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Adiponectin: Identification, physiology and clinical relevance in metabolic and vascular disease

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Abstract

Adiponectin is the most abundant adipose-specific protein. Its expression is reduced in obesity, insulin resistance and type 2 diabetes, and plasma concentrations are inversely related to body weight, especially visceral adiposity. Adiponectin is also inversely associated with other traditional cardiovascular risk factors, such as blood pressure, low-density lipoprotein cholesterol and triglyceride levels, and is positively related to high-density lipoprotein cholesterol (HDL-C) levels. Recent research has indicated that adiponectin has anti-inflammatory, anti-atherogenic and antidiabetic properties. The ability of adiponectin to reduce insulin resistance in conjunction with its anti-inflammatory and anti-atherogenic properties makes this novel adipocytokine a promising therapeutic target, and agents that enhance adiponectin secretion or action have potential for treatment of metabolic and vascular disease. Current management strategies that may increase endogenous adiponectin production in humans include weight loss, soy protein and therapy with peroxisome proliferator-activating receptor gamma (PPARγ) agonists.

Keywords: Adiponectin; Adipocytokine; Visceral obesity; Type 2 diabetes; Insulin sensitivity; PPAR

1. Introduction

Excess body fat, in particular, abdominal visceral fat accumulation, is associated with a number of disease conditions, including dyslipidaemia, hypertension, type 2 diabetes, the metabolic syndrome and atherosclerosis [1–8]. This is of concern since at least 300 million people worldwide are clinically obese [9].

Recent research has shown that adipose tissue secretes various bioactive proteins, collectively referred to as 'adipocytokines' that may directly contribute to the pathogenesis of conditions associated with obesity [10–15]. These bioactive proteins include heparin-binding epidermal growth factor-like growth factor (HB-EGF), leptin, tumour necrosis factor-alpha (TNF-α), plasminogen activator inhibitor type 1 (PAI-1) and resistin. The expression of these adipocytokines increases with visceral fat accumulation, and is implicated in insulin resistance and atherosclerosis [10–15].

More recently, another adipocytokine, adiponectin, was identified which is a collagen-like protein abundantly expressed in adipose tissue [16]. In contrast to other adipocytokines, adiponectin levels are inversely related to visceral fat area, and low levels have been associated with obesity, type 2 diabetes and cardiovascular disease (CVD) [17–21]. This article discusses the identification and physiology of the novel adipocytokine adiponectin, and explores its clinical relevance.

2. Adiponectin

Adiponectin was identified in 1996 [16]. It is a 244 amino acid protein, which is highly expressed in human adipose cells [16]. Under normal conditions the adiponectin gene (AMP1) is expressed exclusively in adipose tissue. AMP1 is located on chromosome 3q27, and recent genome-wide scans have mapped a diabetes susceptibility locus to this chromosome [22–24]. The protein is composed of a collagen-like fibrous domain and a C1q-like globular domain (Fig. 1) [25]. A wide range of multimers have been detected [25]. For example, adiponectin is present in a unique multimer form, which has been shown to be more active than low molecular weight forms [26]. Adiponectin is abundant in plasma and accounts

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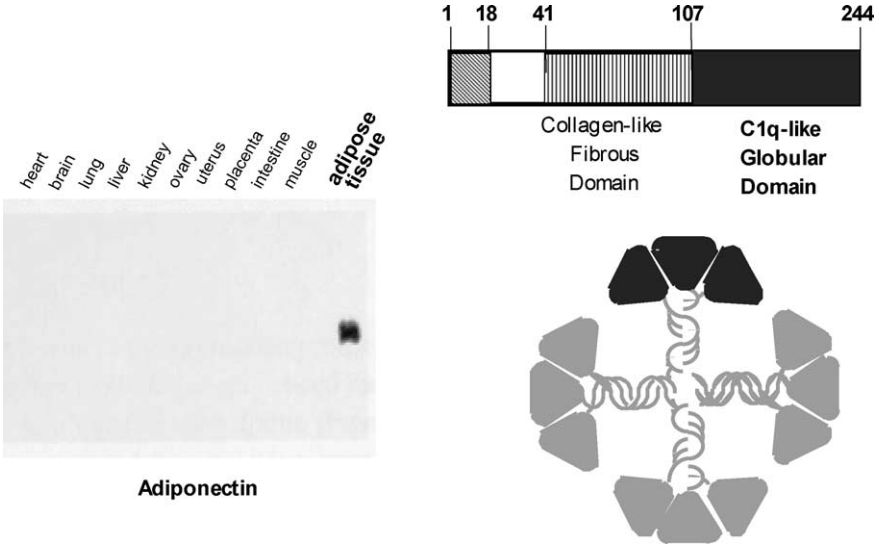

