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New adipokines linked to obesity and obesity-related diseases

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Abstract

Adipose tissue plays essential metabolic roles, not only serving as massive energy reservoir but also producing and releasing hormones and other biologically active molecules that regulate several metabolic activities. Adipocytes secrete a variety of factors, referred to as adipokines. Current research has identified over 50 adipocyte-secreted factors, and more are yet to be discovered. In obesity, increased production of pro-inflammatory adipokines and diminished synthesis of anti-inflammatory factors impacts on multiple functions such as appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure and lipid metabolism. All are linked with higher risk for cardiovascular disease. Various adipocyte-released compounds profoundly affect insulin sensitivity and might potentially link obesity-related diseases, including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, hypertension, dyslipidaemia and insulin resistance.

This review aims to present some of the recent topics of selected adipokine research that may be of particular importance.

Introduction

Abdominal fat accumulation has been shown to play essential role in the development of metabolic syndrome [1]. The metabolic syndrome, a cluster of metabolic disorders often associated with visceral obesity, increases cardiovascular mortality and morbidity. As the body's largest endocrine organ, adipose tissue not only stores excess energy, but also synthesizes and releases several bioactive molecules named "adipokines" [1,2]. The term "adipokines" is restricted to peptides and proteins secreted from adipocytes, excluding signals released only by the other cell types (such as macrophages) in adipose tissue [3].

Obese patients, particularly those with visceral fat accumulation, have diminished plasma levels of adiponectin, the most abundant protective adipose-specific adipokine[4].

Visceral fat accumulation is closely related to the development of cardiovascular disease and obesity-related disorders such as hypertension, hyperlipidemia, diabetes mellitus [1,2] as shown on Figure 1 [5]

