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

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Abstract

The pathogenesis 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. Subsequently, the main parameters for evaluation of energy metabolic system functionality components are 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 AT. AT is one of the largest and highly specialized connective tissues, and that is 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 (AT)

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 are 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 (TGs) in LDs is accessible for rapid hydrolysis and oxidation of fatty acids (FAs). However, WAT-adipocytes are unilocular and contain unique LDs (Fat-organelle), which are able to store TGs at a high energy density [4,5]. Energy storage in this form is efficient because of the following two reasons: 1- the considerable caloric value of lipids compared to carbohydrates and 2- the TGs, 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 TGs decreases the total weight of AT in an obese 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 four water molecules for storage. Therefore, the weight to energy ratio of AT is comparatively less than skeletal muscles [7,8]. Ultrastructurally, BAT-adipocytes have numerous big mitochondria with densely packed cristae containing thermogenic uncoupling protein 1 (UCP1), involved in fatty acid oxidation (FAO) and heat generation. This non-shivering thermogenesis is a cold climate adaptation in many homeotherms [9]. BAT is the only AT present during fetal development and while the child continues to grow until adolescence. In adolescence phase, 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

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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, which is normally highly flexible with a low density. During obesity and type 2 diabetes (T2D), the connective tissue becomes collagenous, calcified and rigid in a fibrotic state. The extracellular matrix of AT is an important place for modulation of systemic metabolism [14]. In this matrix, different cell types are seeded that function together to regulate energy reservoir (Figure 1). These cells are namely preadipocytes, adipocytes, adipose tissue macrophages (ATMs), fibroblasts, endothelial cells (ECs) and stem cells (Figure 2).

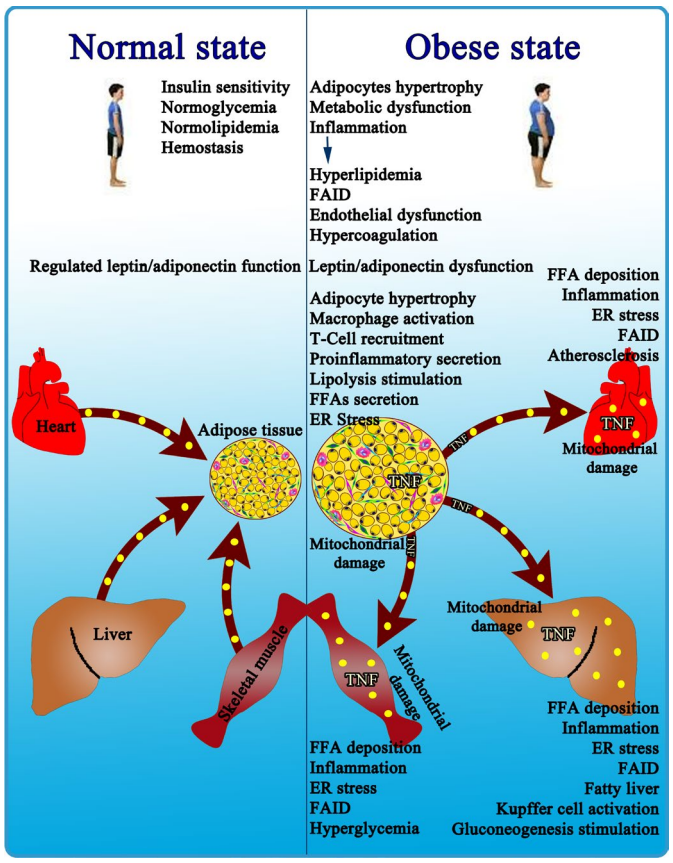

Figure 1: Adipose tissue function in normal and obesity states
Chronic systemic inflammation is the main feature of energy metabolic system disturbances in adipose tissue (AT). In an obese state, expansion of adipocytes and its malfunction lead to AT inflammation, lipolysis, proinflammatory cytokines/chemokines production, and consequently FFAs secretion to the circulation. This leads to the shifting of lipid from AT to peripheral tissues and sedimentation in these tissues. ER stress, mitochondrial dysfunction, systemic inflammation, and FAID are the general outcome of this process. In the normal state, a functional AT takes up lipids from the peripheral tissues to store these lipids in the form of triglycerides in lipid droplets (LDs) within adipocytes.
FFA: Free Fatty Acid; ER: Endoplasmic Reticulum; TNF-α: Tumor Necrosis Factor-α; FAID: Fatty Acid-induced Insulin pathway Disturbance.

