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Some diseases associated with adipose tissue: A Review

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ABSTRACT

The chemicals released by adipose tissues are essential for maintaining metabolic homeostasis. The lack of these molecules, resulting from either excessive adiposity or malfunctioning adipocytes, can induce obesity or diseases linked to obesity. Therefore, adipose tissues are regarded as an endocrine organ, and the way they affect target organs varies depending on where fat depots are located and how it functions. Understanding the secretome of adipose tissues in its entirety may offer critical new perspectives on the roles played by the body's most crucial metabolic regulator. Leptin is one of the most powerful adipokines for controlling metabolism. It communicates feelings of hunger or fullness to the hypothalamus and regulates body weight by releasing neurotransmitters that modify energy expenditure and food intake. Leptin also enhances muscle fatty acid oxidation and suppresses the pathway that leads to fatty acid synthesis, which controls hepatic lipogenesis. Adiponectin, the most prevalent adipokine that is secreted, improves insulin sensitivity and partially reverses insulin resistance. To treat the inflammation and insulin resistance caused by obesity, researchers are currently looking into ways to raise adiponectin levels or adiponectin receptor activity. In women, fat coming from the female sex hormone is stored in the hips, buttocks, and thighs. Because of the difference in sex hormones, men are predisposed to storing belly fat. The percentage of estrogen triggered via the ovaries decreases when a woman reaches menopause, so the fat that was accumulated in the buttocks, hips, and thighs migrates to the middle and is then reserved in the abdomen. Adipose tissues make up 20%–25% of the body mass on average in a healthy individuals and can account for up to 10%–40% in some people depending on different factors. The proportion of this fat in the body may exceed its normal limit, causing many different diseases, including obesity, lipodermatosclerosis, lipoma, lipoatrophy, and Dercum's disease.

Introduction:

White adipose tissue (WAT) and brown adipose tissue (BAT) comprise the adipose system. WAT is the tissue used for storing lipids (fats), while BAT acts to control the temperature of the body by producing heat by releasing stored energy. Fats are organized in the cytoplasm of brown (multilocular) [1] and white (unilocular) adipocytes in multiple droplets, distinguishing the morphology between these two. The large mitochondria in the cytoplasm of brown adipocytes is another characteristic that distinguishes the morphology of these two cell types. Another feature of brown adipocytes is the expression of uncoupling protein 1, which disconnects oxidative phosphorylation from ATP synthesis and consequently produce heat [2].

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Despite the differences in their shapes and functions, white and brown fat cells coexist in different locations to form the multidepot adipose organ [3]. These depots are either in the subcutaneous region (subcutaneous depots) or next to organs in the trunk (visceral depots) [3].

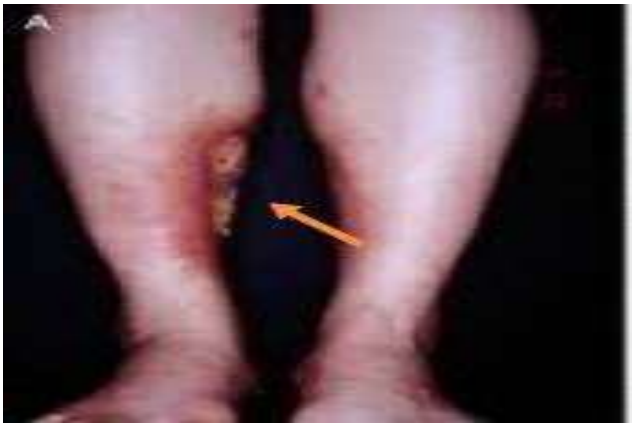
WAT creation starts in the early stages of life. Mesenchymal stem cells develop into adipoblasts, which subsequently give rise to preadipocytes. Preadipocysteines proliferate during the initial phase of adipogenesis and go directly into mitosis until they hit growth arrest. When preadipocytes break out of the cell cycle at this stage, they undergo morphological changes and accumulate triglycerides in the cytoplasm, becoming mature adipocytes and losing the capacity to divide [4]. Although they come from distinct progenitor cells, the mesoderm is the source of brown and white adipocytes. Mesenchymal stem cells can differentiate into two distinct lineages: Myf5-positive brown adipocytes and

Myf5-negative white adipocytes that are both adipogenic and osteoblastogenic [5]. Although adipose cells originate from two distinct lineages, adipocyte development is mediated by a similar transcriptional mechanism involving CCAAT/enhancerbinding proteins (C/EBPs) [6].

