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Obesity and endometrial cancer: the role insulin resistance and adipokines

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Abstract

Obesity has shaped the global pandemic as a major health problem. It is related to chronic metabolic diseases and cancer development, like endometrial cancer. Recent studies have revealed a strong correlation between higher Body Mass Index (BMI) and endometrial cancer, predicting that a higher BMI is a leading cause of endometrial cancer by disrupting the balance of adipocytokines and hormones. This article reviews the current scientific knowledge on the relationship between obesity and endometrial cancer and the role of insulin resistance and adipokines. It also addresses the necessity for additional studies to thoroughly comprehend the underlying processes and create efficient methods for preventing and treating endometrial cancer in obese people.

Introduction

Being overweight and obese is a public health threat not limited to that is present in both developing and developed countries. It impacts the normal lifestyle of people worldwide because obesity is associated with various metabolic syndromes, including cardiovascular diseases, hyperinsulinemia, and hyperlipidemia (Organization, 2000). Studies revealed a prominent link between higher BMI and the pathophysiology of different types of cancer. It is assumed that the underlying mechanism for the higher risk of cancer in obese people is due

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to alteration in their metabolic profile and function of adipocytes (van Kruijsdijk, van der Wall, & Visseren, 2009). The development of cancer prevention and treatment techniques may benefit from understanding the pathophysiological mechanisms underlying the link between obesity and malignancy. A group of researchers found that obesity can lead to hypertension which also increases cancer risk (Tzenios, Tazanios, & Chahine, 2022b).

In this study, the relationship between obesity and the development of several cancers is assessed, and the associated pathophysiological mechanisms are discussed. We suggest that the pathophysiology and development of cancer are strongly influenced by adipokines and insulin resistance.

Epidemiology of obesity and endometrial cancer

Currently, obesity is recognized as a major public health problem of the twenty-first century, and controlling obesity is seen as a significant challenge (Arroyo & Mincey, 2016). The WHO defines overweight and obesity as abnormal or excessive fat accumulation representing a health risk. These conditions are associated with an increased risk of several chronic diseases, such as diabetes and cardiovascular diseases. Moreover, several studies have shown that obesity is associated with an increased risk of numerous cancer types (Bandini, Gandaglia, & Briganti, 2017). Of note, this condition might play a role also in the pathogenesis of endometrial cancer. Several preclinical studies proposed multiple theories to explain the association between obesity and the pathogenesis of Prostate cancer (Tewari, Vargas, & Reizes, 2022). Epidemiological studies conducted by CDC reported that obesity is on elevation in the US, as the percentage is increased from 30.5% to 41.9% in the last decades (Tzenios, Tazanios, & Chahine, 2022a).

The statistics of the World Cancer Research Fund (WCRF) revealed that higher BMI is involved in more than ten types of cancer comprising colon cancer, breast cancer, prostate, endometrial, kidney, epithelial ovarian, renal cell adenocarcinoma, pancreatic and esophageal squamous-cell carcinoma (Arnold et al., 2015).

It is well-recognized that obesity boosts women's chance of developing endometrial cancer (Rodriguez et al., 2021). It is reported that higher BMI is responsible for 57% of endometrial cancer cases in the US. Interestingly, it was found that there is a direct association between higher BMI and the incidence of endometrial cancer (Onstad, Schmandt, & Lu, 2016). Furthermore, a higher body adiposity index (BAI) can elevate the probability of death by cancer. A literature review by the international agency for Research on Cancer (IARC) evident the relationship between BAI and endometrial cancer. It further elaborates that a higher BMI is responsible for 35% of endometrial cancer cases (Saliha, 2021).

The role of adipokines in endometrial cancer

Leptin is a polymer of 16 kDa adipokine secreted by white adipose tissues transcribed from the LEP gene. Likewise other hormones, it is secreted in two forms, free circulating form, which is responsible for controlling the body adiposity index, and in conjugated form with proteins. Besides all these functions, it also regulates and maintains energy expenditure (Chen et al., 2006). Leptin

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has a tetra helix shape, which is quite reminiscent of the cytokine family of proteins, including IL-2, IL-6, IL-12, IL-15, IF, and G-CSF. Leptin controls appetite by acting directly on the neural system and, by its peripheral effect, prevents pancreatic beta-cells triggered by glucagon-like peptide-1 from secreting insulin (GLP-1).

Moreover, it promotes the transfer of carbohydrates, glucose metabolism, and lipid degradation. Leptin participates in osteogenesis, hematopoiesis, and thermogenesis and possesses pro-angiogenic properties. Leptin has been reported to have an impact on immune system efficiency by enhancing pro-inflammatory effects, such as T cell activation, Interleukins-6 (IL6), and Tumor necrosis factor (TNF)production and release, activating the response to Th1 lymphocytes and raising the activity of NK cells, macrophages, and neutrophils by augmenting their chemotaxis (Yiying Zhang et al., 1994).