Adipocytes are the major constituent cells of AT that have the 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 bilayer phospholipid

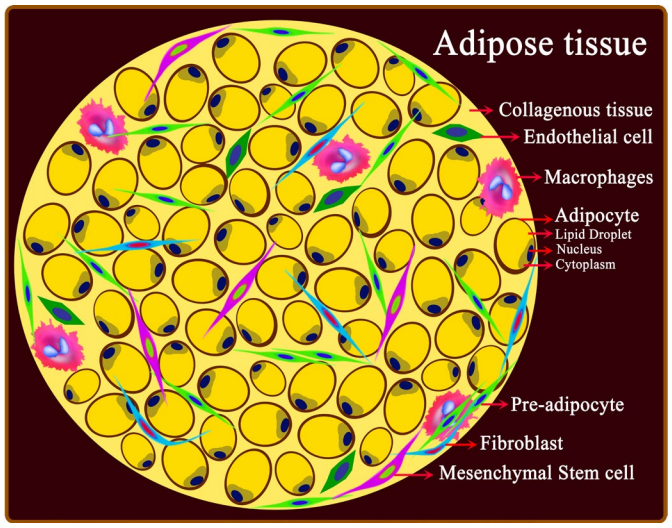

Figure 2: The Structure of adipose tissue
Adipose tissue (AT) is composed of a collagenous background together with different cell types, which are seeded in this connective tissue. Adipocytes are the major constituent cells of AT and the main site for the storage and release of cytokines and chemokines. Metabolic disorders appeared to stimulate adipocytes to prime inflammation and as consequence the resident or regulated macrophages converted to the activated macrophages and then exacerbated by these activated adipose tissue macrophages (ATMs). Preadipocytes are the next most abundant cells and the linker between adipocytes (metabolic cells) and macrophages (immune cells). Lipid droplets (fat organelle) cannot be detected by preadipocytes. Other cells of AT are fibroblasts, mesenchymal stem cells and endothelial cells and each AT-cell has an important role in different pathways including the metabolic, coagulation and inflammatory systems.

membrane from surroundings, containing some cytoplasmic compartments, including nucleus, mitochondria, and highly specialized organelles termed LDs. LDs composed of a highly hydrophobic core containing non-polar lipids covered by a highly hydrophilic monolayer membrane containing polar lipids (phospholipids). LDs occupy most of the mature adipocytes cytoplasm and are considered to store a huge amount energy in the form of TGs (Figure 3). LDs are also present in many (LDs are located in cells and not in tissues, therefore word tissues is not correct) such as skeletal muscle cells-, liver cells, and macrophages etc. [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 TGs 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 state, AT is the main site for fat storage and target of circulating lipids including free fatty acids (FFAs) and lipid contents of lipoproteins [16]. However, in anobese state, LDs of other cells also become enlarged and reserve excess energy but not comparable with energy storage capacity and 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].

