

Obesity pathophysiology and related disorders

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ABSTRACT

Obesity has becoming more common everywhere in the world. Numerous epidemiological studies have shown that obesity significantly increases the risk of developing cancer, cardiovascular disease, type 2 diabetes, liver illnesses, and other disorders. As a result, obesity places a significant annual burden on the general population and the healthcare system. In order to elicit cardiovascular disease and liver illnesses, excessive energy consumption causes adipocyte hypertrophy, hyperplasia, and the

production of visceral fat in other non-adipose tissues. Adipocytes and inflammatory cytokines can also be secreted by adipose tissue to alter the local microenvironment, cause insulin resistance and hyperglycemia, and activate related inflammatory signaling pathways. This aggravates the onset and progression of disorders linked to obesity.

Key Words: *Liver disease; Pleural disease; Interventional pulmonology; Lung injury*

INTRODUCTION

According to the World Health Organization (WHO), obesity is the abnormal or excessive buildup of fat. It has been called a "global pandemic." BMI measurements are used to determine if a person is overweight or obese (BMI). Overweight is defined as a BMI of 25 kg/m² to 29.9 kg/m², while obesity is defined as a BMI of over 30 kg/m². In some populations, there are distinct criteria for being overweight and obese. For Chinese people, for instance, the standard is different from what the WHO recommends. Through increased public health expenses, morbidity, and mortality, obesity, and related diseases place a significant burden on individuals, society, and the economy. An imbalance between caloric intake and energy expenditure is the fundamental cause of obesity. If you consume more energy than you require, it will be stored as fat and journal Subcutaneous Adipose Tissue (SAT) and organs pre-proof glycogen. There are various functionally different depots in Adipose Tissue (AT). While Brown Adipose Tissue (BAT) creates heat in response to adrenergic stimulation or cold exposure, a process known as adaptive thermogenesis, White Adipose Tissue (WAT) is an active endocrine and a significant and safe lipid storage organ. Visceral WAT (VAT) and SAT are the two main depots of WAT in humans, and both have been extensively researched for their potential links to the onset of associated disorders. BAT is only fat, yet it plays a crucial role in preserving homeostasis and has positive effects on blood pressure,

Obesity and overweight have been linked to a low-grade, chronic inflammatory state that is accompanied by increased M1 or "classically activated" macrophage infiltration into AT from the circulation.

These macrophages are capable of being attracted to the AT, where they produce inflammatory cytokines; however, with weight gain, both their abundance and secretion seem to decline as obesity invariably triggers the balance to increase the synthesis of more pro-inflammatory adipokines. Adipokines (such as leptin, adiponectin, visfatin, and resistin) and Extracellular Matrix (ECM) components are also secreted by AT to control associated pathways. Adipose tissue hyperplasia and hypertrophy are caused by an excessive buildup of fat, which alters the secretome and metabolites produced and affects the microenvironment. Along with other variables such as Hepatocyte Growth Factor (HGF), plasminogen activator inhibitor, and monocyte-chemoattractant protein, leptin, one of the most prevalent adipokines with proinflammatory qualities, increases, whereas adiponectin production decreases. The metabolic syndrome, which is well-known as a metabolic disorder resulting from obesity and includes glucose intolerance, insulin resistance, central obesity, dyslipidemia, hypertension, and all risk factors for CVD, is progressed by the inflammatory cytokines released by AT, which also increases the risk for a number of cancers. By upregulating PPAR, which has been linked to tumor growth and initiation through cell-intrinsic and extrinsic mechanisms³⁸, elevated Free Fatty Acids