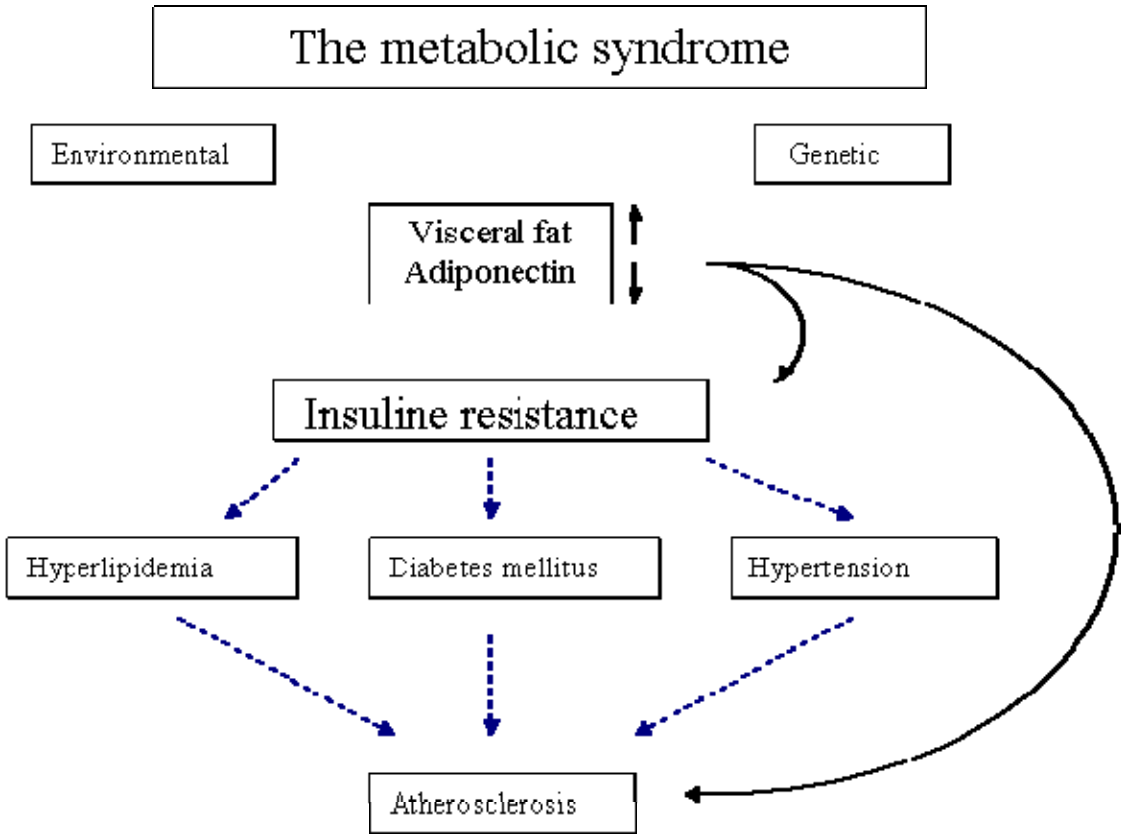

Figure 1. Visceral fat relations to the metabolic syndrome (5).

Adipose tissue has long been regarded as an organ the sole purpose of which was to store excess energy as triglycerides, and release energy as free fatty acids, which itself is an essential self-defense system for survival during starvation [6,7,8]. This point of view has now changed, fat tissue has emerged as an endocrine and secretory organ affecting more than one metabolic pathway [3,9,10]. Its major endocrine function is secreting several hormones, notably leptin and adiponectin. Also adipose tissue releases adipokines involved in inflammation and hemostasis : growth factors (TNFα, transforming growth factor-beta, nerve growth factor, VEGF), cytokines (IL-1β, IL-6, IL-10), chemokines (IL-8), acute-phase proteins (haptoglobin, serum amyloid A) and prothrombotic factor (plasminogen activator inhibitor-1) [3,9].

It is now well acknowledged that the consequences of obesity, particularly diabetes and cardiovascular diseases, are influenced to a great extent by the actions of adipokines. Production of pro-inflammatory adipokines is increased in obesity which has led to the view that chronic low-grade inflammation is a characteristic feature in the obese subjects and that this links causally to insulin resistance and the metabolic syndrome [3,11].

Among various adipocyte-secreted factors adiponectin and visfatin appear as insulin-sensitising adipokines, whereas TNF-α, IL-6 and resistin are considered as compounds increasing insulin resistance. Moreover, leptin regulates apetite and energy balance [4,8,12].

Adiponectin

Adiponectin seems to be the most interesting and promising biologically active molecule released from fat cells since it has profound protective actions in the pathogenesis of diabetes mellitus and cardiovascular disease. This protein is also called ADIPOQ, gelatin-binding protein 28, Acrp30. It was discovered in 1995, at about the same time as leptin, as a product of the adipose tissue most abundant gene transcript [11,13].
Adiponectin, a protein synthesized almost exclusively by fat cells, plays an important role in the regulation of whole body energy homeostasis, glucose and lipid metabolism and anti-inflammatory responses in the vascular system [14,15,16]. Human plasma adiponectin concentration is about 1000 times higher than those of any other hormone and is higher in women than in men. Adiponectin levels are decreased in obesity, subjects with insulin resistance, type 2 diabetes and dyslipidemia and are particularly low in subjects with coronary artery disease. Adiponectin increases insulin sensitivity in various models of insulin resistance and in vitro increases the ability of sub-physiologic levels of insulin to suppress glucose production in isolated hepatocytes. This protein intensifies peripheral tissues sensitivity to insulin and its deficiency can contribute to the development of insulin resistance in type 2 diabetes and obesity [14,16,17].
The most important feature of adiponectin is its lower expression in the adipose tissue and lower concentration in plasma in overweight, obese and diabetic patients.
Plasma adiponectin is negatively correlated with the BMI, visceral fat volume, waist/hip ratio, fasting plasma insulin, plasma glucose and triglyceride concentrations [16,18,19]. Furthermore, it positively correlates with HDL-cholesterol level [20].
Adiponectin is also involved in the regulation of energy balance and body weight and it reduces weight gain. Weight loss leads to increased levels of that adipokine in plasma. Obese patients who received gastric partition surgery (gastric stapling) showed a 21% reduction in mean BMI that was accompanied by 46%, in average, increase in plasma adiponectin values.
Adiponectin plays an important role in the regulation of lipid metabolism (increases fuel oxidation) and carbohydrate metabolism (improves hepatic insulin sensitivity).
Adiponectin has been shown to exert anti-inflammatory and anti-atherogenic properties within the arteries and thus may negatively modulate the process of atherogenesis [6,8,9,11,16,18,19]. The importance of adipokines, especially focusing on adiponectin, is discussed with respect to cardiovascular disease. High concentrations of adiponectin are found in the bloodstream inside the vascular walls. Matsuzawa et al. have shown that adiponectin can enter the vascular walls, bind specifically to collagen types I, III, V and VIII present in the vascular intima and selectively accumulate in injured vessel walls, indicating that it may be involved in the repair process of damaged vasculature [6].
Recent studies suggest that adiponectin may play a role in the modulation of inflammatory vascular response by supressing the expression of adhesion molecules on endothelial cells, inhibiting endothelial cell NF- B signaling and suppressing macrophage function (foam cell formation). In doing so, adiponectin inhibits the development of atherosclerotic plaques [8,9,11,16].

