Role of Adipose Tissue in Metabolic System Disorders: Adipose Tissue is the Initiator of Metabolic Diseases

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Abstract

The pathophysiology of obesity-induced metabolic syndrome is due to the dysfunction of the metabolic system. The metabolic system is composed of different components including energetic molecules, endocrine system and metabolically active tissues like adipose tissue (AT), skeletal muscles and liver. AT plays a significant role in the regulation of metabolic system components. Evaluation of the functionality of this system is one of the main steps in the diagnosis and determination of the severity of metabolic disorders as well as evaluation of the treatment process of patients with metabolic disorders. In this review we have aimed to highlight the physiological role of AT as one of the major determinants in the regulation of the metabolic system and subsequently the energy metabolic system functionality is in details introduced.

Keywords: Adipose tissue; Lipid droplet; Metabolic syndrome; Lipodystrophy; Insulin pathway disturbance; Type 2 diabetes; Inflammation; Cytokines; Chemokines; adipocytes; Mitochondria

Introduction

Fats are one of the most important components of the human body, which are distributed as structural and metabolic molecules. Lipids are sporadically present in different tissues, i.e. bone marrow, brain and adipose tissue (AT). AT is one of the largest and highly specialized connective tissues, which are composed of different cell types. This diversity of cells in the AT represents its vast function and importance in different systems including metabolic system, osteogenic system [1] and immune system [2]. Obesity triggers chronic systemic inflammation and hyperglycemia among other features of the metabolic syndrome (MS) that shows the close association between lipid and carbohydrate pathways [3]. AT is the main energy reservoir organ in the body that together with its connective tissue character has the unique ability of expanding as much as the weight of the body allows in overnutritional states. In this review, the axial role of the AT in regulation and integration of the metabolic system is highlighted.

Properties of Adipose Tissue

Adipose tissue (AT) is classified into two major different types according to the location and the color. Based on color, AT is divided into brown adipose tissue (BAT) and white adipose tissue (WAT) with significant differences in morphology and function. But with respect to the location, ATs are present either as visceral (VIS) or subcutaneous (SC) fat. Since these two fat-types are different from each other with respect to function, this classification is very important in the evaluation of the metabolic system functionality. Although both BAT and WAT present in the SC- and VIS-AT, the percentage of WAT in the SC-AT is higher than VIS-AT.

BAT-adipocytes are multilocular due to numerous small lipid droplets (LDs) in their cytoplasm. Therefore, the storage of energy in the form of triglycerides in LDs is accessible for rapid hydrolysis and oxidation of fatty acids (FAs). However, WAT-adipocytes are unilocular and contain unique LDs (Fat-organelle like), which are able to store triglycerides at a high energy density [4,5], and this form of energy is efficient because of the following two reasons: 1- the considerable caloric value of lipids compared to carbohydrates and 2- the triglycerides, in contrast to carbohydrates, can be stored with little associated water. Therefore, approximately 60-85% of WAT-adipocytes weight consist of lipids [6] and water-weight is excluded from AT-weight. This property of triglycerides decreases the total weight of AT in an obesity state as compared to the same mass of skeletal muscle in a muscular body. Energy storage in skeletal muscles and liver appeared to be mainly in the form of carbohydrates and each carbohydrate requires 4 molecules water for storage. Therefore, the ratio of weight to energy level in AT is comparatively less than skeletal muscles [7,8]. Ultrastructurally, BAT-adipocytes have numerous big mitochondria packed with cristae containing uncoupling protein 1 (UCP1), which its function is to generate heat by non-shivering thermogenesis, involved in fatty acid oxidation (FAO), and in turn, energy release. This non-shivering thermogenesis is a cold climate adaptation in many homeotherms [9]. BAT is the only AT present during fetus development and while the child continues to grow until adolescence. A major amount of BAT converts to WAT [10]. However, the remaining amount of BAT is metabolically highly active [11]. Therefore, age, strain and environmental conditions are considered as factors that stimulate conversion of BAT and WAT to each other [4]. Comparatively, the percentage of BAT in VIS-AT is higher than SC-AT [12].

