Nutrition 29 (2013) 379–386

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Obesity, systemic inflammation, and increased risk for cardiovascular disease and diabetes among adolescents: A need for screening tools to target interventions

Mark D. DeBoer M.D., M.Sc., M.C.R. *

Department of Pediatrics, University of Virginia, Charlottesville, Virginia, USA

ARTICLE INFO

Article history:
Received 31 January 2012
Accepted 3 July 2012

Keywords:
Obesity
Metabolic syndrome
Insulin resistance
Risk
Adolescents
Inflammation
High-sensitivity C-reactive protein
Adiponectin

ABSTRACT

Cardiovascular disease (CVD) and type 2 diabetes mellitus have their roots in childhood, particularly in obese children and adolescents, raising important opportunities for early lifestyle intervention in at-risk individuals. However, not all obese individuals are at the same risk for disease progression. Accurate screening of obese adolescents may identify those in greatest need for intensive intervention to prevent or delay future disease. One potential screening target is obesity-related inflammation, which contributes to insulin resistance, metabolic syndrome, and CVD. In adults, the inflammatory marker high-sensitivity C-reactive protein (hsCRP) has utility for risk stratification and treatment initiation in individuals of intermediate CVD risk. In adolescents, hsCRP shares many of the associations of hsCRP in adults regarding the degree of insulin resistance, metabolic syndrome, and carotid artery media thickness. However, long-term data linking increased hsCRP levels—and increased insulin or decreased adiponectin—in childhood to adult disease outcomes are lacking at this time. Future efforts continue to be needed to identify childhood clinical and laboratory characteristics that could be used as screening tests to predict adult disease progression. Such tests may have utility in motivating physicians and patients' families toward lifestyle changes, ultimately improving prevention efforts.

Introduction

The increasing incidence of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) worldwide has raised interest in means of early identification of risk and preventative treatment in those with multiple risk factors [1]. A major factor in the increase in these adult chronic diseases has been the obesity epidemic: compared with those of normal weight, adults who are obese have a 50% to 75% increased risk of CVD over 3- to 14-y periods [2], whereas obesity starting in childhood carries a higher risk of adult CVD and T2DM [3]. These risks make childhood obesity a logical target for intervention. Nevertheless, not all obese individuals carry the same risk for future disease, which is encapsulated in the concept of the "healthy obese," a subset of obese children and adults who do not exhibit increases in CVD risk factors [4,5]. In addition, outside of intensive lifestyle interventions as part of research protocols, attempts at weight loss for children and adolescents in clinical settings have been modest [6–8]. This raises a question about the need for tools to identify risk for future disease—tools that could be used to trigger more intensive intervention in a subset of children at higher risk.

Currently, there are few evidence-based tools available for use in risk stratification in pediatrics. Such tools could end up being factors related to the underlying processes that connect obesity to future disease. One set of such processes is the metabolic syndrome (MetS), a cluster of CV factors, including central obesity (as assessed by increases in waist circumference), hypertension, increased fasting blood glucose, high levels of triacylglycerols, and low high-density lipoprotein cholesterol [9–11]. MetS itself represents a potential screening tool for risk in adolescents [12] but is not widely used clinically, likely because of its complexity of use, requiring that patients have increases above specific cutoff values in at least three of the five components of MetS [13]. In this sense—if possible—a single blood test would likely represent an easier clinical tool. A further drawback is that MetS exhibits racial/ethnic differences in its accuracy [14].

This work was supported by grants 5K08HD060739-03 and 1R21DK085363 from the National Institutes of Health.

* Corresponding author. Tel.: +434-924-9833; fax: +434-924-9181.
E-mail address: deboer@virginia.edu

0899-9007/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2012.07.003

Another important target for risk-related screening is obesity-related inflammation. One inflammation-associated screening tool that is used for risk stratification in adults is high-sensitivity C-reactive protein (hsCRP). Higher levels of hsCRP have been linked to risk for CVD and T2DM in adults [15–21], although no such long-term data are available in adolescents. In this review, I will consider the processes underlying the connections among obesity, inflammation, and adult disease; the data for hsCRP as a screening tool for future CVD and T2DM in adults; and data regarding obesity-related inflammation in children. Using this as background, I will consider multiple potential screening tools that in the future may be used to identify obese adolescents at highest risk for future CVD and T2DM.

Obesity and systemic inflammation

The concept of obesity as an inflammatory state has continued to develop over the past 15 y, and as our understanding of the process has progressed, multiple factors have been identified that may serve as reasonable screening tools. The model (Fig. 1) that has emerged from multiple studies features adipocytes—and in particular visceral adipocytes—as playing important endocrine roles in the process of inflammation and worsening insulin sensitivity [22]. In response to excess lipid stores, visceral adipocytes secrete increasing amounts of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α and chemokines such as monocyte chemoattractant protein-1 [23]. These chemokines in turn promote the migration of macrophages to the adipose tissue, greatly increasing cytokine release. Another factor in obesity-associated inflammation appears to be the adipokine adiponectin, which is secreted by adipocytes in inverse proportion to the amount of stored lipid and appears to confer insulin sensitivity in animal models of obesity [24,25]. These low levels of adiponectin and increasing insulin resistance are also associated with the clinical features of MetS [9,11,26]. Notably, low levels of adiponectin are associated with higher levels of inflammatory cytokines, whereas infusions of adiponectin in animal models result in a decrease in systemic inflammation from unclear mechanisms [24]. Another factor released from adipocytes is retinol-binding protein-4, which appears to suppress the peripheral expression of glucose transporter-4 (GLUT4)—a key glucose transporter in skeletal muscle—and is associated with an increased expression of monocyte chemoattractant protein-1 adipocytes [27–30].

