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Case Report

The Relationship Between Metabolic Syndrome, Disturbed Vascular Function and Risk of Metastatic Breast Cancer

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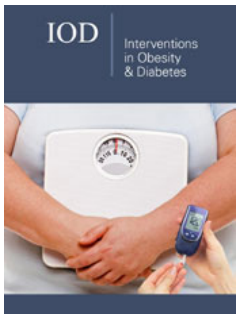

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Abstract

Metabolic syndrome, characterized by at least three metabolic health alterations such as abdominal obesity, hypertension, low HDL-C, high fasting glucose, and hypertriglyceridemia, is associated with increased risks of type 2 diabetes and various vascular complications. This condition also elevates the risk of Breast Cancer (BC), particularly in postmenopausal women, by promoting systemic inflammation, hormonal imbalances, and vascular dysfunction, which collectively create an environment conducive to cancer progression and metastasis. Insulin and IGF-1 signalling pathways, often dysregulated in metabolic syndrome, play significant roles in BC development and recurrence by activating oncogenic pathways in neoplastic tissues. Epidemiological evidence strongly links metabolic complications to increased BC risk, particularly in patients with obesity, hypertension, and diabetes. This review paper discusses current evidence on the associations between metabolic syndrome, vascular complications, and BC risk, emphasizing the role of lifestyle interventions like exercise and the Mediterranean diet in restoring metabolic homeostasis and reducing BC risk. Additionally, impaired lipid metabolism, particularly hypercholesterolemia, is highlighted as a key contributor to BC pathogenesis, with statin therapy showing potential in reducing BC recurrence. Novel therapeutic strategies targeting vascular complications, such as the use of antiangiogenic agents like danthron, are explored for their potential in treating BC in patients with metabolic syndrome. These findings underscore the importance of integrated metabolic and oncological care to mitigate BC risk and improve outcomes in patients with metabolic syndrome.

Keywords: Breast cancer; Metabolic disease; Vascular health; Metastasis

Introduction

Metabolic syndrome is a complex condition which is characterized by presence of at least three out of five alterations in the metabolic health, such as abdominal obesity, high blood pressure, low plasma High-Density Lipoprotein Cholesterol (HDL-C), high plasma fasting glucose, and high triglycerides [1]. These alterations are associated with increased risk of d type 2 diabetes, as well as being linked to various vascular complications, including heart disease, stroke, atherosclerosis, coronary artery disease and microvascular dysfunction. In addition, dysregulated glycaemic/insulin homeostasis demonstrated as fasting hyperinsulinemia and high levels of circulating Insulin-like Growth Factor-1 (IGF-1) often present in patients with metabolic syndrome, are also considered as risk factors for the development and recurrence of Breast Cancer (BC). Not surprisingly, because insulin along with IGF-1 signalling systems is implicated in energy metabolism and growth, also in cancer cells. There is accumulating evidence to demonstrate that these cells, similarly to other tissues, express insulin and IGF-1 receptors, which are important activators of the Akt and mitogen-activated protein kinase signalling networks in neoplastic tissues. Furthermore, mentioned vascular complications can indirectly influence breast cancer risk and progression including alerted formation of new blood vessels in angiogenesis can be crucial for tumour growth

and compromised vascular integrity could potentially facilitate the spread of cancer cells increasing risk of metastasis. Particularly in metastasis in patients with breast cancer, the ability of metabolic syndrome to induce systemic inflammation, hormonal changes, and vascular dysfunction can create an environment promoting cancer progression, although specific mechanisms require further research. So far, several contributory factors were recognized, and they include obesity, as excess of abdominal fat has been associated with higher estrogenic levels, which can promote the growth of hormone-sensitive breast cancers. In addition, the presence of low-grade systemic inflammation, followed by the impaired metabolic homeostasis can increase oxidative stress, potentially damaging DNA and promote cancer formation [2].

A systematic analysis of cohort and case-control studies, including a total of 392,583 female participants of which 19,628 were breast cancer patients, has revealed a statistically significant increase by 52% of the risk of breast cancer in adult females with confirmed diagnosis of metabolic syndrome. Interestingly, postmenopausal female patients with metabolic syndrome may have a twofold risk to suffer from breast cancer. The risk of breast cancer increased markedly with the number of metabolic syndrome component and the risk factors associated with breast cancer were obesity, hypertension, and diabetes [3]. Therefore, the main aim of the following article is to discuss and present current evidence indicating potential associations between presence of metabolic syndrome and vascular complications in determining risk of cancer metastasis.

Epidemiological Evidence Linking Metabolic Complications with Cancer Risk

Recent epidemiological research has increasingly shown a strong link between metabolic complications and cancer risk. This connection is an important area of research in the field of oncology and public health.