Based on the location of AT in the body, it is divided into two forms; apple or pear shapes. In apple-shape adiposity (visceral or central obesity), fat pads (fat depot) accumulate mostly in the abdominal cavity and around intra-abdominal organs. Central obesity increases...
the risk for metabolic problems. However, in pear-shape adiposity (peripheral obesity), extra fat is stored subcutaneously and around hips, thighs and buttocks. This form of fat has immunological and protective effects against obesity-associated metabolic disorders and provides insulation from heat and cold. Peripheral obesity is hallmark for a normal function of the body for storage of excess energy [13].

AT is made from a connective tissue that is normally highly flexible with a low density. During obesity and type 2 diabetes, the connective tissue becomes collagenous, calcified and rigid in a fibrosis state. The extracellular matrix of AT is an important place for modulation of systemic metabolism [14]. In this matrix, different cells are seeded that function together to regulate energy storage (Figure 1), namely adipocytes, preadipocytes, adipose tissue macrophages (ATMs), fibroblasts, endothelial cells and stem cells (Figure 2).

Adipocytes are the major constituent cells of AT that have both metabolic and immunity properties. Mature adipocytes have a very long half-life and the ability to store great amounts of lipids; however, they lose their division ability. They are protected by a very long half-life and the ability to store great amounts of lipids; however, they lose their division ability. They are protected by a bilayer phospholipid membrane from surroundings, containing some cytoplasmic compartments, including nucleus, mitochondria, and LDs (fat organelle). LDs composed of a highly hydrophobic core containing lipids (nonpolar) covered by a highly hydrophilic (phospholipids, polar) monolayer membrane. LDs occupy most of the mature adipocytes volume and are considered to store a huge amount energy in the form of triglycerides (Figure 3). LDs are also present in many cells such as the skeletal muscle, heart, liver, pancreas, kidney and macrophages [15]. However, LDs within adipocytes have a higher capacity for energy storage than other cells. The mature adipocytes contained either medium-sized or single large lipid droplet mainly in WAT, which is formed by the fusion of multiple enlarged intracellular LDs forming a unilocular structure [5] Of note, an overload of energy in the form of triglycerides in LDs within adipocytes is the main cause of adipocytes hypertrophy, which, in turn, these hypertrophic cells are the main cause of obesity. In a normal states, AT is the main site for fat storage and target of circulating lipids (free fatty acids (FFAs) and lipids of lipoproteins) [16]. However, in the obese state, LDs of other cells also become enlarged and reserve excess energy but not comparable with the size of LDs in adipocytes. Adipocytes hypertrophy induces malfunction in the insulin pathway [17,18].

ATMs are the second most important cells in the AT that have a very close interaction with adipocytes mainly during metabolic disorders. In a metabolic syndrome state, macrophages induce inflammation and they play a role in tissue repair in AT utilizing the hedgehog signaling [19,20]. Moreover, ATMs and other AT-cells, via production of coagulation factors, stimulate coagulation activity in obese subjects and increase the incidence of hypercoagulation [19,21].

From endocrinology point of view, adipocytes are the source of a vast number of adipokines, which influence the physiological function of the central nervous system, and metabolic tissues that ensure the maintenance of the energy homeostasis in the body. During obesity state, functions of adipokines are disrupted due to adipocytes hypertrophy and, in turn, its effects on either functionality of the AT or the levels of secreted adipokines [22]. Therefore, secretion of a physiological amount of adipokines [10,23,24] appeared to be crucial for a homeostatic function of the metabolic system. Pro-inflammatory cytokines or innate immune system mediators are other secretion components of AT during initiation of metabolic disorders, and, in turn, inflammation, which is primed by AT-adipocytes [2]: a linking...
between obesity and inflammation. During obesity-induced chronic inflammation, there is a close immunological correlation between AT-adipocytes and ATMs in the AT. Systemic inflammation is the etiology inflammation, there is a close immunological correlation between AT-
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Adipokines, Adipokines, Inflammation, Obesity-Associated Metabolic Disorder