Adipose tissues have regained research attention, and multiple conditions associated with their growth have been reported [7]. Rare afflictions, which are intricate, prolonged, and sometimes obscure, can cause severe health implications and diminished the quality of life. Such ailments are not fully comprehended by doctors in general and specialists alike due to their infrequent occurrence and frequent variation in physical expression. A lack of awareness about these disorders usually results in much-delayed diagnosis and, at times, misdiagnosis, ultimately causing harm to the patients [8].

Lipodermatosclerosis (LDS):

LDS is frequently discovered in people with impaired leg circulation. It also appears in women over the age of 40 years and in males over the age of 70 years. Age, inactivity, obesity, smoking, family history, and previous deep vein thrombosis or damage to the venous system are risk factors of this condition. Although its specific etiology is uncertain, research points to increased capillary permeability caused by venous hypertension as the likely culprit for the infiltration of fibrinogen and white blood cells into the dermis. The formed fibrinogen wraps fibrin around capillaries, impeding oxygen exchange. This pathway ultimately culminates in hypoxia, which causes venous ulceration (picture 1) [9,10].



Picture (1) Venous ulceration that causes lipodermatosclerosis [9].

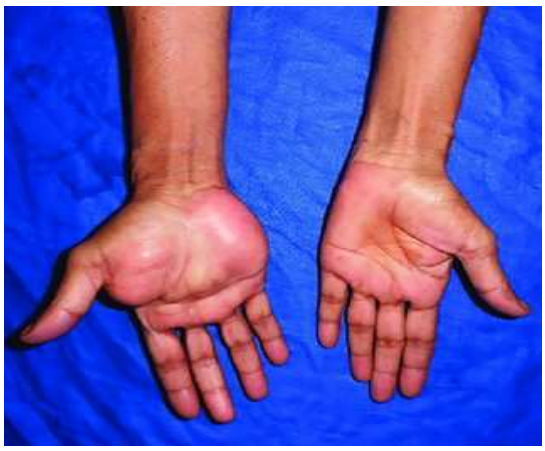
Inflammation of the subcutaneous fat, known as LDS, sclerosing panniculitis, and hypodermitis sclerodermiformis, is frequently linked to chronic venous insufficiency [11]. Traditional locations for LDS include the inner surface of the lower limbs just above the ankle. The phases are divided into acute and chronic. Clinical signs of the acute phase include pain, redness, warmth, and tenderness. The lower limb skin above the malleolus becomes indurated, retracts, and becomes rigid when LDS is chronic and manifests clinically [10]. This condition is known as the chronic, fibrotic phase. Hyperpigmented, the patient often experiences mild discomfort on their own, which becomes acute when the leg is squeezed. The leg eventually takes on the recognizable “inverted wine bottle” form after several years of growth [11]..

LDS makes up a varied spectrum of the inflammatory and fibrotic stages. Biopsies with direct immunofluorescence can assist in identifying dermal pericapillary fibrin deposits without other immunoreactants in early- and late-stage lesions [10]. Therapy for this condition entails graded stockings or elastic bandages to be worn for compression. Rapid improvement has been observed with stanozolol, an anabolic steroid that has consistently produced good results, especially for the onset of LDS [11]. Anabolic steroids can enhance fibrinolysis, decrease pain, lessen the size of the affected area, and decrease the toughness of the skin. However, their use is curtailed by negative consequences, including lipid profile disorders, sodium retention, virilization in women, and hepatotoxicity [12]. Oxandrolone is a therapeutic option with low androgenic effects and hepatotoxicity and is rarely studied [13]. LDS is characterized by an acute, inflammatory phase and a chronic, fibrotic stage characterize lipodermatosclerosis, with a range in between. In studying LDS lesions, one helpful finding is the presence of pericapillary fibrin build-up in the dermis without other immunoreactants. Gradated stockings or elastic bandages can help with compression treatment, which is required to treat this illness. Recent studies reported that anabolic steroid stanozolol consistently and dramatically improves patients’ conditions. A 61-year-old lady previously received treatment for venous insufficiency and was effectively treated with stanozolol and oxandrolone [14]. A double-blind, randomized

inquiry found that the utilization of 4 mg/day of stanozolol causes a momentary, asymptomatic increase in transaminases while significantly depleting high-density lipoprotein levels in patients suffering from LDS and leg ulcers [15].