Role of insulin signalling

For example, insulin signalling, especially circulating levels of IGF-1 were positively associated with the risk of breast cancer recurrence, and is more frequently dysregulated in older people, especially in those with metabolic syndrome and obesity. A study conducted as part of research initiative The Diet and Androgen-5 (DIANA-5; NCT05019989), which included bread cancer survivors, showed that depending on the metabolic syndrome diagnosis, insulin may be considered as the main predictor of elevated IGF-1 levels exclusively in subjects without the metabolic syndrome. Interestingly, further analysis of patients has found an interaction between High-Density Lipoprotein Cholesterol (HDL-C), glycemia, and IGF-1 levels, as HDL-C and IGF-1 have positively correlated in subjects with higher values of glycemia and without a diagnosis of metabolic syndrome. Although further research is needed, these findings could have important clinical implications for planning strategies modulating IGF-1 levels in breast cancer survivors, such as physical activity or dietary interventions [2].

Lifestyle Interventions Restoring Insulin Homeostasis – Case Studies

Case study of walking and eating fruits

Aerobic exercise is widely believed to be effective in improving the dysregulated metabolic state of the body, such as reducing fasting blood sugar, restoring appropriate lipid profile (cholesterol HDL and triglycerides) as well as reducing waist circumference. Nevertheless, resistance exercise can induce positive changes, especially improving insulin sensitivity by maintaining and/or increasing lean body mass, glucose storage, reducing circulating glucose levels, and promoting a decrease in the amount of insulin required by obese people. For example, a prospective study of 1,490 women with breast cancer conducted as part of Women's Healthy Eating and Living have shown that walking 30 minutes a day for 6 days a week plus eating at least 5 servings of fruit and vegetables a week significantly benefited survival, especially in the context of the mortality of ER+ tumours [4].

Case study of the role of Mediterranean diet as preventive approach against breast cancer

The Mediterranean diet is known for wide health benefits for prevention and improving health status, it is also considered as another option to reduce the occurrence of metabolic syndrome, thus reducing incidence of breast cancer and improving its prognosis. The main characteristics of the Mediterranean diet are extensive consumption of fruits, vegetables, unrefined grains, legumes, fish, cereals, nuts, olive oil, and moderate drinking of wine during the main meal, what may lead to reduced risk of disease including breast cancer [5]. Consequently, adopting a Mediterranean diet can improve the imbalance of body metabolism and reducing a low-grade inflammation along with improving insulin sensitivity can reduce not only obesity cases but have found to lower risk of ER- breast cancer in postmenopausal women [6].

Taken together, lifestyle changes including exercise and dietary interventions that activate the anti-aging gene Sirtuin 1 (Sirt-1), what may be critical to the treatment of the metabolic syndrome and breast cancer [7]. Nevertheless, the intake of foods as source of the bioactive acting as Sirt-1 activators, contrastingly to Sirt-1 inhibitors should be consumed in appropriate proportion and relevance to insulin regulations, in particularly in the context of cancer prevention and disease management

Impaired lipid metabolism - focus on cholesterol synthesis

Obesity and diets high in saturated fats are associated with dyslipidaemia and hypercholesterolemia, even though cholesterol is the principal structural component of cell membranes and serves as primary precursor for steroid hormone synthesis, including estrogenic and progesterone. Dyslipidaemia, including high Total Triglyceride (TG) levels, high Total Cholesterol (TC) levels and low serum HDL levels, is also considered to be associated with the occurrence of breast cancer, but the results are inconsistent. Nevertheless, there is evidence to indicate that

hypercholesterolemia is an independent risk factor for breast cancer in postmenopausal women, as cholesterol can impact cancer cell proliferation and potentially induce breast cancer development. This observation was implicated in several clinical studies that have demonstrated a genetic association between high cholesterol levels and breast cancer pathogenesis [8].

Interestingly, breast cancer patients receiving treatment with statins had low breast cancer recurrence, which has been explained by statins ability to inhibit synthesis of cholesterol and its metabolites, including 27-hydroxycholesterol [9] implicated previously in breast cancer metastasis by restoring the tumour microenvironment and promoting tumour resistance [10]. Furthermore, enhanced cholesterol synthesis can stimulate oncogenic signals, leading to cancer cell growth and proliferation, specifically by activating the PI3K/Akt/mTOR and AMPK signalling pathways [11] and binding to specific cancer-related proteins can induce changes in their structure or activity, potentially further contributing to cancer progression [8].