It was also suggested that adiponectin gene variations are associated with risk of myocardial infarction and ischemic stroke; in particular selected gene variants were found

to be associated with diminished cardiovascular risk in subjects with or without diabetes [21].
Engeli et al. suggest that decreased expression and plasma levels of adiponectin may serve as a marker of increased metabolic and inflammatory risk [22]. The association exists between adiponectin gene expression and its plasma levels which results from exclusive secretion of this adipokine by adipocytes. This is not the case for the pro-inflammatory IL-6 or TNF- gene expression in fat cells because these molecules are also secreted by a number of other cell types. It was that found that plasma adiponectin levels and hs-CRP correlate inversely what may suggest that decreased production of adiponectin contributes to the systemic and vascular inflammation commonly found in obesity. Regional differences may exist in adiponectin expression and production in human adipose tissue [22].
Korner et al. have reported that adiponectin levels are significantly reduced in patients with breast, endometrial and prostate cancer. Adiponectin has been shown not only to have anti-atherogenetic, anti-angiogenic and anti-proliferative properties, but may also play a role in cancer development [11].
Many studies support the protective role of adiponectin in the development of obesity-related disorders and the metabolic syndrome, particularly in the pathogenesis of type 2 diabetes and cardiovascular disease. It has been found that in the obese subjects but not in the lean higher adiponectin plasma concentration was connected with more favorable lipid profile (lower triglycerides, LDL-cholesterol and apolipoprotein B, higher HDL-cholesterol) and decreased inflammation (lower CRP and IL-6) [20].
Further elucidation of the mechanisms of action of adiponectin, particularly the identification of inhibitors of adiponectin expression in obesity, has the potential to create novel and powerful targets for developing intervention strategies for obesity-related disorders [4,9,23].

Resistin

The invention of resistin as a novel factor secreted by fat cells with an impact on insulin sensitivity was proposed as a new mechanism to explain the pathogenic sequence of adipocyte-obesity-insulin resistance. Resistin is a cysteine-rich 12.5 kDa polypeptide, with unclear role in the pathogenesis of obesity- mediated insulin resistance and type 2 diabetes mellitus. Recent studies in murine models suggest that resistin (also called Fizz3), secreted by adipocytes, may represent the long-sought link between obesity and insulin resistance [9,11]

Many studies are still unravelling the functionality of resistin in human biology in respect to glucose metabolism and insulin signaling. The possible involvement of resistin in obesity and insulin resistance in humans is largely controversial. Resistin is considered to be a substance increasing insulin resistance, however the exact mechanisms are not well-known. Resistin plasma concentrations are increased in obese subjects and correlate with the inflammatory state that underlies the initiation and progression of atherosclerotic lesions. Correlation between resistin concentration and the extent of atherosclerotic plaques in the coronary vessels has also been found. All these findings suggest that resistin is directly involved in the pathogenesis of atherosclerosis. It has been showed that resitin can be induced by endotoxin and cytokines [9,11,24].