Obesity stimulates an inflammatory state, which implicates in obesity-associated pathophysiological complications such as type 2 diabetes (T2D), dyslipidemia, cardiovascular mortality and morbidity as well as insulin resistance (IR) [27-30]. Since obesity is determined by the mass of AT [28], AT has an established and important role in the development of obesity. Of note, an overload of energy in lipid droplets (fat organelle) of adipocytes is the main cause of obesity. Also, it has been recently shown that AT is able to produce and secrete numerous proteins of which influence the function of many metabolic organs via a network of endocrine, paracrine, and autocrine signals [27,31-33]. These AT derived biologically active proteins called adipokines such as leptin, adiponectin, which are responsible for homeostasis of energy metabolism [27,29,31-35]. Thus, imbalance or dysfunction of AT and particularly adipocytes are resulted in pathophysiological states associated with energy metabolism disorders [27,29,32]. In addition, adipocytes play a prominent role in lipid and glucose metabolism [6,30,36-40]. Although involvement of adipocytes in metabolic pathways is clear, little is known about their role in inflammation. Moreover, AT is recognized as immune organ [37]. Although there are plenty of publications related to adipocytes and their cytokines production, the most of these studies focused on a restricted number of cytokines such as Interleukin 6 (IL-6), Tumor necrosis factor (TNF-α) and resistin [30,36,37]. Notably, AT-adipocytes also synthesize hedgehog components such as Indian hedgehog (IHH), which are involved in the developmental system. This morphogenetic network is not only important at the start of life but also suppress the deterioration of body during ageing [20,41]. Down regulation of these hedgehog signaling components resulted in ageing-associated diseases such as metabolic disorders and T2D [20].

Besides adipocytes, AT contains several other cell types including endothelial cells, macrophages and fibroblast [39,42], and cross talk between these cells affects the adipocytes-associated proteins composition. Although there are many evidences regarding cross talk effect of these cells on AT production and consideration of this tissue as immune organ, in most of published studies, it is believed that behavior of AT as immune organ could be triggered by ATMs [25,43-46]. Moreover, while the role of adipocytes in metabolic pathways is clear, Meijer et al. has been recently reported that adipocytes exhibit immune cell function and these cells are able to prime inflammation and activate CD4+ cells and that is independent of macrophages [2]. Human AT-adipocytes also synthesize hedgehog components such as Indian hedgehog (IHH), which are involved in the developmental system. This morphogenetic network is not only important at the start of life but also suppress the deterioration of body during ageing [20,41]. Down regulation of these hedgehog signaling components resulted in ageing-associated diseases such as metabolic disorders and T2D [20].

Although obesity is the major risk for T2D, the role of insulin insensitivity cannot be ignored in the development of T2D. With respect to insulin, T2D occurs when the body does not produce sufficient amounts of insulin and/or when the tissues become resistant to elevated, normal or slightly decreased levels of insulin [47]. There are four major dysfunctions in T2D, 1- hepatic release: the liver is not able to suppress glucose release properly. 2- Islet Langerhans-associated β cells dysfunction in pancreas: in pre-diabetic state insulin insensitivity is present but β cells are still able to compensate for IR with high
insulin production and T2D occurs only when β cells machinery insulin synthesis become exhausted. 3- Pancreatic-associated β cells: IR is due to a dysregulation in insulin secretory condition. 4- Obesity: adipose tissue-derived factors such as adiponectin, leptin and/or other adipokines have the ability to counteract insulin action. Korc has been recently shown that eighty percent of patients with T2D are obese [47].

Adipose Tissue Function and Correlation to Metabolic Syndrome

AT have different functions such as temperature isolation, structural support of organs, endocrine secretions (adipokines such as leptin, adiponectin, and resistin), immune-associated components (pro-inflammatory cytokines/chemokines), and energy storage depot of triglycerides in LDs of AT-adipocytes.

The major functions of the AT-adipocytes (Figure 1). The expression of adipocytes-associated genes related to LDs such as fat-specific protein 27 (FSP27) influence this property [10,16] (Figure 3). FSP27 enhances unilocularization of separated growing LDs mainly in SC-AT [5,17]. Unilocular LDs have a better capacity for storage of lipids than multinucleolar LDs because of their lower surface contact with lipolytic enzymes such as lipoprotein lipase (LPL). In AT-adipocytes, the expression of FSP27 gene is 100 times more than other cells [17]. This indicates that the AT-adipocytes has higher specialized LDs in storage processes than other cells, i.e. LDs fusion. In an obesity state, dysfunction of LDs resulted in the accumulation of extra cytoplasmic lipid intermediates, which interact with insulin pathway, inducing insulin pathway disturbance in adipocytes [10].