For example, molecular defects present in cholesterol metabolism, including those regulating cholesterol uptake via the Liver X Receptors (LXRs) [12], such as SREBP2 transcription factor, which was found to be significantly higher in breast cancer than normal tissues, thus suggesting a role in increasing breast cell proliferation and migration. Additionally, SREBP2 was also associated with a higher risk of breast cancer relapse and recurrence in patients. Similarly, SREBP1 was found to play a role in the metabolic reprogramming and upregulation of breast cells, leading to the increased production of cholesterol, fatty acid, and triglycerides [13], what may exacerbate the metabolic dysregulation that drives breast cancer progression [14].

Novel Treatment Strategies Focused on Vascular Complications Associated with Metabolic Syndrome

The role played by a sustained angiogenesis in cancer and other diseases stimulates the interest in the search for new antiangiogenic drugs, which can aid treatment of patients with developed vascular complications resulting from acquired metabolic syndrome. Early experimental study indicated a bioactive compound, known as 1,8- dihydroxy-9,10-anthraquinone (danthron), isolated from the fermented broth of the marine fungus Chromolaenicola sp. (HL-114-33-R04) may be considered as a novel inhibitor of angiogenesis. In vitro studies conducted on Human Umbilical Endothelial Cells (HUVEC) revealed that this anthraquinone inhibits certain key functions of activated endothelial cells, including proliferation, proteolytic and invasive capabilities and tube formation. Interestingly, similar experiments conducted on human breast carcinoma and fibrosarcoma cell lines also indicated a possible moderate antitumor and antimetastatic activity of this compound. Furthermore, antioxidant properties of danthron are evidenced by the observation that it reduces the intracellular reactive oxygen species production and increases the amount of intracellular sulfhydryl groups in endothelial and tumour cells. Overall, despite need for further studies, these findings may support a putative role of danthron as a new antiangiogenic drug with potential application in the treatment and angio prevention of cancer and other angiogenesis-dependent diseases in patients with acquired metabolic disturbances [15].

Conclusion

There is growing evidence implicating a significant correlation between metabolic syndrome and an increased risk of breast cancer, particularly in postmenopausal women. Metabolic syndrome, characterized by a cluster of conditions including obesity, hypertension, and dysregulated glucose and lipid metabolism, has been strongly linked to the development and progression of breast cancer. Insulin signalling pathways, especially those involving IGF-1, play a critical role in this association, underscoring the importance of insulin homeostasis in cancer prevention and management. Lifestyle interventions, such as regular aerobic exercise and adherence to a Mediterranean diet, show promise in mitigating the risks associated with metabolic syndrome and, consequently, breast cancer. Furthermore, the study underscores the importance of addressing impaired lipid metabolism, particularly cholesterol synthesis, as a potential therapeutic target. Emerging evidence on novel antiangiogenic treatments, such as the compound danthron, provides a promising avenue for managing vascular complications linked to metabolic syndrome and breast cancer metastasis. Overall, these findings suggest that a multifaceted approach, including lifestyle modification, targeted therapies, and further research into metabolic and vascular pathways, is crucial in reducing breast cancer risk in patients with metabolic syndrome.

Clinical implications

Clinical implications for oncological care:

a. Routine screening for metabolic syndrome in breast cancer patients

Regular assessment of metabolic syndrome components (e.g., obesity, hypertension, dyslipidaemia, and hyperglycaemia) in breast cancer patients can help identify individuals at higher risk for cancer progression and recurrence.

b. Targeting insulin and IGF-1 pathways

Consider therapeutic strategies that modulate insulin and IGF-1 signalling pathways, particularly in postmenopausal women and those with metabolic syndrome, to reduce the risk of breast cancer recurrence.

c. Cholesterol management in breast cancer care

Monitor and manage dyslipidaemia in breast cancer patients, especially those with high cholesterol, as it may contribute to cancer cell proliferation and metastasis. Statin therapy could be considered for reducing breast cancer recurrence due to its potential to inhibit cholesterol synthesis and its pro-cancer effects.

d. Addressing systemic inflammation and oxidative stress

Implement interventions aimed at reducing low-grade systemic inflammation and oxidative stress to prevent DNA damage and

subsequent breast cancer development in patients with metabolic syndrome.

e. Incorporating antiangiogenic therapies

Explore the use of novel antiangiogenic agents, such as danthron, in patients with metabolic syndrome and breast cancer to target vascular complications that may contribute to tumour growth and metastasis.

f. Lifestyle interventions

Encourage aerobic and resistance exercises alongside dietary interventions like the Mediterranean diet to improve insulin sensitivity, reduce systemic inflammation, and lower breast cancer risk in patients with metabolic syndrome.

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