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Review

The Metabolic Syndrome: A Cancer Risk Factor?

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ABSTRACT

Metabolic syndrome (MetS) is characterized by diabetes, high blood pressure, hypertriglyceridemia, abdominal obesity, and a decrease in high-density lipoprotein cholesterol levels. Five components cause serious morbidity and mortality in the process of progression in the living body. In addition, it is stated that they are included in the relationship between MetS and cancer in the studies conducted. In this review article, we discussed the link between MetS and cancer and the effects of components on cancer types.

Keywords: Abdominal obesity, cancer, high blood pressure, hyperglycemia, hypertriglyceridemia, metabolic syndrome

Metabolic syndrome (MetS) is a serious cause of morbidity and mortality of metabolic risk factors that occur in the living body and increases if not controlled. It consists of five main components. The five main components mentioned are abdominal obesity, hyperglycemia, high blood pressure, hypertriglyceridemia, and high-density lipoprotein (HDL) cholesterol contained in the living body.[1-3]

Although the overall prevalence of MetS varies with studies, its prevalence is increasing significantly and alarmingly worldwide. According to studies, especially in Western countries, one of every five adults is diagnosed with MetS. Despite extensive research on cancer, it remains a serious health concern with a high mortality rate. Additionally, the coexistence of metabolic disorders and cancer is prevalent among patients. Therefore, scientists have started to investigate the strong link between MetS and cancer, given the high incidence rates of both these conditions.[4,5]

Many studies examined suggest that people with MetS have a higher rate of developing cancer. When it is examined, cancer recurrence rate and mortality rate are higher in these patients than in other patients. A recent study showed that people diagnosed with MetS had a 33% higher cancer mortality rate than patients without metabolic disorders. Abdominal obesity and hyperglycemia among MetS components have been shown in clinicopathology in association with tumors. In addition, other evidence shows that some of the metabolic disorders seen are at high risk in various types of cancer, including colorectal, prostate, pancreatic, kidney, liver, breast, and endometrial cancer. In addition to these conditions, malignant cells are acquiring changes in anabolic and catabolic pathways to meet their high metabolic and energy needs, known as metabolic reprogramming.[6-9]

Another important part is that metabolic reprogramming has emerged as a hallmark of cancer. In addition to the onset, progression, and metastasis of cancer, it has been shown to play an active role in the survival of cancer cells and their resistance to antitumor treatments.[10]

In general, metabolic reprogramming and the fact that MetS plays an important role in cancer development and progression have been promising approaches for the cancer process. This has led to new methods for the development of metabolism-targeted therapies. In addition, ongoing studies continue to investigate anticancer therapies that target the relationship between metabolism and

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cancer, underlying mechanisms, and metabolism.[11,12]

THE LINK BETWEEN METS COMPONENTS AND CANCER

There is a link between the components of MetS and cancer. But whether the effects of these ingredients are additive or synergistic is still being investigated in other studies.[13]

Abdominal Obesity and Cancer

In one study, it was reported that being overweight and having abdominal obesity caused mortality in 14% of men and 20% of women. Epidemiological studies have shown an increase in waist circumference or body mass index (BMI); it reveals that it increases the risk of colon, postmenopausal breast cancer, endometrium, esophagus, liver, gallbladder, stomach, and kidney cancer. The pathophysiology of abdominal obesity and cancer reveals the active involvement of insulin resistance. Specifically, insulin resistance is shown to play a significant role in both conditions. Chronic high levels of insulin due to insulin resistance increase the bioavailability of insulin-like growth factor 1 (IGF) 1. In addition, apart from insulin resistance, the increase in endogenous estrogen levels and bioavailability play an important role in the development of cancers, especially hormone-dependent cancers.[14-17]

Insulin Resistance and Cancer

Insulin resistance is a pathological condition characterized by the reduction in the efficiency of the insulin signal used to regulate blood glucose. Insulin resistance is a key component of MetS. It also plays a role in cerebrovascular and coronary artery diseases, neurodegenerative disorders, infectious diseases, and cancer, except for metabolic diseases. Due to the continued obesity and other insulin resistance disorders in the world, the common factors involved in the regulation of insulin-like peptides (ILPs), and energy metabolism, have been covered in detailed reviews. In humans, ILPs contain seven peptides of insulin, IGF1, IGF2, and toxin, which share the same basic fold. In current studies, the term 'ILP' is used to indicate insulin and IGF.[18,19]

