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Chapter One - Biomarkers of dysfunctional visceral fat

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Abstract

Dysfunctional visceral fat plays a key role in the initiation and maintenance of chronic inflammation, liver steatosis and subsequent systemic insulin resistance that primes the body for development of metabolic syndrome. These changes, occurring with or without obesity, lead to type 2 diabetes. In this chapter, we first provide a brief overview of the factors that lead to dysfunctional visceral fat and their relative importance. Adipose tissue has a great plasticity which allows for cell hypertrophy and, when needed, angiogenesis to sustain hypertrophy. Due to the prevalence of inexpensive and widely available "junk food," i.e., those enriched in fat, carbohydrate and sugar, this response becomes maladaptive. Hypertrophied adipocytes become hypoxic. Some undergo necrosis which induces macrophage recruitment forming crown structures wherein macrophages and leukocytes surround injured adipocytes. This leads to the ominous triad: inflammation, fibrosis (extracellular matrix hypertrophy) and impaired angiogenesis as well as consequent unresolved hypoxia. Adipokines and cytokines secreted by these crown structures as well as the palmitate fluxes due to excessive lipolysis are released from visceral adipose tissue to portal blood. They inundate the liver causing insulin resistance. In this review we explore the actions of adipokines, proteins and macrophage cytokines (adiponectin, leptin, FABP4,

resistin, PAI-1, ANGPT3/4, IL-6 and TNFα) that normally intervene but whose action goes awry in the presence of inflammation and insulin resistance. We provide an assessment of their relative clinical utility as well as challenges associated with their use as biomarkers.

Introduction

The revolutionary discoveries of the adipokines leptin and adiponectin a quarter of a century ago led to the current prevalent notion that adipose tissue is our largest endocrine organ [1], [2], [3], [4], [5]. Even in the 1950s, before the term adipokine was devised, Kennedy proposed that there were signals secreted from adipocytes that regulated energy intake and expenditure [6], [7]. Subsequently, Mayer's hypothesis asserted that energy homeostasis was regulated by “glucostatic” and “lipostatic” signals [8], [9], [10], [11], [12]. The current model proposed by Bray, entail a feedback mechanism in which adipose tissue, the gastrointestinal tract and other tissues deliver endocrine and neural signals to regulate energy balance [13], [14], [15], [16], [17], [18], [19], [20], [21], [22]. Several new adipokines have been discovered and much has been learned about adipocyte communication with other organs to maintain energy homeostasis. Moreover, adipocytes secrete many other molecules such as lipids, metabolites, noncoding RNAs and even extracellular vesicles that also participate in this process (Fig. 1) [4], [5], [23], [24], [25], [26].

Over the past three decades, epidemiologic studies have demonstrated that visceral adipose tissue (VAT), when measured specifically by gold standard methods (CT or MRI), is an independent risk marker of cardiovascular and metabolic morbidity and mortality [27], [28], [29], [30], [31], [32]. Further evidence shows that ectopic fat, including liver and epicardial fat is associated with increased atherosclerosis and cardiometabolic risk [30], [33].

Regarding the multiple sites of storage of ectopic fat, excess intra-abdominal VAT accumulation belongs to a constellation of factors that constitute a phenotype that comprises dysfunctional subcutaneous adipose tissue (SAT) mass increase accompanied by ectopic fat storage tightly associated with a cluster of cardiometabolic risk factors, i.e., metabolic syndrome (MetS) [28], [32], [34], [35], [36], [37], [38]. Key components of the cardiometabolic dyslipidemia include hypertriglyceridemia, increased free fatty acids, adipose tissue discharge of pro-inflammatory cytokines, hepatic insulin resistance (IR) and inflammation, amplified VLDL secretion, impaired clearance of triglyceride (TG)-rich lipoproteins (TRL), presence of small dense LDL particles (sd-LDL) which are the most atherogenic and reduced HDL cholesterol [37], [38], [39], [40], [41]. Age, gender, ethnicity and hereditary predisposition contribute to differences in VAT accumulation.

