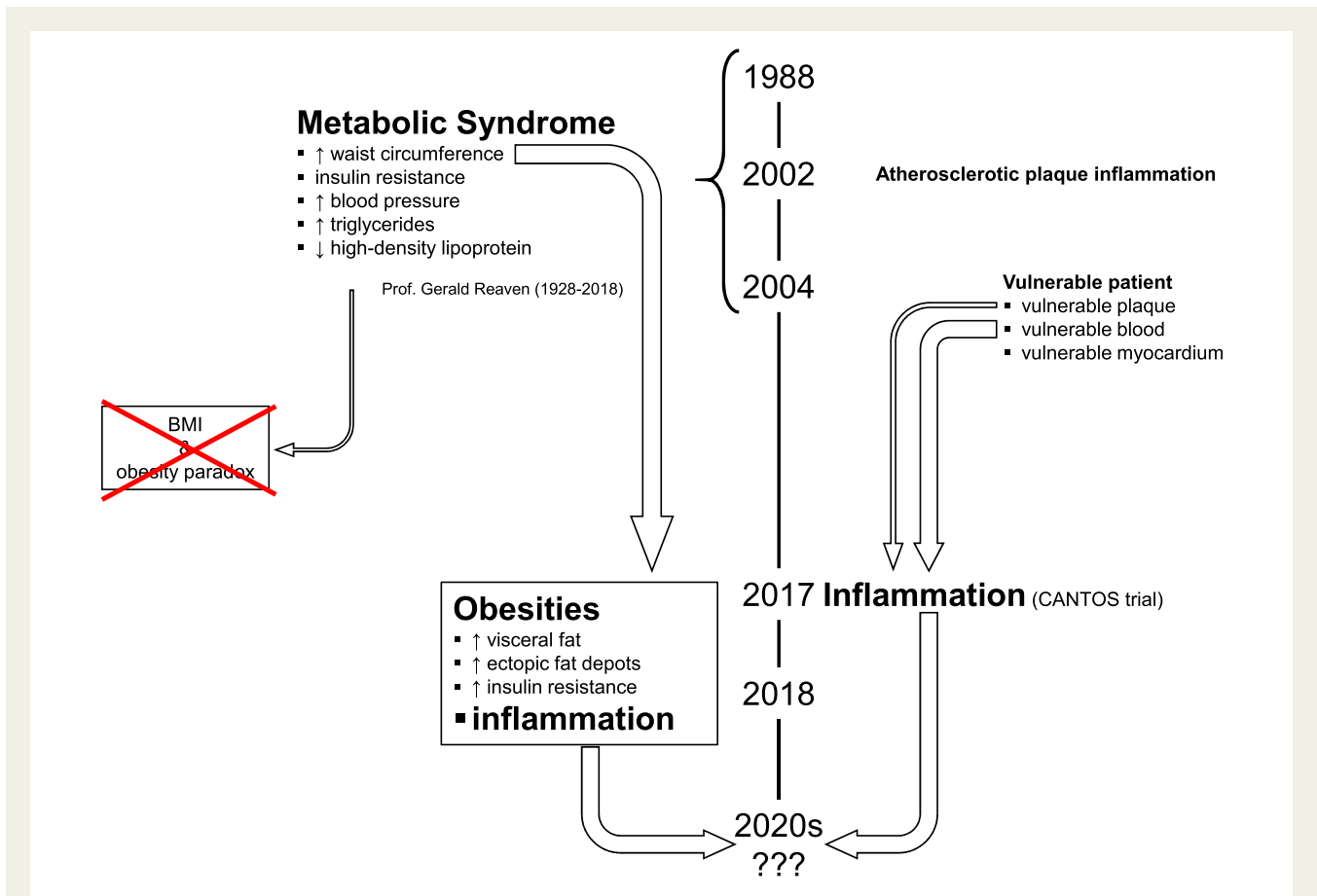
The sick fat, also referred to as ‘adiposopathy’, may be now considered the paradigm of global CardioMetabolic risk. The *sine qua non* of adiposopathy is visceral fat deposition associated with inflammatory/adipokine dysregulation and ectopic fat deposition.<sup>4</sup> This paradigm shift

may allow relevant steps forward and deserves to be deeply discussed. First, the focus on visceral adipose tissue may provide a key to understand the obesity paradox, highlighting the inherent limits of BMI use in clinical practice. As second, the emerging role of inflammation—whose *consecutio* with visceral adipose tissue dysfunction has yet to be clarified—seems to follow what observed at the beginning of the 2000s, when the shift from vulnerable plaque to vulnerable patient occurred. Furthermore, far from being a single entity, obesity encompasses a heterogeneous group of phenotypes: classical, metabolically healthy, normal weight, and osteosarcopenic obesities.<sup>5</sup> Considering inflammatory dysregulation as the underlying mechanism of these different phenotypes is an intriguing hypothesis, a potential ‘theory of everything’, that deserves further investigations.<sup>6</sup> Investigating ectopic fat deposition finally allows at appreciating the full pathogenic potential of dysfunctional adipose tissue, giving an integrated perspective and recognizing the importance of the cross-talk between adipose tissue and other body systems.<sup>7</sup>

The worldwide obesity pandemic claims for urgent interventions at several levels. The failure of BMI flags the need for implementing anthropometric indexes of central obesity. With the contribution of artificial intelligence, advances in body fat imaging will be greatly contributing to validate the concept of adiposopathy and some of these might be soon applied for clinical use (e.g. dual-energy X-ray absorptiometry and rapid MRI scan).<sup>8</sup> The establishment of a working group on visceral obesity should then become a priority for cardiology societies. To date International Atherosclerosis Society and International Chair on CardioMetabolic Risk are the only ones to have produced a consensus statement claiming for waist circumference assessment as a vital sign in clinical practice.<sup>9</sup> AHA has already published a scientific statement on obesity and CV disease,<sup>10</sup> but including visceral adiposity assessment in the next guideline update appears now mandatory. Alongside pathophysiological and diagnostic considerations, there are indeed many therapeutic implications ranging from lifestyle modifications, pharmacotherapy and even surgical interventions. Concerning the latter, results are so impressive that such approach is increasingly known as metabolic rather than bariatric surgery.

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**Figure 1** Step forward in CardioMetabolic Medicine during 20th century. Since the end of 19th century clustering of CardioMetabolic risk factors has become a matter of fact. However, the kind of and the extent to which they contribute to the overall CardioMetabolic risk is still matter of debate. This path would retrace what occurred in the study of atherosclerosis where inflammation has been finally recognized as leading determinant in atherosclerosis pathophysiology. Despite some missteps also obesity is now increasingly recognized as systemic disease with different phenotypes in which inflammation would exert a critical pathophysiological role.

After 20 years, a lot of progresses and some missteps, it is now time to consider CardioMetabolic medicine as a subspecialty for which clinicians from different backgrounds should be trained (Figure 1). Scientific societies are therefore called upon to provide the tools to tackle this silent pandemic.

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