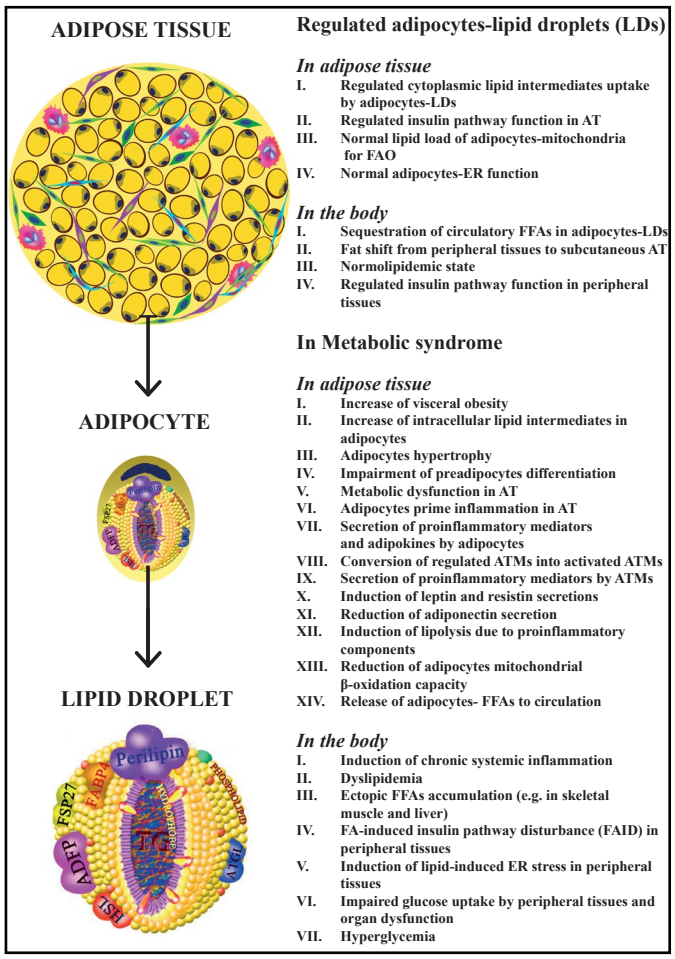

Figure 3: Comparison between local and systemic effects on the function of adipose tissue in normal state and in metabolic syndrome

Adipose tissue (AT) is composed of different cells. Adipocytes are the main constituent cells of AT and are highly specialized to store the excess of energy in the form of triglycerides in lipid droplets (LDs). The main components of adipocytes are plasma membrane, one nucleus, mitochondria and medium-sized or one single large lipid droplet in the mature state. Structure of lipid droplets is similar to plasma lipoproteins; composed of one highly hydrophobic core containing non-polar lipids such as triglycerides covered by a highly hydrophilic (polar) monolayer phospholipids membrane. The function of the lipid droplet-specific proteins (e.g. FSP27) can be divided into two groups; 1- a cluster of the proteins associated with LDs protect the triglycerides from hydrolyzation such as perilipin and 2- the other group of proteins related to LDs try to break down triglycerides such as HSL via hydrolyzation. In normal state, a functional AT accepts FFAs from peripheral tissues to store these lipids as triglycerides in adipocytes-LDs and decrease load of lipids in the circulation and peripheral tissues. While in metabolic syndrome, malfunction of AT, due to the adipocyte hypertrophy, stimulates adipocytes to prime inflammation and as consequence the lipolysis of intracellular triglycerides increase. Release of FFAs to the circulation and peripheral tissues leads to dyslipidemia and FAID in peripheral tissues.

LDs: Lipid Ddroplets; TG: Triglyceride; FSP27: Fat Specific Protein 27; ADFP: Adipose Differentiation-Related Protein; HSL: Hormone-Sensitive Lipase; ATGL: Adipose Triglyceride Lipase; ER: Endoplasmic Reticulum; FAID: Fatty Acid-Induced Insulin Disturbance.

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 (CNS), and metabolic tissues that ensure the maintenance of the energy homeostasis in the body. During obesity, 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 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. Thereafter, local AT inflammation leads to systemic inflammation, which is the etiology of cardiovascular disease (CVD) and atherosclerosis in metabolic syndrome [25]. Moreover, AT also secretes estrogen that has an great impact on the hedgehog signaling pathway for differentiation of adipocytes to fibroblasts or osteoblasts [26].