Lipoma:

Less than 0.1% of intracranial tumors are intracranial lipomas [16], a rare congenital distortion caused by the abnormal persistence growth of a focus of primitive meninges induced to differentiate into adipocytes and manifests at the level of the pia, arachnoid, and dura mater [17]. The majority of these wounds show up close to the midline and frequently in the cerebral cisterns. Other sites of involvement are the suprasellar cistern, superior cerebellar peduncle, cerebellar cistern, sylvian cistern, and cerebellar angle cistern [18]. The majority of lipomas of the corpus callosum are asymptomatic, but headaches are the most frequent symptom depending on the size and extent of the lesion [19]. Adipose tissues collect in a lump called a lipoma, which develops immediately below the skin. When you touch lipomas, they move readily and have a rubbery, not hard, sensation. Lipomas seldom require treatment because they are often not painful and do not pose any health risks [20]. While tumors are common in this anatomical location, hand-specific lipomas only develop between 1% and 3.8% of the time [21]. Lipomas in fingers develop only 1% of the time [22]. Lipoma can occur at any age, although it is less frequent in youngsters than in those in their 50s and 70s [20]. Obesity appears to increase the likelihood of developing lipomas, regardless of gender [23]. Lipomas of the wrist and palm, which are composed of mature adipose tissues, can occasionally exceed 5 cm in size and are derived from mesenchymal cells (preadipocytes) [4]. A lipoma is referred to as “giant” if it weighs more than 1000 g and/or measures more than 10 cm (picture 2) [23]. Although the possibility of lipomas being cancerous remains unknown, large ones likely include cancerous cells. Inadequate surgical removal only causes recurrence in roughly 5% of patients [25].



Picture (2): Giant palmar lipoma [23].

Lipoatrophy:

When no signs of anabolism or starvation are present, a number of unusual lipodystrophy syndromes might develop [26]. Metabolic syndrome is commonly associated with the abnormal accumulation of fat that cannot be properly stored in subcutaneous depots [27]. Overeating (hyperphagia) is typically caused by decreased leptin levels, which regulate the balance of hunger and fullness signals. Excess calories lead to insulin resistance (IR), hypertriglyceridemia, hepatic steatosis, and fat deposition in muscle and liver tissues [28]. Metabolic state and body composition reveal the presence of lipodystrophy based on physical examination and clinical history [29].

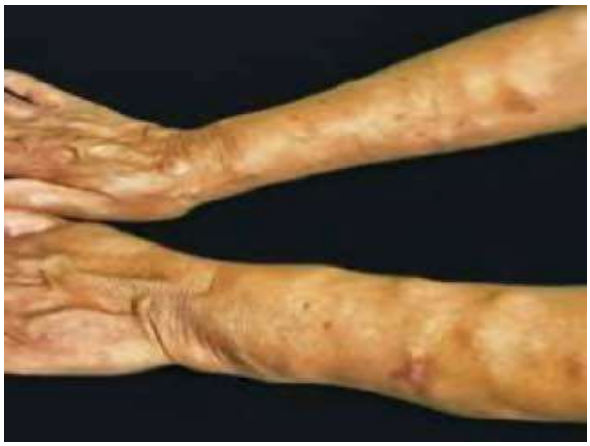
Partial or widespread lipodystrophy in children can be caused by a number of illnesses, including Nakajo–Nishimura syndrome, JMP syndrome, CANDLE syndrome, and others [30]. These illnesses are categorized as autoinflammatory syndromes because they frequently result from the buildup of oxidizing substances in cells with mutant proteasomes–immunoproteasomes [31]. Diet and exercise are also essential for controlling the comorbidities associated with lipodystrophy. Patients are advised to have a balanced diet that contains 50%–60% carbohydrates, 20% protein, and 20%–30% fat. Leptin deficiency, or hypoleptinemia, can increase hunger and calorie intake. Therefore, patients should also get medical care for certain metabolic comorbidities [32]. Leptin replacement therapy with metreleptin (Myalept®, Aegerion) is the sole medication approved for the treatment of lipodystrophy. Metreleptin has not yet been licensed for

the treatment of individuals with lipodystrophy in Europe, despite the fact that many other medications are used to treat a variety of concomitant illnesses [32].