These proinflammatory conditions conferred by excess visceral adipose tissue combine to produce a tonic degree of systemic inflammation that worsens with increasing central obesity. As will become clear, these processes appear to play a central role in the development of insulin resistance and future disease, making these processes a logical target for screening and risk assessment.

C-reactive protein is arguably the most commonly used marker to assess systemic inflammation. CRP is produced by the liver, peripheral leukocytes, and even the adipose tissue in response to multiple cues, particularly increases in interleukin-6 and other systemic inflammatory cytokines [22,31]. In the periphery, CRP has specific roles including the activation of phagocytic cells—at least in part by binding to the Fc-γ-RIIa receptor (Fig. 1) [32]. Although CRP has long been used as a marker of high degrees of inflammation such as in acute infections and chronic inflammatory diseases (with levels typically >0.6 or >6 mg/L), it has been convincingly demonstrated using highly sensitive assays that report hsCRP levels that even mild increases in CRP (range 2–6 mg/L) are indicative of low-grade inflammation that carry relevance in other clinical situations, which are discussed further below [33]. Given the proinflammatory state associated with visceral adipose tissue, it is not surprising that hsCRP is increased in the setting of central obesity. The degree of increase in hsCRP associated with visceral obesity varies by individual [34]; thus, given the known correlations between hsCRP and future CVD, assessing levels of hsCRP may be a way to differentiate “healthy obese” individuals from those at higher risk [4]. Indeed, higher levels of CRP appear to be not only a marker of risk but also have an active role in cardiovascular disease. This has been demonstrated using animal models of atherosclerosis in which human CRP is increased experimentally, resulting in worsening of arterial thrombosis and endothelial injury repair [35]. Besides obesity, other lifestyle factors contribute toward higher hsCRP such as smoking and gender, with women exhibiting stronger associations between waist circumference and hsCRP than men [34]. Higher levels of hsCRP are also associated with incident myocardial infarctions,

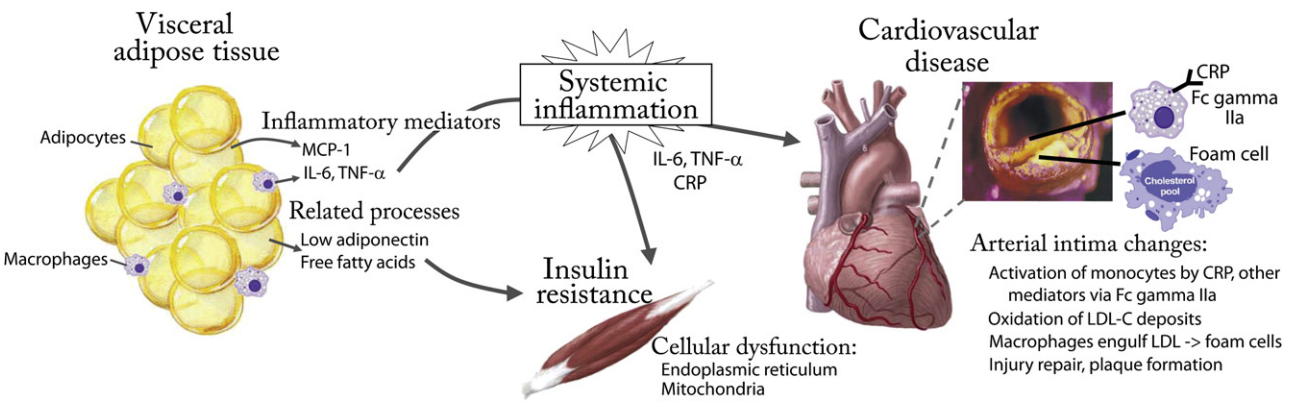

Fig. 1. A simplified model of the role of obesity-related inflammation in disease development. Hypertrophied visceral adipocytes secrete MCP-1, recruiting macrophages that secrete inflammatory cytokines including IL-6 and TNF-α. These enter the systemic circulation and stimulate the production of CRP. These inflammatory molecules contribute to peripheral cellular dysfunction of the endoplasmic reticulum and mitochondria, resulting in a worsening of insulin resistance that is further exacerbated by low levels of adiponectin and high levels of free fatty acids. In the intima of arteries, inflammatory molecules including CRP activate monocytes, contributing to reactive oxygen species and the oxidation of LDL-C, which is then taken up by macrophages to form lipid-laden foam cells. Further injury remodeling and fibroblast migration contribute to a growing atherosclerotic plaque. CRP, C-reactive protein; IL-6, interleukin-6; LCL-C, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α.