Excess White Adipose Tissue Syndrome (eWATS)—A New Clinical Designation for Early Metabolic Intervention

by Daniel Martinez Puig, DVM, PhD.

Introduction

Obesity has reached epidemic proportions globally and continues to grow. Yet, the classification of obesity as a disease is not universally agreed.[1] Historically, obesity was defined in terms of body mass index (BMI), but this approach has been shown to be insufficient. The BMI approach fails to differentiate lean muscle mass from adipose tissue and does not address the fact that white adipose tissue (WAT), while previously regarded as passive lipid storage, is now considered to be a dynamic tissue with endocrine and immune functions.[2]

Obesogenic conditions leading to adipocyte enlargement (hypertrophy) and adipose tissue accumulation (hyperplasia) have been shown to contribute to several cardiovascular risk factors including insulin resistance, atherogenic dyslipidemia and hypertension.[3] Efforts to reduce WAT have been shown to contribute significantly to the normalization of those risk factors.[4]

Together, the cardiovascular risk factors mediated by WAT form the foundational clinical definition of Metablolic Syndrome (MetS).[5] MetS as a diagnostic category has received considerable attention over the last decade, and its definition has been subjected to many changes.[6] Thus, MetS has shown limitations as a clinical entity and diagnostic category.[7] This is partially because MetS is defined as a co-ocurrence of different risk factors and not as a formal disease with a described pathogenic pathway. The absence of a well-characterized pathogenic potential and clinical derangements has made the proper clinical management of this condition difficult.

The intent of this white paper is to introduce Excess White Adipose Tissue Syndrome (eWATS) as a clinical entity in which WAT hypertrophy is on the causal pathway of metabolic dysfunctions collectively known as MetS. eWATS provides for a more concise and actionable diagnostic category with clearly defined biochemical and physiologic abnormalities that precede the development of MetS risk factors.

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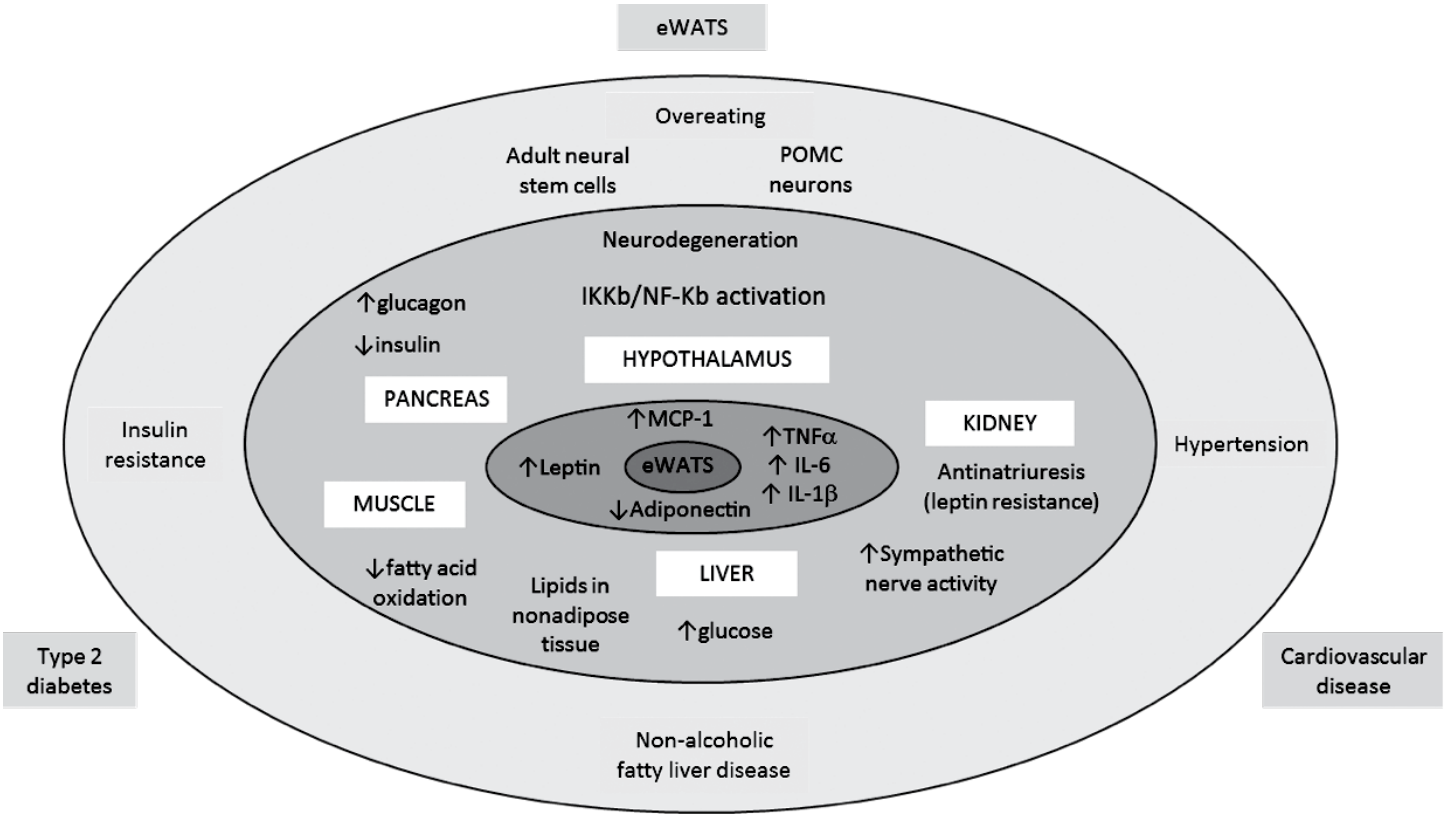
Defining eWATS