Adipokines, Adipocytokines, Inflammation, Obesity-Associated Metabolic Disorder

Obesity stimulates an inflammatory state, which is implicated in obesity-associated pathophysiological complications such as T2D, dyslipidemia, cardiovascular mortality and morbidity as well as insulin unresponsiveness [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 that 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 result in pathological states that are 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- α (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 results in ageing-associated diseases such as metabolic disorders and T2D [20].

Besides adipocytes, AT contains several other cell types including ECs, macrophages and fibroblast [39,42], and cross talk between these cells affects the expression of adipocytes-associated proteins. 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 ATMs [2]. Human AT-adipocytes synthesize many cytokines/chemokines that are biologically functional with a physiological role. This suggests that metabolic dysfunction in adipocytes is the primary event in the sequence leading to inflammation in AT [2].

Although obesity is the major risk factor 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 insensitive 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 insulin pathway insensitivity with high insulin production and T2D occurs only when β cells machinery insulin synthesis become exhausted. 3- Pancreatic-associated β cells: insulin pathway unresponsiveness is due to a dysregulation in insulin secretory condition. 4; Obesity: AT-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 adipokines secretions (such as leptin, adiponectin, and resistin), secreted immune-associated components (such as pro-inflammatory cytokines/chemokines), and energy storage depot of TGs in LDs of AT-adipocytes.

LD-sequestration of excessive energy in adipocytes is one of the major functions of the adipocytes in normal state (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 multilocular 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 than other cells, indicating that LDs fusion play an important role in thestorage processes. In obese state, dysfunction of LDs results in 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 is due to this point that FAID happens following overload of intracytoplasmic lipids and it is reversible by caloric restriction. Therefore, we assume that in the pathogenesis of metabolic disorders, proper function of AT and in particular adipocytes-LDs is considered to be the initiator (this confirm the title what I have suggested) of the proper function of insulin pathway. Moreover, in the evaluation of the severity of insulin pathway disturbances, the seeding of FFAs 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 SC-AT to be used during starvation. This starvation period is either the period between meals or during hibernation period in animals. Therefore, natural life of mammalians depends on this important property of the body. The pathogical complicationsobesity, that happens during prolonged obesity, are accompanied with chronic inflammation in AT. This occurs when overload of energy is not consumed by the body and that could be due to less exercise or physical activity or due to a gene defect. There is a close association between function of the skeletal muscle (as the main consumer of energy in the body) and function of the AT (as the main energy storage organ in the body). In highly functional skeletal muscles (such as 'athletes' muscles) a mild overload of their cytoplasmic lipid intermediates is oxidized [48]. In this state, muscles use the circulatory and AT-lipids as the source of energy. This process decreases the overload of lipids in the adipocytes and a reduction of inflammation as consequence.

Inflammation in AT occurs in genetically susceptible persons (e.g. those who have low-active mitochondria). In such state, intracellular lipid intermediates are overloaded in endoplasmic reticulum (ER) that induce ER stress, which in turn stimulates inflammatory pathways such as Nuclear Factor-KappaB (NFκB) and c-Jun N-terminal kinases (JNKs). Moreover, adipocytes-LDs show a close link with ER [25,49] and FAO 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. Adipocytes secrete proinflammatory mediators (IL-6, IL-8, IL-7, TNFα, TNF-β, and NFkβ) 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 ATMs 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 ATMs (also called regulated ATMs) 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 and consequently these effects 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 metabolic syndrome with the increase of visceral obesity, dyslipidemia, hyperglycemia and hypertension (Figure 4). Thus, catabolic chronic inflammation enhancement and the anabolic insulin pathway disturbances are compensatory mechanisms for consumption of excess energy in the body [55,56].