Insulin-Like Peptides and Cancer

Data that continue the relationship between IGF1 and cancer risk include Mora and friends' recent work.[20] When genetic changes in insulin/IGF1 road genes were examined in the long life, it was indicated that dementia, metabolic diseases, and cancer are associated with the elderly. No definitive data has yet been obtained that evaluates the connection between general cancer mortality and the IGF1 or insulin-like growth factor binding protein (IGFBP)3 levels in circulation.[20,21]

However, a clinical study found that IGF1 has been positively associated and that IGFBP3 is related in reverse to mortality in men with advanced prostate cancer, and that levels of IGF1 and IGFBP3 may have potential as prognostic markers in predicting the risk of death in men with prostate cancer. In another study, a relationship between the concentration of zinc, IGF1, and IGFBP3 and the prostate in prostate cancer was found to be useful in the early diagnosis of prostate cancer of zinc, IGF1, and IGFBP3. In addition, it is stated that IGFBP3 gene polymorphism will be linked to the sensitivity of prostate cancer development.[22,23]

A report by Price et al.[23] shows that increases in circulating levels of IGF1 are associated with a significantly increased risk for prostate cancer development. Interestingly, the study revealed a change in the duration of monitoring or diagnosis of cancer that has been defined for more than seven years after blood intake, depending on stage, degree, and age. After all, he raised the question of whether the reduction of the IGF1 levels in circulation would affect the risk of prostate cancer.[24]

Moreover, for patients with locally developed colorectal cancer (pT3 and pT4), IGF1 serum levels increase compared to less advanced (pT2). Patients with weakened differentiated cancers (G3) are observed at a higher serum level than medium-differentiated cancers, and similarly, higher serum levels in IGF1 are found in men patients over 60 years of age and in mucinous colorectal cancers. It is also shown to be associated with a higher risk of colorectal cancer, IGF1/IGFBP3, or C-peptide levels.[25]

Hyperglycemia and Cancer

Hyperglycemia is defined as glucose concentration above normal in body circulation and is the characteristic finding of diabetes mellitus (DM). Insulin resistance is the main reason for hyperglycemia in type 1 DM (T1DM), while inadequate insulin production in pancreatic β cells is the main reason for type 2 DM (T2DM). Increased glucose use is a well-known feature of malignant cells. Increased glucose metabolism in cancer cells is known as the "Warburg effect" and is defined by Warburg in 1956 by showing that anaerobic glycol in tumoral cells has increased significantly. From this point of view, hyperglycemia acts as an essential fuel for tumoral cells, stimulating faster

proliferation. In some experimental studies, it was observed that hyperglycemia increased tumor growth and proliferation, and insulin treatment reversed this situation. From this point of view, hyperglycemia acts as an essential fuel for tumoral cells, stimulating faster proliferation. In some experimental studies, it was observed that hyperglycemia increased tumor growth and proliferation, and insulin treatment reversed this situation. In contrast, T1DM and related experimental studies with hyperglycemia were found to have decreased in contrast to tumor growth. This suggests that hyperglycemia contributes to carcinogenesis in the presence of insulin found in the environment, not alone, but it is not yet clear whether this hypothesis is true or not.[26-29]

There is data that excessive amounts of sugar intake increase cell proliferation and that high levels of glucose in circulation are bad prognostic factors in cancer patients. However, a recent meta-analysis found that tumor cells continue to use high glucose, regardless of the glucose level in the blood, and better glycemic control in diabetic patients does not reduce the risk of cancer.[30]

Hyperglycemia is thought to contribute to cancer biology through the molecular, antiapoptotic mechanisms, cellular migrations, and invasive and epigenetic changes in key pathways that play a role in carcinogenesis.[31]