The data on association of resistin with obesity or insulin resistance are controversial, some have reported positive correlations while others did not find a relationship. Recently, Al-Harithy et al. assessed the relationship between serum resistin concentrations and insulin resistance in lean, overweight and obese Saudi women with or without diabetes [23]. They have shown that resistin concentrations are elevated in patients with type 2 diabetes and are associated with obesity and insulin resistance, indicating the involvement of this adipokine in the development of diabetes in humans [23].

Another study has shown that resistin is associated with the disorders of glucose and lipid metabolism in type 2 diabetes [25].

Vendrell et al. suggested coordinated roles of adiponectin, resistin, and ghrelin in the modulation of the obesity proinflammatory environment. They found that resistin levels before surgery treatment are predictive of the extent of weight loss after bypass surgery. Like many other adipokines, resistin may possess a dual role in contributing to metabolic disease: first through its direct effects on substrate metabolism and second, through regulating inflammation and the development of endothelial dysfunction [24,26].

Visfatin

In 2004, Fukuhara et al. identified a molecule that is expressed at much higher levels in visceral fat than in subcutaneous fat which was named visfatin [27]. This adipokine is highly expressed in the visceral adipose tissue of both humans and rodents. Visfatin was found to be identical to a cytokine expressed by lymphocytes - the pre-B cell colony-enhancing factor (PBEF). Visfatin binds to the insulin receptor at a site distinct from insulin and exerts hypoglycemic effect by reducing glucose release from hepatocytes and stimulating glucose utilization in peripheral tissues. Since insulin-mimetic actions of visfatin may be part of the feedback regulation of glucose homeostasis, a hypothesis may be raised that visfatin concentrations are influenced by glucose or insulin blood levels in humans. This possibility offers new therapeutic options for diabetics [9,11,27].

Brendt et al. examined whether visfatin plasma concentration and mRNA expression in visceral and subcutaneous fat correlates with anthropometric and metabolic parameters in subjects with a wide range of obesity, body fat distribution, insulin sensitivity, and glucose tolerance [28]. They have found correlations between visfatin plasma concentrations and visceral visfatin mRNA expression and measures of obesity but not with visceral fat mass or waist-to-hip ratio. Surprisingly, they did not found differences in visfatin mRNA expression between visceral and subcutaneous adipose tissue [28].

Haider et al. have shown that elevated plasma visfatin concentrations in morbidly obese subjects are reduced after weight loss. This may be related to changes in insulin resistance over time [29].

Further study of visfatin's physiological role may lead to new insights into glucose homeostasis and its dysregulation in obesity-related diseases, such as diabetes mellitus and cardiovascular disease [1,11,27].

Apelin

A novel adipokine apelin, produced and secreted from fat cells, was discovered recently. This bioactive peptide is the endogenous ligand of the orphan G protein-coupled receptor, APJ. Apelin may act as a potent vasodilator, thus lowering blood pressure, and exerting positive inotropic effects in rats and humans. Furthermore, the apelin system may modulate pituitary hormone release and food and water intake, regulate insulin sensitivity, play a role in stress activation [30]. This neuropeptide is involved in the regulation of body fluid homeostasis and cardiovascular functions. Moreover, recent study showed that apelin acts as an angiogenic factor for endothelial cells and exerts potent diuretic effects through inhibition of arginine vasopressin (AVP) neuron activity and AVP release [11,31,32].

Heinonen et al. investigated basal plasma levels of apelin, orexin-A, and leptin in morbidly obese patients [33]. They have shown positive correlations of apelin, orexin-A, and leptin plasma levels with the BMI. The results of this study also demonstrated that one year after gastric banding with significant loss in BMI basal plasma levels of leptin decreased, while orexin-A remained unchanged [33].

Apelin as a multipotential adipokine has attracted much interest as a target for novel therapeutic research and drug design.