Clinical signs of this phenotype are increased waist circumference and waist/height ratio (which is far superior to more frequently employed BMI) and hypertension [30], [32], [33], [42], [43]. Of note, many problems associated with dysfunctional ectopic fat (including visceral fat) may occur in subjects before they reach the stage in which IR is such that obesity ensues. These subjects, thin on the outside, fat on the inside (TOFI) [44], [45], [46], most often are undiagnosed but may most benefit from intervention. Fortunately, the clinical laboratory provides significant diagnostic power via assessment of glycemia and lipid profile including the very useful TG/HDL-C ratio, which strongly predicts increases in sd-LDL, and IR [30], [39], [40], [41], [42]. These factors constitute, albeit indirectly, markers of dysfunctional visceral fat. The next level of diagnostic tools include specific biomarkers such as adipokines as well as others. In this chapter, we first provide a brief overview of the factors that lead to dysfunctional visceral fat and their relative importance. We focus on the main adipokines that intervene under normal physiologic conditions, but whose action goes awry when inflammation and IR are present. We provide an assessment of their relative clinical utility as well as challenges associated with their use as biomarkers.

Section snippets

Overview

Excessive visceral fat accumulation (with or without obesity) leads to adipose tissue dysfunctionality, a phenomenon central to MetS-related comorbidity. The mechanisms subjacent to adipose tissue dysfunction consist of:

1. adipocyte hypertrophy and hyperplasia
2. low grade sustained inflammation
3. impaired extracellular matrix remodeling (fibrosis) accompanied by a change in the secretion pattern of adipokines [24], [32], [47], [48].

Adipocyte hypertrophy (excessive caloric or sugar intake and/or primary

Excess lipolysis in adipose tissue: Palmitate and lipotoxicity

Adipocytes secrete adipokines as well as other molecules (Fig. 1). Of these, palmitate (main free fatty acid, FFA) is most important. Under normal physiologic rates, fluxes of palmitate are critical for skeletal and cardiac muscle metabolism [59], [64], [65], [66], [67], [68].

Unfortunately, when fluxes become abnormal, i.e., adipocyte hormone sensitive lipase (HSL) dysregulation (not inhibited by insulin due to IR) and/or inflammation, palmitate induces lipotoxicity and inflammation via TLR-4

Dysfunctional visceral fat secretion patterns

All the above mechanisms impact secretion of macrophage cytokines augmented with various adipokines, i.e., anti- vs. pro-inflammatory, especially in visceral fat. In the subsequent sections we review the main adipokines, describe their physiologic action and assess clinical utility. Next, we assess the main macrophage inflammatory cytokines stemming from crown structures. Aspects relevant to clinical laboratory practice are highlighted. For additional information, the reader is referred to

Metabolomics

Due to the complex secretome of visceral fat and the immense variety of lipid molecules produced by this tissue, it is not surprising that significant effort has been dedicated to identification of lipid signatures specific for visceral fat dysfunction. Although in its infancy, metabolomics may provide a useful tool to identify biomarkers of visceral fat and liver fat content that possess additional clinical value. For example, recent study showed that several metabolomic parameters were

Conclusions

Dysfunctional visceral fat plays a key role in the initiation and maintenance of chronic inflammation, liver steatosis and subsequent systemic IR that primes the body for development of MetS then type 2 diabetes with or without obesity. Clinically, the most practical diagnostic approximation is waist circumference together with TG, to discover the “hypertriglyceridemic waist,” a useful marker of MetS. TG/HDL-C adds another diagnostic level due to its association with MetS and the sd-LDL

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References (145)

A. Kennedy
Pathophysiology of obesity
Lancet (1992)

J. Mayer
An experimentalist's approach to the problem of obesity
J. Am. Diet. Assoc. (1955)

G.A. Bray
Obesity
Dis. Mon. (1979)

G.A. Bray
Pathophysiology of obesity
Am. J. Clin. Nutr. (1992)

A.D. Attie *et al.*
Adipocyte metabolism and obesity
J. Lipid Res. (2009)

A.R. Nawrocki *et al.*
The delicate balance between fat and muscle: adipokines in metabolic disease and musculoskeletal inflammation
Curr. Opin. Pharmacol. (2004)

J.P. Despres
Excess visceral adipose tissue/ectopic fat the missing link in the obesity paradox?
J. Am. Coll. Cardiol. (2011)

I.J. Neeland *et al.*
Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement
Lancet Diabetes Endocrinol. (2019)

R. Rodriguez-Mortera *et al.*
Higher ANGPTL3, apoC-III, and apoB48 dyslipidemia, and lower lipoprotein lipase concentrations are associated with dysfunctional visceral fat in adolescents with obesity

Clin. Chim. Acta (2020)

G.S. Hotamisligil
Foundations of Immunometabolism and implications for metabolic health and disease
Immunity (2017)

View more references

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