We introduce this phenomenon in this review as fatty acid-induced insulin pathway disturbance or "FAID". Using disturbance instead of insulin resistance and that is due to the point that FAID happens following overload of intracellular lipid and this is reversible by caloric restriction. Therefore, we assume that in the pathophysiology of metabolic disorders, proper function of AT and in particular adipocytes-LDs is considered to be the initiator of the proper insulin pathway function. Moreover, in the evaluation of the severity levels of insulin pathway disturbances, the seeding of LDs in a proper location is much more important than body weight per se [10]. Obesity is a physiological state of mammalian bodies to reserve extra energy in adipocytes is one of the storage processes than other cells, i.e. LDs fusion. In an obesity state, dysfunction of LDs resulted in the accumulation of extra cytoplasmic lipid intermediates, which interact with insulin pathway, inducing insulin pathway disturbance in adipocytes [10].

Based on above mentioned pathophysiological state, two treatment protocols are designed: 1- thiazolidone medication and 2-transplantation of normal AT. In both protocols, mechanism of action is improvement of lipid distribution in the body and fat shift from peripheral tissues to SC-AT [10,57]. This shifting event decreases FAO, a reduction of ER-fat accumulation and consequently a decrease of ER-stress-induced productions. In a pathophysiological state, ER stress and high levels of intracellular inflammation ameliorate systemic insulin resistance. Thiazolidone is a peroxisome proliferator-activated receptor γ (PPARγ) agonist that acts as sensor for FAs and that is a critical check-point of thermogenesis. PPARγ is expressed abundantly by adipocytes and stimulates adipocyte differentiation and metabolism and, in turn, improves storage of lipids. PPARγ agonist (Thiazolidone) stimulates adipocyte differentiation in mitochondria [50]. Therefore, in AT, the proper function of LDs. mitochondria and ER are crucial in alleviation of ER stress and reactive oxygen species (ROS) production in cells. Functional mitochondria have direct influence on longevity of multicellular organisms. Notably, metabolic disorders and chronic inflammation are also associated with cancer and ageing-associated diseases [51].

Another etiology of inflammation is adipocyte itself. Adipocites secrete proinflammatory mediators (IL-6, IL-8, IL-7, TNFa, TNFβ, and NFKb) and adipokines (e.g. leptin, adiponectin, visfatin and resistin) that have a systematic role in maintenance of energy retour in the body. Immune property of adipocytes is independent of the secretion of immune-associated mediators by ATMs. Innate immune mediators are also secreted by ATMs, which have a close interaction with adipocytes for induction of pro-inflammatory cytokines secretion by AT [25]. However as suggested by Meijer et al. [48], AT-adipocytes prime inflammation and, in turn, it is exacerbated by activated ATM and recruitment of immune cells. During obesity, concentration of ATMs-associated products is increased inducing local inflammation, which leads to necrosis of the AT and more infiltration of circulatory macrophages to necrotic parts in order to phagocytize debrides and repair tissues. The conversion of resident (also called regulated macrophages) macrophages to activated macrophages in AT is considered as a pathological event that occurs during non-controlled obesity. AT secretes a huge number of proinflammatory cytokines and chemokines to circulation and from there transported to other tissues. This event is the main etiology of systemic inflammation during metabolic disorders. Inflammatory pathways in adipocytes interact with insulin and leptin pathways [23]. Local inflammation also leads to impairment of pre-adipocytes differentiation and reduction of lipid storage and disruption in adipokines productions such as adiponectin and leptin secretions, which enhance ectopic lipid accumulation [52].