Based on above mentioned pathophysiological state, two treatment protocols are designed: 1- thiazolidone medication and 2-transplantation of normal AT. In both protocols, mechanisms of action are improvement of lipid distribution in the body and fat shift

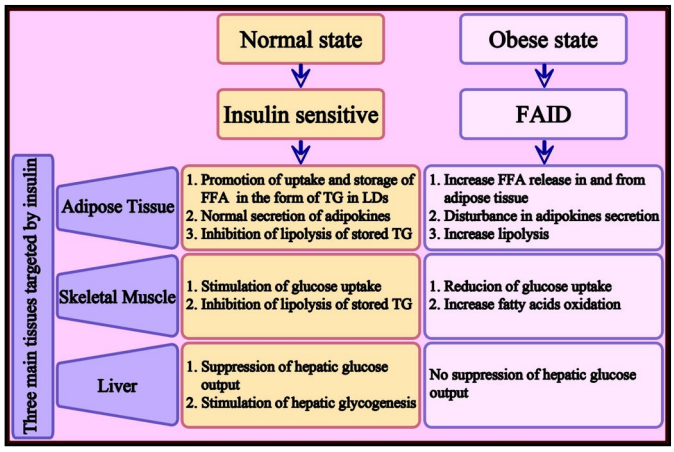

Figure 4: Three main tissues (adipose tissue, skeletal muscle and liver) targeted by insulin in both normal and obesity states
In normal state, a functional adipose tissue (AT) induces the uptake of circulatory and peripheral FFAs to store these lipids in the form of triglycerides in adipocytes lipid 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.
FFA: Free Fatty Acid; LDs: Lipid Droplets; TG: Triglyceride; IR: Insulin Resistance.

from peripheral tissues to SC-AT [10,57]. This shifting event decreases lipid accumulation in peripheral tissues, which it improves significantly the function of mitochondria with respect to FAO, reduc of ER-fat load and consequently decrease ER stress. In pathological states, ER stress and high levels of intracellular inflammation induce systemic insulin unresponsiveness. 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, suppresses inflammation and, in turn, improves storage of lipids and AT functionality as shown by PPARγ agonist (Thiazolidone) studies. Indeed, induction of PPARγ stimulates adipocyte differentiation, perilipin and FSP27 expression. 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 pathogenesis of metabolic syndrome [58]. It is shown that a dysfunctional AT in fat storage increases lipolysis, and circulatory FFAs, leading to dyslipidemia. The dysfunction of AT occurs following adipocyte inflammation (e.g., in metabolic syndrome), adipocyte atrophy (e.g., in lipodystrophy) and FSP27 knockout animals. In metabolic syndrome, AT dysfunction is appeared to be due to an imbalance between energy intake and energy expenditure. In lipodystrophy, lack of the functional AT is the trigger of metabolic disorder. In several studies, it has been shown that FSP27 protein promotes energy reservoir in the form of TGs within LDs and knock out of FSP27 gene in mice led to the increase of intracytoplasmic lipids. In all these states, the final outcome is enhancement of insulin unresponsiveness and hyperglycemia [5,10,17], Therefore, lipid intermediates are transferred and accumulated in other metabolic tissues (e.g. skeletal muscle and liver) that are not specialized organ for lipid storage. In this process, the function of both insulin and leptin pathways are disturbed and as consequence the development of T2D.

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 pathological 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 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. Of note, the sedimentation of FFAs in non ATs form hepatic and myocellular steatosis [60]. Furthermore, in these catabolic tissues, overload of intracellular energy levels increase production of lipid intermediates such as ceramide and diacylglycerol (DAG) [50], resulting in inflammation, ER stress and FAID [24]. In the initial stages, disturbance of insulin pathway compensatory stimulates pancreatic β cells to induce hyperinsulinemia. There are also disturbances in insulin-induced gene expression 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), 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 adipocytes 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 pathological events in body. Among adipokines, leptin and adiponectin as mass-related adipokines play an important role in metabolic disorders. During enlargement of AT, the level of leptin increase while adiponectin level decreases. In metabolic syndrome and lipodystrophy, the leptin levels and cellular leptin sensitivity is converse. In lipoatrophy, leptin level low and cells are sensitive to it; therefore, leptin replacement therapy [62] is a main treatment of choice. However, in lipohypertrophy, leptin level high but the function of leptin pathway is disturbed. This might be due to the influence of inflammation [63] or the effect of TGs [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 lipoatrophic 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 level high during normal state and caloric restriction. Adiponectin improves the sensitivity of insulin pathway in the body. The level of adiponectin during metabolic syndrome is downregulated; therefore, the incidence of inflammation and insulin unresponsiveness increases. Furthermore, adiponectin is able to decrease the distractive influence of FAID on the insulin pathway via activation of adenosine monophosphate kinase (AMPK) and FAO. Adiponectin also shows an inhibitory effect on the adhesion of macrophages to ECs and in this way appeared to have a protective effect on atherosclerosis [46].

