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Adipokines in nonalcoholic fatty liver disease

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ABSTRACT

Since the discovery of adipose tissue as a higly active endocrine tissue, adipokines, peptides produced by adipose tissue and exerting autocrine, paracrine and endocrine function, have gained increasing interest in various obesity-related diseases, including nonalcoholic fatty liver disease (NAFLD). Data regarding the association between NAFLD and circulating leptin and adiponectin levels are generally well documented: leptin levels increase, whereas adiponectin levels decrease, by increasing the severity of NAFLD. Data regarding other adipokines in histologically confirmed NAFLD populations are inconclusive (e.g., resistin, visfatin, retinol-binding protein-4, chemerin) or limited (e.g., adipsin, obestatin, omentin, vaspin etc.). This review summarizes evidence on the association between adipokines and NAFLD. The first part of the review provides general consideration on the interplay between adipokines and NAFLD, and the second part provides evidence on specific adipokines possibly involved in NAFLD pathogenesis. A thorough insight into the pathophysiologic mechanisms linking adipokines with NAFLD may result in the design of studies investigating the combined adipokine use as noninvasive diagnostic markers of NAFLD and new clinical trials targeting the treatment of NAFLD.

Abbreviations: AMPK, 5′-adenosine monophosphate–activated protein kinase; APJ, apelin receptor; ASP, acylation-stimulating protein; BMI, body mass index; C5L2, chemoattractant receptor-like protein; CAP, adenylyl cyclase-associated protein; CCRL, chemokine (CC motif) receptor-like; ChemR, chemerin receptor; CMKLR, chemokine receptor-like; DCN, decorin; ERK, extracellular signal-regulated kinase; FFA, free fatty acid; Fox, forkhead box protein; GLP-1R, glucagon-like peptide receptor 1; GLUT, glucose transporter; GPR, G protein coupled receptor; HCC, hepatocellular carcinoma; HMW, high-molecular-weight; HSCs, hepatic stellate cells; IL, interleukin; IR, insulin resistance; IRS, insulin receptor substrate; JAK, Janus kinase; LepR, leptin receptor; LMW, low molecular weight; MAPK, mitogen-activated protein kinase; MMW, middle-molecular-weight; MMP, matrix metalloproteinases; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, nonalcoholic fatty liver disease; NAMPT, nicotinamide phosphoribosyl-transferase; NASH, nonalcoholic steatohepatitis; PBEF, pre-B cell colony-enhancing factor; PI3K, phosphatidylinositol-3 kinase; PPAR, peroxisome proliferator-activated receptor; RBP, retinol-binding protein; RELMs, resistin-like molecules; ROR, receptor tyrosine kinase-like orphan receptor; SH2-B, src homology 2 domain-containing adapter protein B; SOCS, suppressor of cytokine signaling; SS, simple steatosis; STAT, signal transducer and activator of transcription; STRA, stimulated by retinoic acid; T2DM, type 2 diabetes mellitus; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VLDL, very low-density lipoprotein.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a global public health problem [1], with a prevalence of 6–45% (median 20%) in the general population, depending on the studied population and the method of diagnosis [2]. It is considered to be the hepatic component of metabolic or insulin resistance (IR) syndrome, increasing in parallel with the epidemics of obesity and type 2 diabetes mellitus (T2DM) [3,4]. Contemporary research renders NAFLD more than a simple "component" or "manifestation" of IR, because there is evidence that NAFLD increases the risk for cardiovascular disease, including subclinical atherosclerosis, independently from IR syndrome and other conventional risk factors [5], thereby implying an additional synergistic effect of NAFLD and IR on cardiovascular morbidity.

NAFLD ranges from nonalcoholic simple steatosis (SS) to nonalcoholic steatohepatitis (NASH), characterized by inflammation and/or fibrosis [3]. NAFLD has hepatic and systemic consequences: NASH may lead to subacute liver failure, liver cirrhosis and/or hepatocellular carcinoma (HCC); it is also related with systemic metabolic complications, chronic kidney and cardiovascular disease, mainly contributing to liver-related, cardiovascular and cancer-related mortality observed in NAFLD patients [6].