AT-inflammation increases AT-lipolysis and results in high concentration of FFAs in circulation and dyslipidemia as consequence [53]. Overload of FFAs in circulation is sedimented in other tissues such as the skeletal muscle and liver [10]. These organs are the main glucose consumers in body, which is appeared to have nonfunctional LDs. That could be then reason why an overload of FFAs in these organs leads to FAID and consequently organ dysfunction and hyperglycemia [16,54]. A disruption in this process is a risk for the development of MS with the increase of visceral obesity, dyslipidemia, hyperglycemia and hypertension (Figure 4) as result. Catabolic chronic inflammation enhancement and the anabolic insulin pathway disturbances are compensatory mechanisms for consumption of excess energy in the body [55,56].

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The former is associated with a shortage or absence of AT, while in two different forms; 1-lipodystropic or lipoatrophic and 2-obesity. Lack of a metabolically active AT. Based on the AT-mass, they appear [55,59]. The main common pathophysiology trait in these diseases is hyperglycemia, dyslipidemia, osteoporosis, hepatic steatosis and CVD metabolic disorders that have the same clinical manifestation such as obesity induced-metabolic syndrome or hypertrophic adipocytes, the excess levels of AT appeared to be dysfunctional. AT metabolic defect leads to impairment of homeostatic regulation of adipokines secretion, energy distribution, and lipid sequestration. Sedimentation of FFAs in non-AT forms hepatic and myocellular steatosis [60]. Furthermore, in these catabolic tissues, overload of intracellular energy levels increases production of lipid intermediates (ceramide and diacylglycerol (DAG)) [50], resulting in inflammation, ER stress and FAID phenomena [24]. In the initial stages, disturbance of insulin pathway compensatory stimulates pancreatic β cells to induce hypervinsulinemia. There is also disturbances in insulin-induced gene expressions and recruitment of intracellular vesicles containing glucose transporters (GLUTs) to the cell surface to allow that glucose enter the cell via diffusion. This resulted in the cell energy metabolic disorders, which make the cells use intracellular lipids as fuel instead of glucose, leading to hyperglycemia [10,61].

Adipokines and their Influence on Metabolic System

Adipokines are a group of proteins that are secreted by adipocytes. These adipokines include leptin, adiponectin, resistin, visfatin, plasminogen activator inhibitor-1 (PAI-1), tissue factor (TF), tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), Regulated on Activation Normal T Cell Expressed and Secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-8, IL-4, IL-13, MHC-II-related components, acute phase proteins, and inducible nitric oxide synthase (iNOS) [2,48] (for the complete production of adipokines please see reference 2). Since AT spread out in whole body and has a great line of production of different categories, it is reasonable to consider AT as the largest endocrine organ in human. During metabolic disorders, disturbance in secretion of adipokines initiates pathophysiological events in body. Among adipokines, leptin and adiponectin play an important role in the regulation of AT-mass. During enlargement of AT, the levels of leptin increase while adiponectin levels decrease. In metabolic syndrome and lipodystrophy, the leptin levels and cellular leptin sensitivity is converse. In lipatrophy, leptin levels are low and cells are sensitive to it; therefore, leptin replacement therapy [62] is a main treatment of choice. However, in lipohypertrophy, leptin levels are high but leptin is resistance. This might be due to the influence of inflammation [63] or the effect of triglycerides [64] on the leptin pathway [65]. Leptin also stimulates oxidative stress, vascular inflammation and hypertrophy of the vascular smooth muscle [63] as well as influences the sympathetic nervous system [66], which can be the reason for hypertension and CVD in obese individuals [67]. The etiology of hypertension in ohotrophic patients could be lipid pathway disorders and formation of foam cells in atherosclerotic plaques, which is an inflammatory event. Moreover, the influence of hedgehog signaling on the metabolic system [20], endothelial dysfunction, hyperglycemia and hyperlipidemia following leptin and insulin pathways disturbance might have a role in atherosclerosis [68].

Adiponectin is considered as anti-inflammatory adipokine whose levels are high during normal state and caloric restriction. Adiponectin improves the sensitivity of insulin pathway in the body. The levels of Adiponectin during metabolic syndrome is downregulated; therefore, the incidence of inflammation and insulin unresponsiveness increases. Furthermore, adiponectin is able to decrease the depressive influence of FAID on the insulin pathway via activation of AMPK and FAO. Adiponectin also shows an inhibitory effect on the adhesion of macrophages to endothelial cells and in this way appeared to have a protective effect on atherosclerosis [46].

