Review Article

Molecular challenges of adipocytes biomarkers related obesity updates

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Abstract

Overweight is an urgent concern of majority of health organizations where it is rising incidence of metabolic syndromes and diseases. Molecular genetics studies on obesity investigated several adipocyte biomarkers with clinical significance. Increased non-blocked synthetic pathways in adipose tissues caused by excess calories consequence overweight and obese populations. Visceral fat adipocytes are strictly associated with metabolic dysfunctions, insulin resistance, heart conditions and others than subcutaneous fats. Adipocytes are the key endocrine like cells that release verities of biological protein adipokines derivatives causing different anti-inflammatory events. Disbalance in the adipokines synthesis and excretions will affect different fat tissues causing complications and pathogenesis related obesity. To combat obesity and its progression, the current study is focusing on the benefits of adipokines as a new trend biomarker for detecting obesity updates.

Key words

Diabetes mellitus, Obesity, Brown adipocytes, White adipocytes, Biomarkers.

Introduction

Obesity is a common public health problem that decreases life expectancy with increasing morbidity and mortality through many diseases. Obese classes individuals gain BMI of > 30 kg/m2 or more with different physical changes [1]. They enlarge visceral and subcutaneous white adipose tissues based increasing number of white adipocytes (WAC) and their sizes till accumulations of fats in different other tissues of liver, pancreas, heart and skeletal muscle. WAC stores and releases fats, while brown adipocytes (BAC) oxidize fats to energetics and protecting

systemic metabolisms [2]. Conversion of BAC to white unilocular cells BAC decrease their numbers and activities [3], White adipose tissues develop inflammations and aggregates of macrophages around dead adipocytes causing dysfunctional adipocytes and activating synthesis of proinflammatory adipokines and cytokines [4].

Increased visceral fat masses are associated with increasing risks for insulin resistance with developing diabetes mellitus type2 (DMT2), metabolic syndromes and cardio-vascular diseases [5-6]. Approximately, 30% of visceral adipocytes genes encode bioactive proteins as pro-inflammatory and/or anti-inflammatory agents. They secrete different cytokines and adipokines. Cytokines "e.g., interleukin-6 and tumor necrosis factor alpha (TNF-α)", induce critical molecular changes in the progress of endothelial dysfunction for getting atherosclerosis [7-8]. Adipokines include adiponectin, leptin, resistin, visfatin, adipsin, apelin, omentin and others that take parts in the different molecular challenges of obesity changes. Past researches were focusing synthesis and secretion of adipokines related to WAC [9-10]. They explored adipokines diversity levels, dysregulation and abnormalities that contribute varieties of obesity diseases parallel bio mass indexes comparing to overweigh and obese cases [11-12]. There are substantial studies to understand the biochemical features and interactions of adipokines that promise discovery of new assessment biomarkers trend for investigation of obesity updates.

White adipocytes

White adipocyte (WAC) is a large fat droplet marked with little cytoplasm flattened non-centrally nucleus, few mitochondria and surrounded with a single large membrane. Visceral WAC is a source of many fats derived like hormones "adipocytokines" and inflammatory mediators as a causing adipose tissue vascularization and perfusion. It secretes adiponectin, leptin, resistin, visfatine, adispin apelin and omentin. The majority of WAC modulates many receptors in various metabolic pathways, including insulin, growth hormone, cortisol, and adrenaline. Thus, excesses of WACs in visceral fat are associated with different metabolic syndromes and risks development of metabolic disorders e.g. DMT2 and heart diseases. They are willing to serve as obesity biomarkers and are engaged in the development of disorders linked to obesity [13-14]. Recently, the subcutaneous WAC can be induced to get brown adipocyte features in healthy populations, but it is reduced in WAC from obese and/or morbid obese cases [15].

Brown adipocytes

Brown adipocytes (BAC) generates body heatbased uncoupling of oxidative metabolic pathways of glucose and fats from adenosine triphosphate synthesis. They have an inverse relationship with visceral fat mass and body mass index (BMI). They generate glucose homeostasis, energy production and body weight reduction that in turn improve insulin sensitivity. Thus, BAC will initiate channels to get rid of obesity and metabolic disorders [16].