Although NAFLD is a field of intensive research, its underlying pathophysiologic mechanisms are not fully elucidated and its treatment remains an unmet medical need [7]. Since its pathogenesis is multifactorial [8], multiple and diverse factors ("hits") have been proposed to contribute, some of which are regarded as classic, including dietary factors (e.g., fructose, especially when combined with excess energy intake [9]), IR and adipokines [3], whereas other needs further verification, including genes, innate and adaptive immunity, dysbiosis of the gut microbiota [10], *Helicobacter pylori* infection [11] and endocrine disruptors [12].

Adipokines are polypeptides produced by adipose tissue and exert autocrine, paracrine and endocrine function. There is increasing evidence that adipokine alterations, which occur during the expansion of adipose tissue, contribute to the development of SS, but also to the progression to NASH and possibly to NASH-related cirrhosis [3]. This review summarizes evidence on the association between adipokines and NAFLD. The first part of the review provides general consideration on the interplay between adipokines and NAFLD, and the second part provides evidence on specific adipokines involvement in NAFLD pathogenesis. A thorough insight into the pathophysiologic mechanisms linking adipokines and NAFLD may result in the design of studies investigating the combined adipokine use as noninvasive diagnostic markers of NAFLD and new clinical trials targeting the treatment of NAFLD.

2. General Insight Into the Relationship Between Adipokines and NAFLD

Traditionally, adipose tissue was regarded as an inert energy-storage organ and even classic textbooks of physiology did not devote over a couple of paragraphs to describe its role. Since the discovery of leptin, the prototypical adipocyte-secreted hormone or adipokine, in 1994 [13], this conventional consideration has been radically changed. Currently, adipose tissue is considered to be the major and possibly the largest endocrine organ, with a network of signaling pathways enabling the organism to adapt to a wide range of different metabolic challenges; its functional pleiotropism relies on its ability to synthesize and release a variety of hormones, cytokines, complement and growth factors, extracellular matrix proteins and vasoactive agents, collectively called adipokines, with multi-potent effects on health and disease [14]. More than 700 different proteins have been described as being potentially secreted by the adipose tissue; however, these proteins need further study and validation regarding their expression, secretion and function, before full characterization as putative novel adipokines [15]. Furthermore, publications are accumulating on the endocrine function of adipose tissue, and the new editions of physiology textbooks devote many pages to describe the endocrine function of adipose tissue [14].

Generally, adipokines include peptides that are mainly, although not exclusively, produced by adipocytes (e.g., adiponectin, leptin). Adipose tissue also produces other peptides (including classical cytokines), which are mainly, but not exclusively, produced by immune cells infiltrating adipose tissue (e.g. tumor necrosis factor [TNF]-α, interleukin [IL]-6) or endothelial cells of adipose tissue [3,16]. Numerous immune cells, including macrophages, B-cells, T-cells and neutrophils have been identified in adipose tissue; obesity influences both the quantity and the nature of immune cell subtypes; when adipose tissue expands, it is infiltrated by more and different immune cells, which increase the burden of low-grade, but chronic inflammation of adipose tissue [17]. A complicated communication network between adipocytes and immune cells with potential consequences on NAFLD seems to exist: for example macrophages serve as the source of the majority of adipose-derived inflammatory factors, but they are affected by ever changing inputs from surrounding adipocytes to exert their inflammatory potential. Conversely, cytokines produced by immune cells may affect the adipocytes to change their secretory profile, thereby establishing a vicious cycle [3,18]. In this regard, both the innate and the adaptive immune systems play a significant role in the pathogenesis of NAFLD; the organ-specific immunity is involved in the onset and progression of this disease, which draw complex pathways and offer various possible targets for future treatment.

Adipokines may be also divided, according to their potential impact on NAFLD, into those having a positive or negative impact. Adiponectin is an adipokine with potential beneficial effect on NAFLD [19], whereas others, including resistin, TNF-α, IL-6 have possibly an adverse effect on NAFLD. It seems that a continuous dynamic cross-talk between adipokines with a positive or negative impact on NAFLD exists, resulting in a beneficial or detrimental final effect, respectively. However, this final effect is not permanent, but temporary, since an ever-changing metabolic milieu affected by both innate (e.g., genetic susceptibility) and exogenous factors (e.g., lifestyle) leads to an ever-changing adipokine profile and subsequent an ever-changing effect on NAFLD. The deeper knowledge of these sophisticated interactions and the their ever-changing, possibly non-linear,