**Figure 4:** Three main tissues (adipose tissue, skeletal muscle and liver) targeted by insulin in both normal and obesity states. In normal state, a functional adipose tissue (AT) induces the uptake of circulatory and peripheral FFAs to store these lipids in the form of triglycerides in adipocytes lipid droplets (LDs), AT in such regulated state suppresses negative effect of lipids on insulin pathway, resulting in the enhancement of glucose uptake by cells and in particular by skeletal muscle cells and, in turn, inhibition of lipolysis of stored triglycerides. Consumption of glucose by cells inhibits intracellular lipolysis. Existence of enough intracellular glucose in peripheral tissues inhibits hepatic glucose output. An obese state resulted in IR and that is due to chronic inflammation and dysfunction of AT, which in turn lipolysis increases and release of FFAs from AT and sedimentation in peripheral tissues decreases the function of the insulin pathway, leading to the induction of hepatic glucose output. The final consequence of this process is dyslipidemia, hyperglycemia and liver-gluconeogenesis.

and AT functionality by induction of the PPARγ, Perilipin, and FSP27 expression in adipocytes. Notably, perilipin is major constituent protein of LDs. This event consequently induces sequestration of fats from peripheral tissues to the AT and in particular AT-adipocytes [10].

Transplantation of normal AT in patients is another strategy for the improvement of insulin sensitivity. This highlights the importance of a functional AT in the pathophysiology of MS [58]. It is shown that a dysfunctional AT in fat storage increases lipolysis, and circulatory FFAs, leading to dyslipidemia. The dysfunction of AT occurs appeared to be due to an imbalance between energy intake and energy expenditure, which could lead to obesity or cachexia. In several studies, it has been shown that FSP27 protein promotes energy reservoir in the form of triglycerides within lipid droplets and knock out of FSP27 gene in mice led to the increase of lipolysis and as consequent the enhancement of insulin sensitivity, protecting mice from diet-induced obesity and insulin resistance [10,61].

**Lipodystrophy and Metabolic Syndrome**

Lipodystrophy and metabolic syndrome are a group of metabolic disorders that have the same clinical manifestation such as hyperglycemia, dyslipidemia, osteoporosis, hepatic steatosis and CVD [55,59]. The main common pathophysiology trait in these diseases is lack of a metabolically active AT. Based on the AT-mass, they appear in two different forms; 1-lipodystropic or lipoatrophic and 2-obesity. The former is associated with a shortage or absence of AT, while in...
Resistin is another important adipokine that has a great influence on the metabolic system. Resistin is one of the inducers of insulin unresponsiveness and has an opposite effect, as compared to adiponectin, on the metabolic system [69]. The adiponectin-resistin (AR) index is considered as one of the main biomarkers in evaluation of the functionality of the metabolic system [70]. Resistin is expressed mainly by macrophages, hypothalamus and pancreatic cells and a low degree expression by adipocytes. Resistin is primarily expressed by macrophages and recruits other immune cells to the AT and stimulates proinflammatory cytokine secretion. Moreover, resistin stimulates atherosclerosis via formation of foam cells, proliferation of endothelial cells and migration of smooth muscle cells [71]. It is speculated that FFAs, via induction of resistin secretion, have an inhibitory effect on insulin pathway [72].

Acute phase proteins such as C reactive protein (CRP) are other secretion products of the AT that have a close association with chronic inflammation and insulin pathway dysfunction in the body [73]. CRP is considered as a potential circulating inflammatory biomarker that can be used for detection and prevention of the CVD and metabolic disorders [74]. Importantly, CRP is also synthesized by adipocytes [2,48].

Proinflammatory chemokines such as monocyte chemoattractant protein-1 (MCP-1), and RANTES as well as cytokines such as IL-4, IL-6 IL-8, IL-10, and MIP-2 are other secretory mediators of the AT. RANTES is chemokine, which is upregulated in AT during obesity. This shows that T cells together with macrophages have a crucial role in chronic inflammation and metabolic disorders. One of the subgroups of T cells is regulatory T cells (T-regs) that have anti-inflammatory properties. It has been shown that during insulin pathway disorders, the number of T-regs dramatically decreases. These findings represent the therapeutic effect of T regulatory cells in alleviation of the progress of the metabolic disorders [75-79].