Eotaxin

Eotaxin is a chemokine produced by fat tissue. The eotaxin family comprises three distinct peptides (eotaxin, eotaxin-2 and eotaxin-3) which have been implicated in eosinophilic inflammation.Eotaxin binds with high affinity and specificity to the chemokine receptor CCR3 and plays an important role in the pathogenesis of allergic disease.Eotaxin belongs to CC chemokines with selective activity for eosinophils and basophils and it is important in extrinsic asthma, an inflammatory disorder. Asthma is often more severe in the obese subjects. Eotaxin and cytokines produced by adipose tissue may possibly directly influence airways hyperresponsiveness, leading to an increased prevalence and severity of asthma symptoms in obese individuals.

Circulating eotaxin levels are increased in diet-induced obesity in both mice and humans, and eotaxin mRNA levels were high in visceral adipose tissue in both species. Diet-induced weight loss in humans led to a reduction in plasma eotaxin levels [34,35,36].

The other study showed that reduced level of circulating eotaxin-3 may represent a potentially powerful biochemical marker for predicting future adverse cardiac events in patients with coronary artery disease (CAD). In vitro and clinical studies suggest that eotaxins could play a role in vascular inflammation, but no data are available on their prognostic significance in patients with angiographically documented coronary artery disease[36,37].

This adipokine may be regarded as a potential non-invasive marker for assessing airways inflammation in asthmatics and predicting cardiac events in patients with CAD [36,37].

We aimed to provide a concise summary of actual knowledge on the important adipokines, and to give an update on the latest findings and current fields of adipokine research in association to obesity and obesity-related diseases. The molecular effects of adipokines are a challenging area of research and their in-depth understanding will undoubtedly lead to the discovery of effective therapeutic interventions. The disturbances in expression, synthesis and release, function and balance of adiponectin, resistin and eotaxin may be considered not only as a link between visceral adiposity and cardiovascular risk but also as independent risk factors of coronary heart disease. Elucidation of the mechanisms linking obesity, diabetes and atherosclerosis is fundamental for developing the new ways of therapeutic interventions.

References

1. Matsuzawa Y: Therapy insight: adipocytokines in metabolic syndrome and related cardiovascular disease. Natl Clin Pract Cardiovasc Med: 2006, 3, 35-42
2. Matsuzawa Y: The metabolic syndrome and adipocytokines. FEBS Lett: 2006, 22;580,2917-21
3. Trayhurn P, Wood IS: Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr. 2004;92,347-55
4. Okamoto Y, Kihara S, Funahashi T et al.: Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci: 2006,110,267-78
5. www.phoenixpeptide.com/Catalog/Adiponectin/adiponectin.htm
6. Matsuzawa Y, Shimomura I, Kihara S, Funahashi T: Importance of adipocytokines in obesity-related diseases. Horm Res , 2003, 60(suppl 3), 56-59
7. Schaffler A, Scholmerich J, Buchler C: Mechanisms of disease: adipocytokines and visceral adipose tissue-- emerging role in intestinal and mesenteric diseases. Nat Clin Pract Gastroenterol Hepatol. 2005;2,103-11
8. Kopff B, Jegier A: Adipokines: adiponectin, leptin, resistin and coronary heart disease risk. Przegl Lek. 2005; 62 (Suppl 3),69-72
9. Ronti T, Lupattelli G, Mannarino E: The endocrine function of adipose tissue: an update. Clin Endocrinol. 2006; 644, 355-365
10. Chudek J, Adamczak M, Nieszporek T, Wiecek A: The adipose tissue as an endocrine organ-a nephrologists' perspective. Contrib Nephrol. 2006;151,70-90
11. Koerner A, Kratzsch J, Kiess W: Adipocytokines: leptin-the classsical, resistin-the controversial, adiponectin- the promissing, and more to come. Best Practice&Clinical Endocrinology&Metabolism 2005; 19, 525-546
12. Kralisch S, Klein J, Bluher M et al.: Therapeutic perspectives of adipocytokines. Expert Opin Pharmacother. 2005; 6, 863-872
13. Szopa M, Malczewska-Malec M, Wybrańska I: Adiponectin--adipocytokine with a broad clinical spectrum. Przegl Lek. 2004; 61,109-14
14. Simońska E, Gumprecht J, Skubala A et al.: Adiponektyna-znaczenie w patogenezie cukrzycy typu 2. Diabetologia Doświadczalna i Kliniczna 2004; 4,249-254
15. Trayhurn P: Endocrine and signalling role of adipose tissue: new perspectives on fat. Acta Physiol Scand. 2005,184,285-93
16. Pańkowska E, Szalecki M: Adiponektyna- hormon tkanki tłuszczowej i jej związek z zespołem metabolicznym i chorobami układu krążenia. Endokrynologia,Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego 2005;11,187-190
17. Scherer P.E : Adipose Tissue: From Lipid Storage Compartment to Endocrine Organ.