Obesity has been traditionally defined as the presence of excess body fat as WAT. WAT is a specialized connective tissue constituted mainly by adipocytes, which are differentiated cells specialized in storing energy in form of fat. When energy intake exceeds energy expenditure, excess energy is accumulated in the body through the expansion of WAT. Expansion of WAT is caused by a combination of two processes: size increase of preexisting adipocytes (hypertrophy) and de novo adipocyte differentiation (hyperplasia).[8]

WAT was previously thought to be merely an energy storage system, but research at the molecular level has shown that WAT is a metabolically active organ that secretes several cytokine signaling molecules, known as adipokines, into systemic circulation. Adipokines secreted by WAT include inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6),[9] and hormones such as leptin and adiponectin.[10] The secretion of adipokines, plays a key role in the cross talk between WAT and the Central Nervous System (CNS). The systems of energy homeostasis are ultimately controlled by the CNS, but CNS regulation is, in turn, impinged by adipokines produced by WAT.[11] In healthy conditions, the cross talk between WAT and CNS regulates satiety/hunger, thermogenesis, and nutrient partitioning between tissues to maintain body weight and adiposity.[12] However, in obesity the homeostasis is lost, and the resulting dysregulation of adipokines has been associated with MetS.[6] In turn, MetS has been recognized as a risk factors for cardiovascular disorders.[10]

Because adipokine dysregulation resulting from the hypertrophy and hyperplasia of WAT appears to precede a series of events leading to several recognized disorders and elevated risk profiles, ***we propose the definition of Excess White Adipose Tissue Syndrome (eWATS) as an actionable clinical entity for early intervention.***



Adipokines Exert Broad Influence

Among adipokines, leptin has emerged as an important regulator with potentially broad actions on several organ systems, such as the brain (hypothalamus) and the skeletal muscle. In normal conditions, leptin regulates feeding behavior, suppressing appetite and increasing energy expenditure (thermogenesis).[12] In obesity, leptin gene expression is increased in the WAT, which leads to elevated leptin concentration in the blood (hyperleptinemia). As leptin levels rise, however, receptor sensitivity declines—a phenomenon known as "leptin resistance."[13-15]

Leptin resistance has been shown to have a selective nature: when levels of leptin are chronically elevated, the sensitivity to CNS-mediated effects is decreased while pro-inflammatory activity and sympathetic over-activity are preserved.[9] This resistance has deleterious effects on body homeostasis: Sympathetic over-activity leads to elevation of blood pressure,[16] and release of inflammatory cytokines (ex. TNF-α) favors insulin resistance.[17-19]

Hyperleptinemia also leads to the abnormal accumulation of fat in non-adipose organs, including the liver, the heart, and skeletal muscle.[20,21]Fat accumulation in non-adipose tissues is considered to favor the appearance of MetS and particularly T2DM. It is estimated that between 60% and 90% of cases of T2DM are associated to obesity.[22]

The dysregulation of other adipokines also drives the development of low-grade inflammation, which is considered to be on the causal path of dyslipidemia, hypertension and hyperglycemia.[23] When WAT is hypertrophied due to excess energy intake and/or lack of physical exercise, an infiltration of inflammatory cells such as macrophages, neutrophils, and T-cells, appear. In macrophage-infiltrated WAT, there is an increased production of pro-inflammatory adipokines, such as TNF-α and MCP-1, while the production of anti-inflammatory adiponectin is decreased, leading to chronic inflammation.[24]

Adiponectin is also related to insulin resistance. Adiponectin has been shown to have a role in sensitizing target organs including liver, muscle and adipose tissue to the action of insulin through the stimulation of AMPK phosphorylation.[25] In obesity, circulating levels of adiponectin are reduced, limiting its insulin-favoring effects and thus promoting insulin resistance.[26,27]

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Identifying eWATS—Diagnostic Recommendations

It is widely recognized that visceral fat mass is the predominant source of chronic systemic inflammation and an important factor in the development of eWATS-related disorders.[28] Therefore, the use of DEXA scans is preferred over body fat scales for improved accuracy and the ability to calculate fat percentages in every body segment.

Common tools used in diagnosing obesity, such as BMI, may be a helpful tool in diagnosing eWATS, but not determinant. Other anthropometric parameters like waist circumference and body fat percentage are more useful to determine if a patient has eWATS.

Abnormalities in the leptin/adiponectin ratios have previously been reported to better correlate with metabolic abnormalities, like MetS, than the BMI itself.[29-34] Blood tests for these adipokines, as well as for inflammatory markers such as MCP-1, TNF-α, IL-6, IL-1β, are recommended.

eWATS Management

Currently eWATS is being treated with the same general therapeutic approach as obesity. First-line intervention consists of lifestyle modifications in the form of increased activity levels and healthier dietary patterns designed to reduce overall weight. For addressing eWATS specifically, however, overall weight reduction should not be the focus. Rather, clinicians and patients should seek to restore healthy metabolic function by reducing visceral WAT and systemic inflammation.

Currently there are no OTC or prescription products available specifically for eWATS management. Therefore, the existing protocols for eWATS-related comorbidities should be used. However, this approach may result in patients being overly poly-medicated while the baseline problems remain unresolved.

Compounds targeting WAT-mediated adipokine imbalance and the restoration of healthy metabolic function are being investigated. While pharmacologic approaches have shown limited efficacy,[35] natural compounds have shown promise in early clinical trials.[36] More investigation is warranted to identify intervention strategies that can produce significant and sustained metabolic change.

About the Author

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