Leptin stimulates STAT3 proteins in endometrial cancer that enhance efficacy by modulating proliferation and neoangiogenesis and avoiding the control of the immune system (Deng, Grande, & Neamati, 2007). A group of scientists reported that the expression of activated STAT3 proteins increases the concentration of anti-apoptotic genes, including Bcl-xL and Mcl-1, in endometrial cancer cell lines, making the epithelial cells immortal and chemo-resistant (Gao et al., 2009). Another study found that greater levels of serum leptin correspond with the involvement of lymphatic vessels and a low degree of neoplasia differentiation (Yun Zhang, Liu, Li, & Ai, 2014).

Adiponectin is another prominent adipocytokine involved in the pathophysiology of endometrial cancer. It encodes by the apM1 gene, consisting of 244 amino acids with homotrimeric and oligomeric structures. Mainly, it is involved in regulating glucose-glucagon concentration and lipids (Boroń, Nowakowski, Grabarek, Zmarzły, & Opławski, 2021). Different studies revealed the association between low concentration of adiponectin, higher BMI, and progression of endometrial cancer (Yunusova et al., 2018). Another study reported that lower concentrations of adiponectin in plasma-prone women to endometrial cancer without any dependency on body adiposity index and other obesity-induced metabolic risk factors (Kelesidis, Kelesidis, & Mantzoros, 2006).

Low levels of adiponectin in blood serum (less than 8 mg/L) are related to increased neoplastic malignancy, more likely lymph node metastasis, and a lack of histological differentiation (Cust et al., 2007). In contrast, high pretreatment adiponectin levels are a favorable predictive factor in endometrial cancer patients regarding disease-free duration and overall survival (Ashizawa et al., 2010).

The role of insulin resistivity in endometrial cancer

Insulin resistivity is defined as the condition in which the decrease in sensitivity of tissues toward insulin which are responsible for regulating glucose concentration inside the blood. To compensate for the lower response of these tissues, pancreatic beta cells start producing higher insulin concentrations, leading to hyperinsulinemia. It owns a diverse range of physiology inside the human body. An excessive amount of this polypeptide may initiate harmful effects like cancer

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development. It was confirmed by a study that a higher concentration of insulin in women is directly linked with the pathophysiology of endometrial cancer (Gunter et al., 2008).

Insulin resistivity and the development of endometrial cancer are linked through common molecular pathways and factors like inflammatory mediators, adipocytokines, and an excessive concentration of androgen.

Elevated insulin levels caused by insulin resistivity can have various physiological consequences that may promote EC development. Insulin is an established growth factor that acts on various cell types by interacting with both cognate and non-cognate receptors. A group of researchers manifested that Ishikawa 3-H-12 EC cells express insulin receptors and that exposure to insulin-stimulated multiplication prevented apoptotic activity in a dose- and time-dependent manner. These mitosis-stimulating and anti-apoptotic effects were induced by molecular signaling of insulin via insulin receptor interaction (Zhao, Xue, Hua, & Zhang, 2007).

Upon insulin binding, IR is activated, triggering the activation of IRS-1, which then activates the PI3K and mitogen-activated protein kinase (MAPK) pathways. The PI3K/Akt pathway targets several key proteins that regulate lipid and carbohydrate metabolism as well as cell proliferation and apoptosis

Upon binding of insulin with insulin receptor (IR), it triggers the insulin receptor substrate-1 activation, which acts as an activation signal for P13K and mitogen-activated protein (MAP) kinase molecular pathways (Zhao et al., 2007). The P13K/Akt molecular signaling pathway interacts with essential enzymes involved in the hemostasis of lipids and carbohydrates and the regulation of mitogenic and apoptotic processes (Funaki, Katagiri, Inukai, Kikuchi, & Asano, 2000). The mitogen-activated protein (MAP) kinase is responsible for regulating the mitogenic process and cell survival (Davis, 1993).

These two regulatory pathways are very crucial in the pathophysiology of cancers (Müssig, Häring, endocrinology, & diabetes, 2010). Another study reported that six different endometrial cancer cell lines manifested that higher expression of pathways mentioned above was essential for the development of most endometrial cancers (Ogawa, Sun, & Horii, 2005).

Conclusion

Obesity is a known risk factor for endometrial cancer. The underlying process is considered to include insulin resistance and adipokine release. Insulin resistance causes higher insulin levels, which stimulate endometrial cell mitogenesis, and adipokines such as leptin and adiponectin also contribute to the development of endometrial cancer. While more study is needed to fully understand the complicated relationship between obesity, insulin resistance, and endometrial cancer, it is obvious that maintaining healthy body weight and treating insulin resistance can help minimize the risk of endometrial cancer.

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