The development of cancer due to hyperglycemia occurs independently of BMI. One study followed the health status of 140,000 adults for about eight years. One of the similar studies was conducted in Korea. About 1.3 million Korean citizens have had fasting glucose levels monitored for ten years. In the results obtained, it was revealed that the increase in fasting glucose levels was associated with pancreatic, liver, and kidney cancer. It has been noted that individuals with plasma glucose greater than one hundred forty have a higher risk of developing cancer than individuals with plasma glucose below 90 mg/dl. Another study indicated an increased risk of colorectal cancer with T2DM in both men and women. It has been noted that this is linked to colon cell proliferation triggered by hyperinsulinemia and increased IGF1 levels. In addition, it is also included in the studies that the risk of colorectal adenoma is increased in T2DM patients in chronic insulin treatment.[32-38]

Cholesterol and Cancer

There is a reported association between low levels of HDL and an increased risk of lung cancer. Especially in individuals with very low HDL levels, the incidence of lung cancer has been reported to increase by about 6.5 times. In addition, low HDL levels are not only associated with lung cancer but also with the development of hematologic malignancy.[39,40]

High Blood Pressure and Cancer

Studies do not indicate a definitive relationship between high blood pressure and cancer. However, it is estimated that it is associated with increased cancer mortality and that inhibition of apoptosis may play a role.[41]

As mentioned above, there are links between MetS components and cancer, and each component plays a role in the occurrence of different cancer as a result of studies. In addition, apart from MetS components, it is necessary to talk about the mechanisms that play a role in cancer formation.[42]

METABOLIC SYNDROME AND CANCER

Obesity is due to inflammation and insulin resistance in the living body and it is caused by hypoxemia in adipose tissue as a result. It is also stated that insulin resistance in obese individuals is associated with tumor necrosis factor-alpha (TNF-α). TNF-α secreted from adipose tissue disrupts the intracellular insulin signaling pathway. It raises free fatty acid levels and causes adiponectin levels to decrease.[43,44]

Insulin resistance-hyperinsulinemia-IGF1 system, many states occurring in MetS are seen as one of the main responsible mechanisms. Research shows that the strongest evidence of the relationship between MetS and cancer is obesity and hyperinsulinemia, or insulin resistance. In the normal process, insulin is an anabolic hormone that stimulates cell proliferation. In the process of cancerization, cancer cell proliferation is realized by IGF1 stimulation. Growth hormone stimulates the production of IGF1 in the liver and insulin stimulates the production of IGF1 by regulating growth hormone receptors. According to studies in breast and colon cancers, the IGF1 pathway is overexpressed. As a result, the p21, ras/MAPK pathway, and phosphatidylinositol-3 kinase/AKT pathway are activated.[45,46]

In addition to the proliferative and anti-apoptotic properties of IGF1, its angiogenetic feature is stated to play a role in the development of colon, endometrium, breast, and prostate cancers. Also, hyperinsulinemia and IGF1 have been shown to inhibit the synthesis of sex-binding globulin in the liver. This condition is

thought to trigger hormone-related cancers such as breast, endometrium, and prostate cancer.[47,48]

In females with obesity, insulin, and IGF1 have an effect on increasing estrogen biofuel levels. In addition, aromatase activity comes into play as a result of the increase in adipose tissue in the body and menopause of individuals. The aromatization process occurs and the level of estrogen increases. Therefore, there is an increase in breast and endometrial cancers in postmenopausal women.[49,50]

Another factor that is associated with MetS and cancer and also plays a role in the connection between these two factors is adipokines. Adipokines; appetite and body energy balance, inflammation, insulin sensitivity, angiogenesis, lipid metabolism, cell proliferation, and atherosclerosis are the signal group that plays a role.[51]

The body of obese individuals is resistant to leptin. That's why they have hyperleptinemia and are more sensitive to MetS. High leptin levels are thought to be associated with prostate, colon, breast, and endometrial cancer. It has also been suggested that leptin may stimulate the mechanism of angiogenesis and contribute to cancer metastasis.[52,53]