Dercum's disease (adiposis dolorosa):

Adiposis dolorosa or Dercum's disease is an uncommon condition that presents with subcutaneous adipose tissue deposits that are painful and can vary in size, location, and number. While its symptoms may vary, it is commonly related to overweight or obesity, exhaustion, and mental issues, such as depression, emotional instability, anxiety, and insomnia. However, the appearance of these accompanied symptoms is not always predictable in this disease.

Dercum's disease is infrequent; it is commonly associated with overweight and obesity and may present multiple tender lipomas, especially on the upper extremities and trunk. The pain, by definition, is chronic, and it has to last more than 3 months. The classification and treatment of Dercum's disease are still debatable owing to its opaque etiology and the deficiency of diagnostic criteria (picture 3) [33]. The condition itself was initially documented in Philadelphia by Francis Xavier Dercum, an American neurologist who lived from 1856 to 1931 [34].



Picture (3): Skin nodules in Dercum's disease [33].

Appearing mostly in adults, Dercum's disease is a rare condition that affects individuals aged 35–50 years [35]. Some cases on children have been reported, albeit limited [36]. The disease predominantly affects women, with an estimated women to men ratio of 30:1 [35]. Although it affects postmenopausal women, four-fifths of female patients develop the disease before menopause. Studies on its prevalence and incidence are nonexistent, and almost all case descriptions are sporadic. Only a few reports have mentioned the familial occurrence of Dercum's disease, but differential diagnosis is a challenge [37]. Liposuction is a commonly reported management method that has reduced pain levels through subjective and objective measurements in some patients [38]. The long-term pain relief effect diminishes but remains lower than that in inoperable subjects and baseline values, even after 5 years [39]. Other methods include a recently suggested subcutaneous adipose tissue therapy and pharmacological management through various medications, including lidocaine, nonsteroidal anti-inflammatory drugs, and frequency rhythmic electrical stimulation. Single reports showed the effectiveness of several medications such as pregabalin, corticosteroids, and infliximab with methotrexate [40]. A new breakthrough has been recently reported in the approved use of deoxycholic acid for the reduction of submental fat [41].

Deoxycholic acid injections have been utilized with great success for managing lipomas in patients diagnosed with Dercum's disease [42]. However, further investigation is necessary to assess the efficacy of this technique [31].

Obesity

Obesity is a tissue disturbance stemming from numerous factors and is an international health issue on the rise, causing detrimental health effects on individuals and forming a major public health concern. Miscellaneous diseases are connected to this condition, necessitating a complex therapy approach that emphasizes the importance of multidisciplinary assessment by healthcare professionals [43]. Expressed as an abnormal or heightened accumulation of fat, obesity poses dangers to body health. Its emanates originate from the interplay of insufficient food intake and/or overeating, inactivity and sedentary habits, and genetic, psychological, and environmental factors [44]. Immoderate adiposity makes the process of reverting the disease more complicated, since either the capability for the engagement in physical activity is diminished or metabolic and satiety signals are dysregulated. Persistent

expansion of adipose tissues caused by a surplus of macronutrients and calories leads to an increase in circulating free fatty acids (FFAs), initiating dysregulation in the body. This dysregulation exemplifies structural and systemic changes at local and systemic levels [45]. The abundance of adipose tissue leads to a chronic inflammatory condition known as lipoinflammation, which causes adipocyte hypoxia [46]. Hypoxia and inflammation in adipose tissues are associated with a heightened likelihood of developing IR, cardiovascular diseases, and type 2 diabetes mellitus (T2DM) [46].