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 adiponectine, on the metabolic system [69]. The adiponectin-resistin (AR) ratio 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. Importantly, the expression of resistin by ATMs recruits other immune cells to the AT and stimulates proinflammatory cytokine secretion. Moreover, resistin stimulates atherosclerosis via formation of foam cells, proliferation of ECs 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 circulatory inflammatory biomarker that can be used for detection and prevention of CVD and metabolic disorders [74]. Importantly, CRP is also synthesized by adipocytes [2,48].

Proinflammatory chemokines such as MCP-1, RANTES and Il-8 as well as cytokines such as IL-4, IL-6, IL-10, and MIP-2 (human IL-8 homolog) 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 are regulatory T cells (Treg) 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 therapeautic effect of Treg 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 obesity state, malfunction of skeletal muscle also exists, and that is very crucial in pathogenesis of disease [80,81]. Therefore, exercise 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 retour throughout the body [82].

Pattern of adiposity

The pattern of adiposity is one of the parameters that determine whether the high BMI in individualis is because of the existence of a metabolic syndrome or it is a physiological obesity. 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 appeared to be seen more in men and in women during menopause and that is corresponded with low level of estrogen. Visceral obesity increases 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 as well as observed in immune system deficiency states 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. In this regard, leptin and adiponectine are important because these adipokines are directly correlated to the size and mass of LDs [85-87]. There is also a significant negative relationship between CRP levels (WHERE?) (positive acute phase protein) and adiponectin (anti-inflammatory) mRNA levels in AT [87]. Adiponectin, via a reduction of serine phosphorylation of insulin receptor substrate 1 (IRS-1), improves the insulin pathway function. Caloric restriction during lipohypertrophy via increase of adiponectin levels appeared to be a potential strategy to overcomes inflammation and insulin pathway dysfunction [65,88]. Adiponectin and increased AMP/ATP ratio stimulate AMPK pathway and FAO, which can enhance insulin sensitivity and that appeared to be due to the decrease of negative effect of FAs on insulin pathway. In

both lipoatrophy and lipohypertrophy, 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 problems. Moreover, in lipohypertrophy, the adiponectin levels decreased to a non functional level that influences the leptin pathway. Therefore, in investigation of metabolic disorders, leptin/adiponectin ratio is a strong parameter in determination of lipid pathways functionality [89]. Resistin is also an 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 lipodystophic 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 is 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 synergetic 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 features of the metabolic syndrome [90].

Ratio of oxidized to reduced nicotinamide adenine dinucleotide (NAD^+/NADH)

Oxidized 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]. NAD^+ occurs in two forms; 1-NAD^+ and 2- oxidized nicotinamide adenine dinucleotide phosphate ($NADP^+$). The former is involved in catabolic reactions (degradation), and the latter is involved in anabolic reactions (synthesis). 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 their oxidized and reduced form (NAD^+/NADH ratio) is also crucial parameter in evaluation of 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 larger 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 state, physiological post-prandial insulin induced-lipogenesis facilitates 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 pathway disturbance. The link between accumulation of FFAs within adipocytes and capacity of FAO by mitochondria play an important role in a homestatic 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 ratio, insulin / glucagon ratio, NAD^+ / NADH ratio and levels of CRP and pro-inflammatory cytokines. Abnormal levels of these parameters in high risk situations like ageing, obesity, chronic stress or diseases represent increased susceptibility of these patients to FAID.

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