In obese individuals, adiponectin levels are low, unlike other hormones secreted from adipocyte tissue. Adiponectin has anti-inflammatory, anti-atherosclerotic properties, thanks to which it increases insulin sensitivity in muscle and liver, and reduces the concentration of fatty acids independent of plasma. It is thought to be inversely related to breast, endometrium, and stomach cancer. Another factor secreted from adipocytes is the vascular endothelial growth factor. Insulin, IGF1, estrogen, leptin, TNF-α, and hypoxia play a role in its secretion. The vascular endothelial growth factor is a proangiogenic factor and is important for angiogenesis, tumor development, and metastasis.[54,55]

Another condition that may play a role in the relationship between MetS and cancer is cytokines and prostaglandins. Cyclooxygenase-2 (COX-2) is noted as high in many types of cancer, including colon, breast, prostate, and pancreas. Increased prostaglandin; the inhibition of apoptosis is due to its stimulating effects on the increase during the stimulation of angiogenesis, inflammation, and conversion of procarcinogens into carcinogens. Overall, these characteristics suggest that COX-2 could be a promising target for cancer treatment.[55]

Metabolic Syndrome and Prostate Cancer

Prostate cancer is the second most common diagnosis of cancer in men and the fifth major cause of death worldwide. Prostate cancer can be asymptomatic at an early stage and usually has a constant route that may require only active surveillance. Global Cancer Observatory (GLOBOCAN) 2018 estimates that 1,276,106 new cases of prostate cancer have been reported worldwide in 2018 and higher prevalence has been obtained in developed countries. Differences in the worldwide incidence ratios reflect differences in the use of diagnostic tests. Prostate cancer is strongly related to age.[56,57]

African-American men have a higher incidence rate and more aggressive prostate cancer type than white men. Although there is insufficient evidence regarding the prevention of prostate cancer, it is suggested that the risk of developing this type of cancer can be reduced by adopting a healthier lifestyle. Specifically, limiting the intake of high-fat foods, increasing consumption of vegetables and fruits, and engaging in regular exercise are recommended. In addition, current statistics on prostate cancer formation and results, as well as a better understanding of etiology and precautionary risk factors, have a very important place in preventing this disease at the primary stage.[58]

Research indicates a link between MetS and prostate cancer; however, some studies suggest that certain individuals with MetS may have a reduced risk of developing prostate cancer. Although there is an established connection between cancer and obesity, it is still uncertain whether there is a conclusive association between prostate cancer and obesity. For example, in one study, the minimal risk of prostate cancer was found to be 1.05 for a 2-fold increase in BMI to 5 kg/m. And it has also been noted that there is a greater increase in individuals with advanced diseases. Of course, it has been noted in other studies that there is a positive relationship between obesity and advanced-stage or metastatic prostate cancer, and on the contrary, the risk of prostate cancer that has not metastasized decreases with weight loss. In contrast to the relationship between cancer and obesity, the link between diabetes and cancer has distinct characteristics. Publications show that the risk of prostate cancer is moderately low in male individuals with diabetes.[59-63]

Metabolic Syndrome and Breast Cancer

Breast cancer is caused by breast tissue. This means that when breast cells are mutated and form

a tumor, they're out of control. Like other cancers, breast cancer can penetrate and grow into the tissue surrounding the breast. It can also go to other parts of your body and create new tumors.[64]

Breast cancer is one of the most common among women, and the second cancer is skin cancer. It probably affects women over 50 years old. In rare cases, men can also have breast cancer. In the United States, about 2,600 men have breast cancer every year, which results in less than 1% of cases. Transgender women are more likely to develop breast cancer than men. In addition, transgender males are less likely to develop breast cancer than drizzle women.[65]

The data show a link between MetS components and insulin resistance and postmenopausal breast cancer. The components of MetS alone are indicated by a poor prognosis indicator. Studies have indicated that MetS is linked to breast cancer through several mechanisms. These include the production of extra-gonadal estrogen, increased estrogen bioavailability resulting from low levels of sex hormone-binding globulins, and the mitogenic effect triggered by insulin resistance and hyperinsulinemia on neoplastic breast epithelial cells.[66-67]