In instances of positive energy balance, excess energy is preserved in adipose tissues, leading to the hyperplasia of subcutaneous adipose tissues (SCATs) until it reaches a physiologically allowable limit when energy reservation is achieved. Excess energy is stored in VAT when surplus happens, yet this depot lacks the expansive capacity of SCATs, causing adipocyte hypertrophy and subsequent visceral, central, or android adiposity [47]. Adipocytes and adipose tissue macrophages create proinflammatory molecules, and weight gain due to adipose tissue expansion additionally perpetuates chronic inflammation by elevating circulating cytokine thresholds. Attentive efforts are necessary to invert the infrared process, highlighting the need for a healthy diet alongside regular exercise. These acts aid in eliminating the pro-inflammatory state, coinciding with the downregulation of interleukin-6 (IL-6) expression and tumor necrosis factor-α (TNF-α) in adipocytes. Exercise also improves mitochondrial FFA metabolism, stemming their storage [48]. Dietary selections and their effect on gut microbiota are associated with inflammation. Extreme consumption of saturated fat can cause the enlarged production of bacterial lipopolysaccharides, contributing to systemic inflammation [45]. The initial steps that set off the inflammatory response have been clarified. In practical studies employing murine models of obesity caused by HFD, HIF-1α levels are discovered before the onset of substantial adiposity. Under these conditions, adipocyte hypoxia and HIF-1α serve as early triggers of IR and inflammation [46].

Inflammatory pathway of obesity

Adipose tissues' intricate and various functions carry implications throughout the body, with cytokines participating in its physiological reply. In obesity, the principal cytokines released by adipose tissues encompass IL-6 [49], monocyte chemoattractant protein-1 (MCP-1), chemerin, TNFα, resistin, and leptin. Adipose cells exhibit hyperplasia and hypertrophy, thereby triggering the inflammatory process in this situation. Adipose tissue dysregulation fosters wrong restructuring and ensuing inflammation, with the recruitment of macrophages and the secretion of chemotactic cytokines such as chemerin, TNFα, and MCP-1. The phenotype involved, the M1 pro-inflammatory, and evidence show that this condition is not solely local but also systemic, stimulating further inflammation and elucidating how obesity can result from other disturbances [50].

IR

Glucose is released from the liver into the blood within fasting to provide euglycemia and fuel for glucose-consuming tissues. The decomposition of hepatic glycogen (glycogenolysis) and the de novo synthesis of glucose (gluconeogenesis) employing fatty acids and glycerol from adipose tissues constitute this pathway known as hepatic glucose production (HGP) [51]. Following meal intake, insulin excretion by pancreatic β-cells boosts anabolism and represses catabolic programs. Glucose uptake in skeletal muscles and adipose tissues is evoked by insulin, which then stimulates glycogen and lipid synthesis in the liver, skeletal muscles, and adipose tissues [52]. Insulin represses the expression of gluconeogenic genes and lipolysis in adipose tissues, thereby hindering HPG. In WATs, insulin's major physiological function is the constraint of lipolysis, which subsequently represses HGP by lowering gluconeogenic substrates (Figure 1) [53].

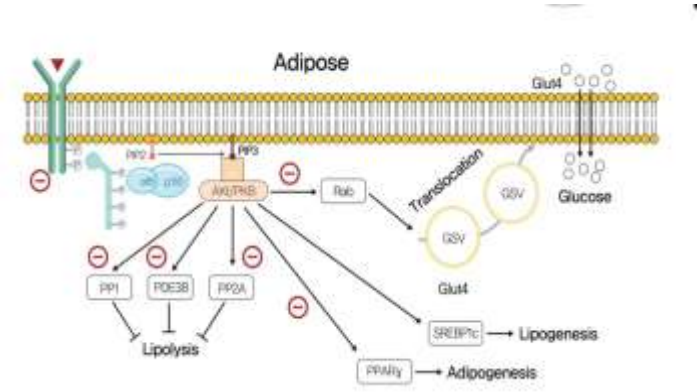


Figure 1: Role of insulin in suppressing white adipocyte lipolysis [53].