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(FFAs) in the serum of obese individuals promote the expression of vascular endothelial growth factor (VEGF-A) and vimentin, leading to insulin resistance and steatosis. The overexpression of TNF- and leptin can prevent the activation of the insulin receptor, cause insulin resistance in the muscle, liver, islet -cells, and AT, and ultimately result in T2DM. Additionally, obesity can result in lipid buildup in tissues other than the adipose tissue, including the liver, muscle, pancreas, epicardial, and perivascular tissues. In particular, the buildup of lipids in EAT and PVAT causes hypoxia, tissue dysfunction, and macrophage infiltration, which increases the inflammatory factors linked to CVD. A comprehensive overview of the primary disorders and related mechanisms connected with obesity will be provided by this article. The development of cutting-edge treatments for these illnesses is urgently needed, which in turn necessitates a thorough understanding of the underlying molecular pathways. According to the International Agency for Research on Cancer (IARC) Working Group, obesity is known to be linked to several malignancies, including multiple myeloma, esophageal, stomach, colon/rectal, liver, gallbladder, pancreatic, renal, and meningeal cancers. According to 204 meta-analyses, the risk of cancer rises by 9% for male rectal cancer and 56% for biliary tract system cancer for every kg/m² increase in BMI. The World Cancer Research Fund and the American Institute for Cancer Research evaluated a cohort of over 9 million men, including 191,000 men with prostate cancer, as part of a systematic review and meta-analysis. They identified a 6% increase in the risk of advanced disease for every 5% kg/m² rise in BMI⁵¹ and concluded that there was a solid level of evidence supporting an 8%-11% increased risk of advanced prostate cancer and prostate cancer-specific death in obese men. A higher BMI was also linked to a higher risk of colorectal cancer (CRC), according to a meta-analysis of observational studies including more than 7 million people and instances of the disease; the risk of CRC rose by 18% for every 5% kg/m² increase in BMI. Obesity among cancer patients is linked to worse cancer outcomes, according to expanding observational research. Women with obesity have a 41% relative increase in all-cause mortality when compared to women of normal weight, according to a meta-analysis of studies involving breast cancer survivors. Similarly, endometrial, prostatic, pancreatic, colorectal, ovarian, and certain hematologic malignancies have been linked negatively to obesity and survival. Obesity, on the other hand, does not always indicate a favorable relationship with cancer and is actually linked to better prognoses in kidney, esophageal, and lung cancer. The link between fat and cancer is complicated biologically⁶¹. Numerous studies have suggested that the creation of reactive oxygen species in response to obesity may have effects on the DNA damage and/or repair pathways, leading to genetic instability (ROS). Oxidative stress (OS), which can be brought on by the production of ROS, encourages the oxidation process, which changes the structural makeup of proteins, carbohydrates, phospholipids, and nucleic acids. ROS generation is known to be induced by circulating pro-inflammatory cytokines⁷¹, and this may speed up cell mutation rates and/or interfere with DNA repair systems, leading to an increase and accumulation of genetic events⁶³. Adipocyte hypertrophy also causes tissue to become ischemic and hypoxic, which elevates OS and triggers the generation of ROS, which in turn causes DNA damage and mitochondrial dysfunction. Hyperglycemia, hyperlipidemia, and hyperinsulinemia, which are obesity-related diseases, raise OS and