Adiponectin

Adiponectin (ADN) is a collagen-like protein and secreted in the peripheral blood circulation. It is composed of 244 amino acids (29 kDa). The transcribed gene is located on chromosome 3 that ensemble the cytogenetic band (3q27.3). Circulated human blood ADN level is (5-10) μg/ml and decreased in obese cases with a negative correlation with BMI. ADN level is high in non-obese young subjects [17]. Obese cases recorded decreased plasma ADN levels with decreased insulin sensitivity. Mutations in ADN gene are associated with ADN deficiency. Thus, it develops low serum levels of ADN (<4 μg /ml) [18]. Although data among (2020-2023) was starting management of obesity-based behaviors of AND levels, IR and weight loss, they didn't achieve the ambitious results. They tried different treatment strategies based on exercises; diet alters or combined with therapeutic agents. They expected that increasing circulating blood ADN concentrations may get

protection against atherosclerosis and DMT2 [19]. Plasma ADN levels are low in overweight cases with visceral fats. Low levels of ADN affect the pathogenesis of visceral fats [20].

Leptin

Leptin (LN) is a protein of 167 amino acids (16kd) transcribed by gene allocated on chromosome 7 and ensemble cytogenetic band (7q32.1). LN receptors are expressed within central nervous-system particularly in hypothalamus including the mode of action related some peripheral organs e.g. lung, pancreas and immune cells. It regulates body weight by signaling pathways that inhibits food intake and/or energy stores pathways [21]. LN is a multi-tasking e.g. thermoregulation, energetic homeostasis, proinflammatory immune responses, bone metabolism. Obese cases have elevated levels of LN in correlation to mass of white fat tissues [8, 22]. Mutations in genes coding LN and its own receptor sequences consequence severe or morbid obesity and hypogonadism that may inhibit fertilization due to loss of signaling. It is related to hypothyroidism-based rise in thyroid-stimulating hormone, low thyroxine and raise of autoimmunity [23].

LN stimulates signaling of phosphatidylinositide-3-kinase pathways as an insulin receptor substrate to manage glucose homeostasis. It inhibits adenosine monophosphate kinase (energy sensor in the brain) to reduce food uptake by rising signals of anorexia [24]. LN and insulin induce weight reduction and browning of white fat cells. This is due to removal of certain phosphatases supporting insulin and LN to communicate neurons to stop diet-induced obesity and to create browning fat cells that require energy expenditure [25].

LN deficiency is related to severe IR and correlated to endocrinal disorders among uncontrolled DM [26, 27]. There is a significantly increased LN levels parallel to decreased ADN levels of among those obese cases in comparing to those of non-obese cases DMT2 [28]. Research studies recommended managing blood plasma LN levels in uncontrolled diabetics for extra homeostasis of blood glucose levels or body weights [29, 30].

Resistin

Resistin (RN) is a protein with 11.4 kD composed of 108 amino acids rich with cysteine. It is expressed by a gene located within chromosome-19 resembling band of (19p13.2) [31, 32, 33]. Since 2005, RN is a biomarker for the adiposity developing DMT2 in humans getting hyperresistinemia and hypertension [34]. This is due to increasing hepatic glucose production leading to hyperresistinemia [35]. RN is expressed in monocytes, macrophages and peripheral blood mononuclear cells. It activates pro-inflammatory cytokines synthesis e.g. IL-12, inhibits chemotaxis proteins and reduces expression of TNF receptor-associated factor-3 [36]. It promotes the production of chemotactic proteins that attract CD4-positive T-lymphocytes migration and other vascular cells into vessels with developing lesions participating in LDL accumulation in arteries with getting early arteriosclerosis risk [37, 38].

Visfatin

Visfatin "VIS", is an autocrine peptide chain of 491 amino acids. It is and expressed by a gene located within chromosome7 resembling cytogenetic band (7q22.3). VIS is secreted in both cytoplasm and nucleus of different cells of brain, kidney, lung, spleen, testis, synovium and cartilage. It is mainly expressed in visceral fats more than subcutaneous fats. VIS increases cell proliferation, hypoglycemic effect and synthesis of nicotinamide mono- and dinucleotide [39]. Imprint studies investigated increasing serum levels of VIS in obese and overweight among a wide range of populations e.g. adolescents' children, and adults with and/or without metabolic risk factors [40].

VIS levels are reduced later weight loss regarding to low calories diets research in obese cases [41]. Their levels were correlated with hyperinsulinism and hyperglycemia. It promotes

glucose consumption in adipocytes and decreasing glucose release from hepatocytes. VIS causes different biochemical effects: (i) providing evidences for central obesity regarding to increasing insulin, glucose, triacylglycerides and physical inactivity, (ii) promotion of DM pathogenesis with two folds concentrations comparing to normal conditions [42].

Adipsin

Adipsin (AN) is a serine protease protein with 253 AAs (27 kDa.) It is coded by gene located on chromosome 19 that ensemble the cytogenetic band (19p13.3). It is expressed in macrophages and adipocytes [43]. AN is a regulator for preserving beta cell functions in pancreas-based binding the peptide receptor (C3a) based insulin secretion activate. In vitro studies explored that lacking of AN gene will get glucose intolerance with insulin deficiency. So, it is expected that DMT2 patients with β cell failure will get AN deficiency. Pancreatic β cell failure causes insulin deficiency, hyperglycemia and disbalance of glucose homeostasis [44].