Insulin's inhibition of lipolysis in white adipocytes reduces gluconeogenic substrates and accordingly inhibits hepatic glucose production, possibly mediated by protein phosphatase-2A, phosphodiesterase 3B, and PP1. Likewise, insulin promotes adipogenesis, glucose transport, and lipogenesis. FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; GPAT1, glycerol-3-phosphate acyltransferase 1; GCK, glucokinase; PCK1, phosphoenolpyruvate carboxykinase 1 (PEPCK); G6PC, glucose-6-phosphatase; mTORC1, mechanistic target of rapamycin complex 1; PKB, protein kinase B; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PIP2, phosphatidylinositol-4,5-bisphosphate [53]. Disorders of these tissues lead to inability to respond to normal insulin levels, causing IR [54].

IR in muscles could affect metabolism in the whole body [54]. Augmented susceptibility to hepatic steatosis and raised adiposity in animal models produced from muscle-specific IR are caused by the muscle-specific deletion of insulin receptor tyrosine kinase (IRTK) or glucose transporter type 4 (GLUT4) [55]. Impaired GLUT4 translocation is attributed to IR, affecting insulin-stimulated muscle glucose as evidenced by numerous molecular studies. Hypoxia or exercise, via AMP-activated protein kinase (AMPK)-mediated regulation of GLUT4 storage vesicle translocation [56], promotes the translocation of GLUT4 to the plasma membrane and glucose conveyance in T2DM. Abnormalities in IR glucose transport are consequences of defects in the insulin signaling pathway rather than defects in the transport system per se. Moreover, imperfections at the proximal level of insulin signaling, comprising the activities of AKT, PI3K, IRS1, and IRTK, may produce insulin resistance in skeletal muscles (Figure 2) [53].

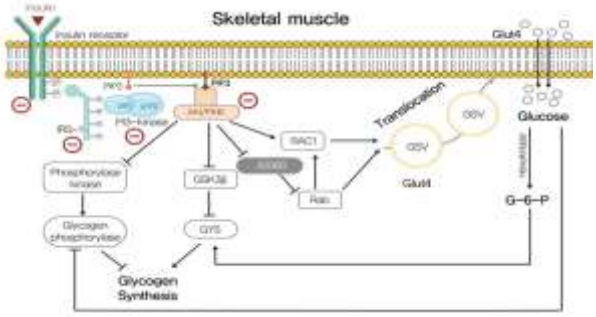


Figure 2: Role of insulin in skeletal muscles [53].

For hepatic IR, insulin cannot regulate hepatic glycogen synthesis or due to lipolysis dysfunction in adipose tissues and desuppression of forkhead box O1 transcription factor in the liver [57].

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Leptin resistance

The hormone leptin, released by adipocytes, controls appetite and is an important factor in obesity, a substantial medical, economic, and social problem in the modern community [58]. Recognized over 20 years ago, leptin and its receptors have been pivotal in understanding and controlling body weight and energy homeostasis (Figure 3) [58]. Although minimal increases in leptin concentration reduce appetite and lead to lessened body weight, the efficacy of leptin's anorexic effect declines in obesity due to the development of leptin resistance [59], which is owing to defects in intracellular signaling linked with the leptin receptor or reductions in leptin transport across the blood–brain barrier (BBB) [59]. Serum leptin exceeding the limit of 25–30 ng/mL does not lead to an increase in leptin concentration in brain tissues and cerebrospinal fluid. Excessive leptin levels in the blood lead to declined BBB permeability, potentially participating in the development of leptin resistance and obesity. Under these circumstances, low leptin concentrations were observed in the spinal fluid of obese individuals [60].

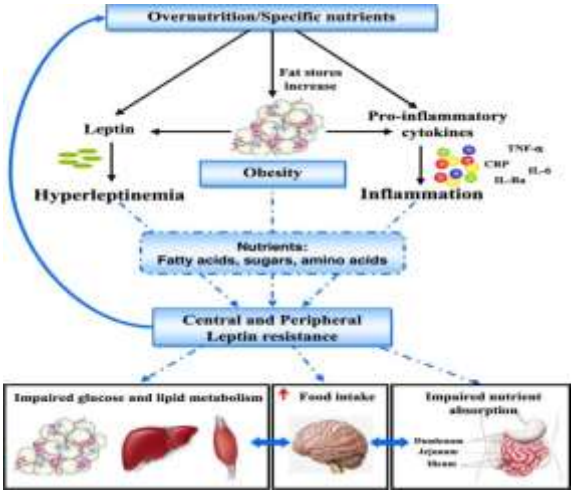

Figure 3: Leptin resistance development and the involvement of nutrients [58].

