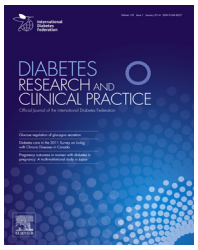
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Invited Review

Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes

Nathalie Esser [a,b,*], *Sylvie Legrand-Poels* [a], *Jacques Piette* [a], *André J. Scheen* [b], *Nicolas Paquot* [a,b]

[a] *Virology and Immunology Unit, GIGA-Research, University of Liege, Liege, Belgium*
[b] *Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, University Hospital of Liege, Liege, Belgium*

ARTICLE INFO

Article history:
Received 28 March 2014
Accepted 7 April 2014
Available online 13 April 2014

Keywords:
Type 2 diabetes
Obesity
Insulin resistance
Macrophages
NLRP3 inflammasome
Metabolic syndrome

ABSTRACT

It is recognized that a chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes. Systemic inflammatory markers are risk factors for the development of type 2 diabetes and its macrovascular complications. Adipose tissue, liver, muscle and pancreas are themselves sites of inflammation in presence of obesity. An infiltration of macrophages and other immune cells is observed in these tissues associated with a cell population shift from an anti-inflammatory to a pro-inflammatory profile. These cells are crucial for the production of pro-inflammatory cytokines, which act in an autocrine and paracrine manner to interfere with insulin signaling in peripheral tissues or induce β-cell dysfunction and subsequent insulin deficiency. Particularly, the pro-inflammatory interleukin-1β is implicated in the pathogenesis of type 2 diabetes through the activation of the NLRP3 inflammasome. The objectives of this review are to expose recent data supporting the role of the immune system in the pathogenesis of insulin resistance and type 2 diabetes and to examine various mechanisms underlying this relationship. If type 2 diabetes is an inflammatory disease, anti-inflammatory therapies could have a place in prevention and treatment of type 2 diabetes.

Contents

* *Corresponding author at*: Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liege, B-4000 Liege, Belgium. Tel.: +32 43667238; fax: +32 43667068.
E-mail address: Nathalie.Esser@ulg.ac.be (N. Esser).

http://dx.doi.org/10.1016/j.diabres.2014.04.006
0168-8227/

1. Introduction

Obesity, in particular excess visceral adiposity, is associated with insulin resistance, hyperglycaemia, dyslipidaemia and hypertension, which together are termed ''metabolic syndrome'' [1]. These metabolic disorders increase the risk of development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases and contribute to high rates of mortality and morbidity [1]. T2DM is the most prevalent metabolic disease in the world and is characterized by defects in insulin secretion and a peripheral insulin resistance in the skeletal muscle, the adipose tissue and the liver. The progression from obesity-related insulin resistance to T2DM remains poorly understood but implicates a failure of pancreatic β-cells to compensate for insulin resistance leading to chronic hyperglycaemia. A chronic low-grade inflammation and an activation of the immune system are observed in abdominal obesity and may have a role in the pathogenesis of obesity-related metabolic disorders [2–5]. This review summarizes data implicating the immune system in the pathophysiogy of insulin resistance and T2DM. We will also examine the biological, tissular and cellular inflammatory markers associated with obesity-related metabolic disorders that may predict the development of T2DM. Molecular mechanisms underlying this inflammatory activation state will be reviewed and preliminary results obtained with anti-inflammatory therapies in the prevention and treatment of T2DM will be described.

2. Systemic markers of inflammation

2.1. *Inflammatory markers in obesity, metabolic syndrome and T2DM*

White blood cell counts and plasma levels of coagulation factors (fibrinogen and plasminogen activator inhibitor 1 (PAI-1)), acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6), and chemokines are elevated in obese and T2DM patients and shown to be reduced when these patients are engaged in a more intensive lifestyle causing weight loss [6–11]. These pro-inflammatory markers also positively correlated with insulin resistance and the features of the metabolic syndrome, in most cases, independently of the degree of obesity [6,7,12–14].

2.2. *Inflammatory markers for development of T2DM in obese patients*

Subclinical chronic inflammation seems to be an independent risk factor for the development of T2DM. Indeed, high levels of many inflammatory factors at baseline in diverse human populations are correlated with incident T2DM, regardless of the initial degree of insulin resistance and obesity. Prospective studies have identified white blood cell count [12,15], pro-inflammatory cytokines [16], chemokines [17], and other several indirect markers of inflammation such as fibrinogen, sialic acid and PAI-1 [15,18] as predictors of T2DM. In contrast to all these inflammatory biomarkers, CRP measurement is less expensive, standardized and widely available. Particularly a highly sensitive measurement of CRP has been developed to detect this protein with greater accuracy at lower levels. A number of prospective studies have shown that high sensitivity-CRP (hs-CRP) levels predict development of T2DM in different non-diabetic populations regardless the degree of adiposity, fat distribution and insulin resistance. All these studies were included in a recent review and meta-analysis which provided further evidence that elevated CRP levels are significantly associated with increased risk of T2DM (relative risk [RR] 1.26 [95% confidence interval or CI 1.16–1.37]) [19]. This meta-analysis also detected a significant dose–response association between IL-6 (its inducer) and T2DM risk (RR 1.31 [95% CI 1.17–1.46]) [19].

2.3. *Inflammatory markers for cardiovascular disease in T2DM patients*

Since hs-CRP plasma levels have been associated with cardiovascular diseases and death in the general population [20] and in patients with metabolic syndrome [21], an important question is the possible association of inflammatory markers with these risks in T2DM patients. The Hoorn population-based study was the first to show that CRP is a predictor of mortality in T2DM individuals over a 5- to 7-year period [22]. Other observational studies in T2DM populations