Recent results marked AN/ C3a pathways to band adipocyte function to pancreatic β cell functions. AN and complement factor D is considered as an important biomarker for obesity and metabolic diseases. It controls the rate restrictive step in the alternative complement pathways for cleaving complement factor B from activated C3. The AN/complement factor D is decreased in most obese cases. Mostly, overweight cases with the metabolic syndrome are accompanied with an anti- inflammatory response of adipose tissue derived adipocytokines [45, 46].

Apelin

Apelin (APLN) is an adipokine peptide chain with 77 amino acids (8.6 kDa) in adipose tissue. It is activated by the G-proteins coupled receptors. The coding gene is sited on chromosome X that ensemble a cytogenetic band (Xq25). It is expressed in different tissues then cleaved into three active forms including APLN-13, APLN-17 and APLN-36. APLN takes part in the regulation of the biological function's diversity including fluid homeostasis via activation of tissue-specific signaling pathways and energetic pathways [47].

APLN is synthesized in central gastrointestinal tract, heart, lung, nervous system, mammary gland, placenta and white adipose tissues [48]. It increases basal activities of BAC secretions and block the inhibitory effect of TNFα on brown adipogenesis. It promotes increasing mitochondrial biogenesis and oxygen consumption [49]. APLN has a role in glycemic balance and even insulin sensitivity where it is increased in plasma levels of diabetics. Others reported that APLN plasma level was greater in DM type1 than DM type2 [50]. Through signaling pathways, APLN activates blood-derived phagocytes, causing them to release TNF-α, interleukin-1β, and IL-6 over normal ranges, which in turn causes retinal damage in patients with retinopathy. It activates developing BAC, white adipocyte and metabolic activities with suppressing releasing of fatty acids and reactive oxygen species of WAC. Thus, it controls activities of LP, ADN, and energy metabolism [51, 52].

Omentin

Omentin (OMN) is a secretory protein with 313 amino acids of 35-38 kDa. OMN is expressed by both OMN-1and OMN-2 coding genes are the coding genes in visceral WAC. The coding genes are located on the chromosomal band 1q22-q23. OMN increases insulin signal transduction by activating different insulin stimulated glucose transport, protein kinases and the uptake into isolated adipocytes [53]. Circulating OMN-1 concentrations increase after weight loss. It is reduced in obese cases and is inversely related to BMI, waist circumference, LN levels, and metabolic syndrome. OMN levels are prognostic for comorbidities accompanying obesity. It is significantly lower in morbid obese cases [54, 55]. OMN serves as an anti-inflammatory mediator by blocking TNF-α inducing superoxide's production [56]. OMN-1 levels were decreased in heart failure patients.

Therefore, OMN-1 plays an important role as a therapeutic target and prevention of atherosclerosis [57].

Adipose tissue macrophages

Obesity is related to increased macrophages quantity. Macrophages are phagocytic cells for removing dead adipocytes. They induce proinflammatory cytokines and share pancreatic dysfunction development [58]. Both macrophages and crucial cells lead to increased levels of nicotinamide adenine dinucleotide synthesis via VIS. It is involved in developing inflammatory and metabolic disorders e.g. obesity and atherosclerosis. Thus, peroxisome proliferator-activated receptor-β adapts central pathways in differencing of adipocytes and lipid metabolism that in turn impact on insulin sensitivity and glucose metabolism [59].

Discussion

Biomarker panels are not a replacement for current management strategies, but to aid minimizing frequencies of panels of diseases. Developing biomarkers is expected to share early detecting and protection against body disfiguring, cancer risks and metabolic diseases. Getting effective biomarkers for obese classes around WAC excretions will get early detection of undesired clinical pictures and complications. Researchers indicated adiponectin AND) as anti-inflammatory, anti- diabetic and anti-atherosclerotic effecter [12-16]. Hypoadiponectinemia are predicted to develop cardiovascular events and DMT2 [14]. ADN serum rates are considered as a superior biomarker for many metabolic disorders, especially those obese cases before getting morbid obesity. These findings are agreed with obese cases that scored decreased plasma ADN [15-16].