Diabetes. 2006;55,1537-1545
18. Galvani M, Scarfone A, Granato L et al.: Restoration of Adiponectin Pulsatility in Severely Obese Subjects After Weight Loss. Diabetes 2004; 53,939-947
19. Schulze M,B, Grimm E,B, Shai I et al.: Relationship Between Adiponectin and Glycemic Control, Blood Lipids, and Inflammatory Markers in Men With Type 2 Diabetes. Diabetes Care 2004; 27,1680-1687
20. Kantarzis K., Rittig K., Balletshofer B. et al.: The relationship of plasma adiponectin with a favorable lipid profile, decreased inflammation and less ectopic fat accumulation depend on adiposity. Clin Chem 2006; 52, 1934-42
21. Hegener H.H., Lee I-M., Cook N.R. et al : Association of adiponectin gene variations with risk of incident myocardial infarction and ischemic stroke : a nested case-control study. Clin Chem 2006; 52, 2021-27
22. Engeli S, Feldpausch M, Gorzelniak K et al.: Association between adiponectin and mediators of inflammation in obese women with diabetes. Diabetes 2003; 52, 942-947
23. Al-Harithy RN, Al-Ghamdi S: Serum resistin, adiposity and insulin resistance in Saudi women with type 2 diabetes mellitus. Ann Saudi Med. 2005;25, 281-2.
24. McTernan PG; Kusminski CM; Kumar S: Resistin. Curr Opin Lipidol. 2006;17,170-5
25. Lu HL, Wang HW, Wen Y et al.: Roles of adipocyte derived hormone adiponectin and resistin in insulin resistance of type 2 diabetes. World J Gastroenterol. 2006;12,1747-51
26. Vendrell J, Broch M, Vilarrasa N et al.: Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res. 2004;12, 962-71.
27. Fukuhara A, Matsuda M, Nishizawa M et al.: Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005; 307,426-430
28. Brendt J, Kling N, Kralishc S et al.: Plasma Visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005; 54, 2911-2916
29. Haider DG, Schindler K, Schaller G et al.: Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. J Clin Endocrinol Metab. 2006; 91,1578-81
30. Boucher J, Masri B, Daviaud D et al.: Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005; 146,1764-71
31. De Mota N, Reaux-Le Goazigo A et al.: Apelin, a potent diuretic neuropeptide counteracting vasopressin actions through inhibition of vasopressin neuron activity and vasopressin release. Proc Natl Acad Sci USA. 2004; 101,10464-9
32. Lee DK, George SR, O'Dowd BF: Unraveling the roles of the apelin system: prospective therapeutic applications in heart failure and obesity. Trends Pharmacol Sci. 2006; 27,190-4
33. Heinonen MV; Purhonen AK; Miettinen P et al.: Apelin, orexin-A and leptin plasma levels in morbid obesity and effect of gastric banding. Regul Pept. 2005; 130,7-13
34. www.thedoctorslounge.net/chest/articles/obesity_asthma/index.htm
35. Vasudevan AR, Wu M, Xydakis AM, Jones PH et al.: Eotaxin and obesity. J Clin Endocrinol Metab 2006; 91, 256-261
36. Falcone C; Minoretti P; D'Angelo A et al.: Markers of eosinophilic inflammation and risk prediction in patients with coronary artery disease. Eur J Clin Invest. 2006; 36, 211-7
37. Emanuele E, Falcone C, D'Angelo A et al.:Association of plasma eotaxin levels with the presence and extent of angiographic coronary artery disease. Atherosclerosis. 2006;186, 140-5