Evaluation of Functionality of Metabolic System

One of the main points to which the medical society should pay close attention in the metabolic system disorders is evaluation of functionality of the metabolic system. This evaluation is essential to determine precisely the severity of the disease and the progress of treatment protocols. In this evaluation, two questions are crucial; (i) which one of the metabolic tissues has the most determinant role in maintenance of the metabolic system? and (ii) how can we measure the levels of the metabolic system functionality? A list of criteria is introduced here to reply these two questions.

Adipose tissue vs. skeletal muscle

Body-mass index (BMI) is one of the factors used for the evaluation of severity of obesity. BMI is defined as body mass divided by the square of height and is calculated by the following equation: (mass (kg) / (Height (m))^2. These parameters appeared not to be sufficient in our evaluation. AT and skeletal muscle are the main organs that determine body weight. Overnutrition (too much energy intake) increases the mass of AT, while exercise increases the mass of skeletal muscle. If we compare an obese body versus a muscular one with the same BMI, the function of the metabolic systems between these two tissues is just the opposite. While an obese individual is susceptible to chronic inflammation and MS due to adipocytes hypertrophy and dysfunction of AT, a muscular athlete has an active and functional mitochondria and metabolic system because of the high functional skeletal muscles. In an obesity state, malfunction of skeletal muscle also exists, and that is very crucial in pathogenesis of disease [80,81]. In obesity, exercise as therapy is one of the main ways for increasing the size and function of skeletal muscles and consequently the activity of the metabolic system that leads to the decrease of AT-mass. The comparison between lipoatrophic patients and normal athletes with exercise-based lipoatrophy showed that the manifestations of their metabolic system functionality are converse. While in the lipoatrophic state there is a nonfunctional AT that leads to lipid sedimentation and disturbances of skeletal muscle function, in athletes the AT levels are low because of hyper-functionality of their skeletal muscles. In conclusion, balance between AT-mass and skeletal muscles-mass is one of the main subjects in evaluation of the metabolic system functionality and energy return throughout the body [82].

Pattern of adiposity

The pattern of adiposity is one of the parameters that determine whether the high BMI is individual-based or it is because of the existence of a metabolic syndrome or a physiological-based obesity per se. This pattern is represented as two forms of apple or pear shapes. In the apple-shape adiposity, fats are stored mostly in the abdominal cavity and therefore it is also called visceral adiposity. This type of adiposity causes (seen more in men and in women during menopause (with low level of estrogen)), the increase of the susceptibility of the patients to metabolic problems such as CVD, hyperglycemia, inflammatory diseases and other age-related diseases. However, in pear-shape adiposity the extra fat is stored subcutaneously in the hips, thighs, and buttocks. SC-AT has an immunological and protective effect for the body and provides insulation from heat and cold [13,83]. In metabolic diseases, subcutaneous FFAs are transferred to VIS-AT and triggers metabolic disease. This event is represented as floppy skin shape in patients (old-looking-face) as it is seen in an ageing state followed by a deficiency in the immune system like HIV infection and cachexia (too little energy) in malignancies [84].

The levels of adipokines

Secretion of physiological amount of adipokines in the body is crucial for a proper function of the metabolic system, because these adipokines are directly correlated to size and mass of LDs [85-87]. Adiponectin, via a reduction of serine phosphorylation of insulin receptor substrate 1 (IRS-1), improves the insulin pathway function. During lipohypertrophy, an increase of adiponectin levels appeared to be a potential strategy to overcome inflammation and insulin pathway dysfunction [65,88]. Adiponectin and increased AMP/ATP ratio stimulate AMPK pathway and FAO, which in turn resulted in a decrease of the negative effect on insulin pathway, can enhance insulin sensitivity. In both lipolysis and lipophagy, hypoadiponectinemia increases the prevalence of metabolic disorders, coronary heart disease (CHD), and hypertension as well as CRP and pro-inflammatory cytokines levels [25]. In lipodystrophy, adiponectin replacement therapy (with/without leptin) is able to improve metabolic issues. Moreover, in lipophagy, the levels of adiponectin are decreased to a non functional level that influences the leptin pathway. Therefore, in investigation of metabolic disorders, the leptin/adiponectin ratio is a strong parameter in determination of lipid pathways functionality [89]. In addition, resistin is another adipokine that has a close association with insulin function. The levels of resistin could be one of the main parameters that cannot be ignored in the evaluation of metabolic system functionality.