Leptin (LN) are decreased during starvation and are increased in obese cases. Uncontrolled insulin-deficient cases have reduced plasma LN levels and take part in the genesis of metabolic syndromes independent of adiposity and cytokines [18]. In obese diabetic subjects, there is a crosstalk between insulin signaling and LN. LN mediates insulin activities in liver hepatocytes. Now, LN is considered as an anti-obesity because of its ability in increasing energy consumption and reducing food intake signaling pathways. In cases of obesity, instability of LN serum levels can predict the overlapping of illnesses. These facts investigated LN is graded to be a specific marker for getting obesity [15-20]. further studies are recommended for understanding different facts: (i) To investigate relationship among leptinemia, obesity scales and DMT2. (ii) To answer whose is the initial sensitizer for presented metabolites LN, insulin or fatty acids metabolism. (iii) To explore effects of obesity on autoimmune thyroid diseases and risk factors on LN serum levels [60].

In obese cases, increasing serum level incidences of resistin (RN) activate rising those of early DMT2, visceral adiposity and extensive pattern of arteriosclerosis. Basically, RN upswings low-density lipoproteins, cholesterol and destruction of their specific receptors that increases adherence into blood arteries causing heart disease. Researchers have linked RN to other physiological effects such as inflammation and energy homeostasis. It is noted that serum LN, RN, ADN, and VIS levels are measured as risk elements for postmenopausal of breast cancer. They are talented as unique biomarkers for postmenopausal breast cancer [61]. Before, it was too late, there is an urgent need for prospective pathophysiological studies to develop using RN biomarker for getting an early investigation of obesity risks and consequent changes for healthy or those borderline obese cases.

Little research studies are known to explain biochemistry contests for human visfatin due to a shortage of approved normal human VIS concentrations and its metabolic pathways correlations among adults' metabolic disorders [62]. Researches inspected increased VIS levels in overweight and obese among populations [63]. Uncontrolled irregular excess blood VIS causes

unpredictable disorder where VIS increases glucose uptake in adipose cells with an excess of triglycerides biosynthesis or storage. VIS is a prognostic proinflammatory cytokine for gastric cancer [64]. VIS levels were related to lymph node metastasis, tumor node metastasis stage, tumor size, invasion depth, distant metastasis and peritoneal dissemination [65]. Extra research studies are recommended around: (i) Relations between VIS and the other adipocytokines secretions. (ii) Revising the alterations of gene expressions in adipocytes over signaling pathways of adipocytokines biosynthesis (iii) Re-evaluation the relation between different WAC adipokines in early prediabetic patients and/or with metabolic syndromes.

Researchers are in agreement with decreasing adispin (AD) serum levels among those with increased obesity levels until getting uncontrolled cases [66]. They confirmed decreasing serum AD levels in many subgroups of DMT2 subjects. It may ensure a diagnostic assessment to identify cases with a high risk of developing a pancreatic cell failure [47, 48]. Future studies are required for the following suggestions: (i) Assessing of serum AD rates in among prediabetic subjects. (ii) Assessing of AD in different populations for getting more information around factors suppressing AD expression in obese and/or morbidly obese patients. (iii) Assessing of the relationship between serum AD levels and metabolic diseases.

The role of apelin as, a regulator for inflammatory factors is still under discussion. Researchers suggested a potential therapeutic route of APLN to resist obesity in relation to different metabolic diseases. In addition, it takes part in the body weight reduction and improvement of insulin sensitivity [50-52]. Further studies are recommended for clearance the mode of APLN secretions among tissues comparing to adipose tissues. No doubt that OMN can be applied as a specific biomarker for metabolic disorders [46-48]. This is because of circulating serum levels of OMN are negatively correlated with many metabolic risk factors. Brandt, et al. (2015) enrolled Circulating OMN levels are correlated with indices [67].

Conclusion

White adipocytes produce signaling biomolecules to pancreatic islets initiating increased levels of insulin triggering insulin resistance within DMT2. WACs identified several adipokines (omentin, apelin, adiponectin, adipsin, leptin, visfatin and resistin) as abundant and specifically expressed adipose proteins. Adipose tissue dysfunctions in obese cases are calling to discover sensitive biomarkers for measuring altered adipose tissue distributions. They are willing to provide measurement tools for early diagnosis of different metabolic diseases. Future studies are recommended for looking at specific biomarkers necessary for the achievement of good spectrum diagnosis of obesity complications. More studies are needed for molecular characterization of sensitivity and specificity for such circulating biomarkers for early diagnosis of obesity and different metabolic diseases among populations. Integrity of both anthropometric indices and white fat cell adipokines are required for clinical diagnosis of metabolic diseases in obese cases. Additional information is mandatory to get alternatively the biochemical effects on the corresponding tissues and effects of cell biology in different tissues among different types of adipocytes.

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Abbreviations

WAC: White adipocytes; BAC: brown adipocyte; IR: insulin resistant; DMT2: diabetes mellitus type 2; AND: adiponectin; LN: Leptin; RN: resistin; VIS: Visfatine; AN: adispin; APLN: Apelin; OMN: Omentin.

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