Conclusion:

Adiposes tissues are an endocrine type, and their effect on target organs varies depending on where fat depots are located and how it functions. Women are susceptible to fatty tissue disorders as a result of sex hormone disorders at different age stages. When a woman reaches menopause and the percentage of estrogen secreted by the ovaries decreases, fat migrates from the buttocks, hips, and thighs to the middle and is stored in the abdomen. Depending on many different factors, such as IR and leptin resistance, the proportion of this fat in the body may exceed its normal limit and cause many different diseases, including obesity, lipodermatosclerosis, lipoma, lipoatrophy, and Dercum's disease

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بعض الامراض المتعلقة في النسيج الدهني : مراجعة

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الخلاصة:

تعتبر المواد الكيميائية التي تطلقها الأنسجة الدهنية ضرورية للحفاظ على التوازن الأيضي. يمكن أن يؤدي نقص هذه المواد الكيميائية، الى السمنة المفرطة أو اعتلال الخلايا الدهنية ، الذي قد يسبب السمنة أو مجموعة متنوعة من الأمراض المرتبطة بالسمنة. لذلك، تعتبر الأنسجة الدهنية جزءاً من الغدد الصماء، وتختلف الطريقة التي تؤثر بها على الأعضاء المستهدفة اعتمادًا على مكان وجود مستودعات الدهون وكيفية عملها. إن فهم ودراسة الأنسجة الدهنية الأدوار المهمة التي يلعبها في تنظيم التمثيل الغذائي في الجسم. أحد أقوى الأديبوكينات المتكمة في عملية التمثيل الغذائي هو الليبتين. من خلال إيصال شعور الجوع أو الشبع إلى منطقة ما تحت المهاد، والذي ينظم وزن الجسم عن طريق إطلاق الناقلات العصبية التي تعدل استهلاك الطاقة وتناول الطعام. بالإضافة إلى ذلك، يعزز الليبتين أكسدة الأحماض الدهنية في العضلات ويمنع المسار الذي يؤدي إلى تخليق الأحماض الدهنية، والذي يتحكم في تكوين الدهون الكبدية. الأديبوكين الأكثر شيوعًا الذي يتم إفرازه هو الأديبونيكتين، فهو يحسن حساسية الأنسولين ويعكس مقاومة الأنسولين جزئيًا.

يبحث الباحثون حاليًا عن طرق زيادة مستويات الأديبونيكتين أو نشاط مستقبلات الأديبونيكتين لغرض علاج الالتهاب ومقاومة الأنسولين الناجمة عن السمنة، اذ يسبب الهرمون الجنسي الأنثوي في تخزين الدهون في الأرداف والفخذين والوركين عند النساء، عندما تصل المرأة إلى سن اليأس وتقل نسبة هرمون الاستروجين الذي يفرزه المبيضان، تهاجر الدهون من الأرداف والوركين والفخذين إلى المنتصف، ولاحقاً يتم تخزين الدهون في البطن. وتشكل الأنسجة الدهنية 20–25% من كتلة جسم الشخص السليم، ويمكن أن تتراوح بين 10–40% عند بعض الأشخاص، وذلك اعتماداً على العديد من العوامل المختلفة، إلا أن نسبة هذه الدهون في الجسم قد تزيد بشكل كبير لتتجاوز الحد الطبيعي لها. وهذا يسبب العديد من الأمراض المختلفة، بما في ذلك السمنة، وتصلب الجلد الدهني، والورم الشحمي، وضمور الدهون ومرض الورم الشحمي الحميد.

الكلمات المفتاحية: النسيج الدهني ،السمنة ، تصلب الجلد الدهني، الورم الشحمي، الضمور الشحمي.