Pro-inflammatory cytokines

Another feature of AT dysfunction could be due to the secretion of TNF-α, a list of cytokines/chemokines, and stressor components
such as JNK by ATMs and AT-adipocytes. These pro-inflammatory cytokines are secreted in lipodystrophic disorders and can be used for discrimination between a metabolic disorder and a normal metabolic reaction.

**Metabolic hormones**

Insulin and glucagon are the most important hormones involved in insulin pathways. Their secretions are opposite to each other and they regulate secretion of each other. Insulin produced by pancreatic β cells and glucagon synthesized by α cells. Their levels or ratio could be one of the determinant parameters in the evaluation of metabolic system functionality. Another important hormone that acts as a synergic hormone with glucagon is growth hormone. In a normal state, the levels of glucagon and growth hormone increase in fasting and in periods between meals and, in turn, the insulin levels decrease. However, fasting hyperinsulinemia is one of the main characteristics of the metabolic syndrome [90].

**Ratio of nicotinamide adenine dinucleotide (NAD+/NADH)**

Nicotinamide adenine dinucleotide (NAD+) is a coenzyme (electron acceptor), which is involved in redox reactions. It is the key regulator of stress resistance, metabolism and longevity [91]. nicotinamide adenine dinucleotide (NAD+) occurs in two forms: 1- NAD+ and 2- nicotinamide adenine dinucleotide phosphate (NADP+). The former is involved in catabolic reactions (degradation), and the latter is involved in anabolic reactions (to make). Of note, NADH is an electron donor involved in oxidation (that is the reduced form of NAD+). Also, NADPH is the reduced form of NADP+. NADH as electron donor is considered as mobilized energy storage, which comes free when NADH converted (oxidized) into NAD+. The same is valid for NADPH. Thus, a regulated balance between redox and oxidation reaction (NAD+/NADH) is also crucial process and helps us to evaluate the normal function of metabolic system in the body [3,92]. Moreover, this indicates that the link between adipocytes-LDs and adipocytes-mitochondria is crucial and remained to be studies [93].

**Ratio of weight to volume of body**

Storage of lipids in the form of triglyceride in AT and in particular adipocytes-LDs is the most efficient way for storage of the huge amount of energy in the least volume and mass. When the same amount of skeletal mass is compared with AT-mass, AT- mass is lighter. This means that the volume of an obese body is higher than an athlete with the same weight. The ratio of weight to volume of body could be representative of this difference and an easy parameter for evaluation of functionality of the metabolic system.

**Conclusion**

The energy balance is under control of a tightly regulated process, which is mediated by a close interaction between different tissues and pathways. Energy homeostasis is one of the fundamental tasks of the body in which lipid metabolism and mainly function of the AT are crucial and vital. In normal states, physiological post-prandial insulin induced-lipogenesis facilitate storages of excess energy in SC-AT. However, in disease states like MS and chronic inflammation, visceral obesity or malfunction of AT is the initiator systemic insulin disturbance. The link between accumulation of FFAs within adipocytes and capacity of FAO by mitochondria play an important role in a homostatic energy metabolic system. In this review, a collective criterion of proper evaluation of metabolic system functionality is introduced. These criteria are composed of morphological parameters (e.g. weight, height, pattern of lipid distribution, surface or volume of body) and biochemical parameters including adiponectin / leptin ratio, adiponectin / resistin index, insulin / glucagon ratio, NAD+/NADH ratio and levels of pro-inflammatory cytokines, CRP, adrenal and thyroid. Abnormal levels of these parameters in high risk situations like age, obesity, chronic stress or diseases represent increased susceptibility of these patients to FAID.

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