ROS, aggravating the inflammatory process. Furthermore, obesity-induced cellular lipid modification affects a variety of physiological aspects crucial to the development of cancer. Direct lipid transfer from adipocytes to cancer cells resulted in the induction of lipolysis in the adipocytes and -oxidation in the cancer cells. Lipids from nearby adipocyte reserves can be transported into cancer cells to be used as an energy source and to drive tumor growth. By converting fatty acids into protumorigenic signaling lipids like prostaglandins, sphingolipids, and phosphatidylinositols, which can then activate cancer cells through paracrine or autocrine interactions to trigger oncogenic responses like proliferation, tumor growth, immunological responses, motility, invasiveness, and metastasis, obesity may be a major contributor to the development of cancer. The innate immune system becomes chronically activated as a result of AT's low-grade inflammation, hastening the development of cancer. The PI3K/AKT/mTOR and RAS/MAPK signaling pathways, which are involved in cancer cell proliferation and protein synthesis, are activated by obesity, which also increases insulin secretion and causes a hyperinsulinemic state in vivo. In particular, elevated insulin levels increase insulin-like growth factor (IGF) levels, which are linked to inflammation and immune system impairment. Inhibiting apoptosis and promoting mitogenesis and angiogenesis, increased IGF-1 production aids in the advancement of cancer. Low sex hormone-binding globulin levels and high estrogen bioavailability are connected with high insulin levels or hyperinsulinemia, which promotes the growth of hormone-related malignancies including breast cancer after menopause. After menopause, estrogen production is primarily promoted in obese adipose tissue. Here, aromatase converts adrenal androgens into estrogens, and this process is sped up by the activation of the NF- κ B pathway and the elevation of pro-inflammatory cytokines. Additionally, increased aromatase activity in obese people transforms testosterone into estradiol, leading to higher estradiol concentrations, which may encourage the development of prostate cancer. More than 15 adipokines, including adiponectin, leptin, adipon, and apelin, are also released by AT and encourage the development, invasion, angiogenesis, and metastasis of cancer cells. Leptin is crucial in the emergence of both cancer and obesity. It is largely produced by AT, and it uses a brain-based feedback system to regulate both food intake and energy expenditure. In many cancer cells, leptin exhibits growth-promoting, mitogenic, and antiapoptotic qualities and raises the production of antigenic, TNF-, and IL-6 proteins. Leptin signaling regulates intracellular pathways like the PI3K/AKT/mTOR, JAK2/STAT3, and ERK/MAPK pathways involved in the control of cell proliferation, differentiation, survival, migration, and invasion. When leptin circulates in plasma, it binds to its receptors (OB-Rs) and activates Notch signaling to control downstream effector molecules or signaling events. Additionally, it has been discovered that leptin stimulates the production of Nitric Oxide (NO), Phospholipase C (PLC-), Phosphokinase C (PKC), p38, and Phospholipase C (PLC-). These enzymes can activate several genes related to cell proliferation, including *C-FOS*, *CJUN*, *JUNB*, *EGR-1*, and *SOCS3*, as well as upregulate the expression of antigenic through the activation of the aromatase gene expression and aromatase activity, leptin raises estrogen levels, which promotes tumor growth and the emergence of antiestrogen resistance in obese breast cancer patients. Leptin also improves the stability of the Estrogen Receptor Alpha (ER-alpha),

which maintains ER-dependent transcription in breast cancer cells in the presence of antiestrogens. Several in vitro studies have shown that leptin stimulates cell invasion and migration in a variety of cancer cells. For instance, leptin increased the expression of Acetyl-CoA Acetyltransferase (ACAT2) through the signaling pathway to enhance the proliferation, migration, and invasion of breast cancer cells. It also stimulated the expression of IL-18 in Tumor-Associated Macrophages (TAMs) via NF- κ B/NF-B1 signal. On the other hand, leptin occasionally displayed positive action. Leptin has been proven to counteract the immunosuppressive effects of acute fasting in rats. Additionally, leptin has been discovered to exhibit antitumoral properties in human pancreatic cancer cell lines. Another significant adipokine produced by adipose tissue, Adiponectin (APN), plays a role in the development of various malignancies. The insulin pathway is activated and the levels of the adipose-derived cytokines IL-6, IL-8, and TNF- drop in obese individuals due to a lower amount of APN in plasma. Both beneficial and detrimental effects of APN on tumor growth have been demonstrated by research. It has been demonstrated that obesity increases the incidence of "obesity-related malignancies." As obesity progresses, serum concentrations of lipids, leptin, estrogen, resistin, and inflammatory cytokines tend to rise, whereas IGF-binding protein and adiponectin levels tend to fall. Each of these factors has been implicated in the etiology of cancer. It's interesting to note that recent epidemiological research suggested that obesity may operate as a protective factor against the incidence and mortality of several cancer forms, such as Non-Small Cell Lung Cancer (NSCLC) and head and neck cancers. The use of BMI as a measure of general adiposity may be one of the possible causes for the "obesity paradox" in cancer patients, which happens when the risk of the outcome, often mortality, is dramatically decreased for BMI values above this referent, where increased risk is expected. Cycle, glycolysis, pyruvate metabolism, and mitochondrial electron transport chain discovered that exosomes produced by CAFs unexpectedly influenced the metabolism of tumors in prostate and pancreatic cancers. The aberrant fat buildup surrounding the heart, which has been consistently linked to an increased risk of CVD, is caused by the ectopic deposition of AT in other organs. For instance, in healthy persons, the majority of ATP produced by cardiomyocytes comes from the mitochondria, which is also where ROS are produced. Excess FFAs build up in cardiomyocytes in patients with obesity and IR, increasing ROS production through fatty acid oxidation and finally resulting in mitochondrial dysfunction.