Fig. 1. Structure and adipose tissue-specific expression of AMP1 [16] [reprinted with permission from Elsevier (Maeda K et al. Biochem Biophys Res Commun 1996;221:286–9)].

for 0.01% of total plasma proteins in humans and 0.05% in rodents [17,27].

Two adiponectin receptors have recently been identified. AdipoR1 is a receptor for globular adiponectin and is abundantly expressed in skeletal muscle, whereas AdipoR2, a receptor for full-length adiponectin, is mainly expressed in the liver. However, neither the physiological role of the receptors nor the signal transduction pathways have yet been fully elucidated [28].

3. Adiponectin as a marker of disease

Research has shown that a low plasma adiponectin level, namely hypoadiponectinaemia, is associated with a number of disease conditions.

3.1. Obesity

The adipose tissue expression and plasma concentration of adiponectin is reduced in different animal models of obesity, such as leptin deficient ob/ob mice [27], leptin-resistant db/db mice [29] and high-fat diet-fed mice [29]. Adiponectin levels are also reduced in obese humans [17,27]. Arita et al. showed that mean plasma levels were 3.7 μg/ml in obese patients versus 8.9 μg/ml in non-obese subjects [17]. Plasma adiponectin concentrations were also shown to decrease with increasing adiposity in a longitudinal study of children (evaluated at 5 and 10 years of age) [30]. In particular, adiponectin levels have shown an association with visceral fat accumulation [18,20]. However, the mechanism by which visceral fat decreases adiponectin levels is not yet clear.

3.2. Insulin resistance and type 2 diabetes

Low levels of adiponectin have been associated with insulin resistance and type 2 diabetes [17,19,31,32]. Plasma adiponectin concentrations were decreased in obese rhesus monkeys and in monkeys with type 2 diabetes [33]. An important observation in this study was that the plasma levels of adiponectin decreased before the onset of diabetes, in parallel with the decrease of insulin sensitivity [33]. These results support data observed in humans [17,19,31]. In a study of Pima Indians, plasma adiponectin levels were measured before the onset of diabetes [31]. Individuals with high levels of adiponectin were less likely to develop type 2 diabetes than those with low concentrations (incidence rate ratio 0.63; 95% CI 0.43–0.92; $P = 0.02$; Fig. 2). High adiponectin was a stronger protective factor against development of type 2 diabetes than low waist circumference, fasting glucose, 2-h glucose or fasting insulin levels [31]. Other studies in different populations, including Japanese and Asian Indians, have

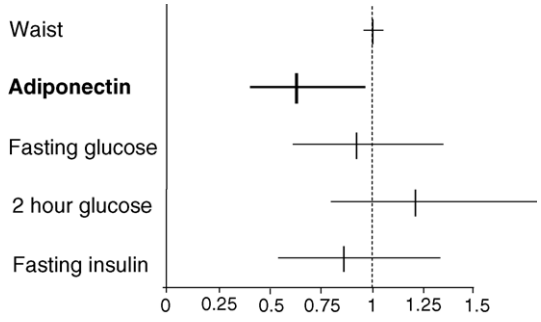

Fig. 2. Low risk for type 2 diabetes in subjects with high adiponectin levels [31] [reprinted with permission from Elsevier (The Lancet, 2002;360:57–8)].