Metabolic Syndrome and Colorectal Cancer

Colorectal cancer is a type of cancer that begins as a tumor or tissue growth in the inner lining of the rectum or colon and develops slowly. If this abnormal growth, known as polyps, eventually becomes cancerous tissue, it can form a tumor in the wall of the rectum or colon, and then develop into blood vessels or lymph vessels and metastasize to other tissues. The vast majority (more than 95%) of cancers that start in the colorectal region are classified as adenocarcinomas. These begin in the mucus-making glands that cover the colon and rectum. Other less common cancers of the colorectal region are carcinoid tumors, gastrointestinal stromal tumors, lymphomas, and sarcomas.[68-69]

Epidemiological studies indicate that the risk of colorectal cancer and adenoma is increased in MetS patients. A study involving about 370,000 patients found that the risk of colon cancer is increased, especially in men with a high BMI index and overweight. An increase in waist circumference again increases the risk of cancer in both women and men. Apart from these studies, a study called "Health Studies of Physicians" states that the risk of colorectal cancer in individuals with two or more MetS components is approximately 1.5 times higher than in healthy individuals. In particular, this increase has been reported to be greater in diabetes and obesity.[70,71]

Research suggests that the association between MetS and cancer is stronger in males compared to females. In this study, researchers examined the relationship of MetS and its components with colorectal cancer and noted a direct link with both colon and rectal cancer in males alone. It is thought that the reason why the risk of colorectal cancer is higher in men with MetS than in women may be due to the different rates of fat distribution in the male and female bodies.[72,73]

Metabolic Syndrome and Pancreatic Cancer

Pancreatic cancer are one of the deadliest types of cancer, characterized by an increasing incidence in Western industrialized countries. The Global Burden of Disease report showed that the number of deaths from pancreatic cancer worldwide has increased by a factor, from 196,000 in 1990 to 441,000 in 2017. Pancreatic cancer is more common in men than women and is predicted to continue to be the leading cause of cancer deaths within the next decade. Due to poor survival and limited treatment options, pancreatic cancer poses significant challenges for clinical medicine and public health.[74,75]

To date, several risk factors have been identified for pancreatic cancer, such as male sex, advancing age, family history of chronic pancreatitis, genetic mutation, DM, non-O blood group, and smoking. Occupational exposures, obesity, alcohol consumption, a high-fat diet, and possibly hepatitis B virus and helicobacter pylori infections and periodontal disease, but the etiology of pancreatic cancer cannot be fully explained by these factors and further research is needed.[76]

Metabolic syndrome is a cluster of metabolic disorders such as central obesity, hypertension, decreased levels of HDL, cholesterol, high triglyceride levels, and insulin resistance. Epidemiological studies have shown that MetS and its components, independently or in combination, can increase the risk of many types of cancer, such as liver, endometrial, kidney cell, breast, prostate, and colon cancer. There has been some association between the MetS components and the development of pancreatic cancer. Metabolic syndrome is estimated to increase the risk of pancreatic cancer by 55%.[77,78]

Despite some results from previous research, a few questions remain unclear. First, there are inconsistent findings regarding the critical MetS component that

may be associated with the risk of pancreatic cancer. For example, Johansen et al.[78] suggest that in a prospective analysis of more than 500,000 people with MetS, the risk of pancreatic cancer is increased in individuals with high blood pressure. Second, previous studies often focus on the separate or combined effect of its components. Since the MetS components are highly related, it is not known whether their effects on pancreatic cancer risk are independent and which is the dominant factor. Third, it is suggested that certain MetS components may have an association with specific cancer risks, such as waist circumference and primary liver cancer.[80,81]

However, nonlinear relationships between MetS components and pancreatic cancer risk have rarely been investigated. Finally, MetS is highly associated with the C-reactive protein (CRP), which was previously recommended as a component of MetS. Circulating CRP is a cell compound that also acts as a sensitive biochemical indicator for assessing the changing inflammatory state in disease conditions such as DM and obesity. Previous studies have found that patients with various types of cancer have higher levels of CRP compared to healthy patients. They also suggested that high CRP may play a causal role in carcinogenesis. While the link between the MetS and cancer is, at least in part, associated with inflammation, the supposed co-effect of the MetS and CRP for pancreatic cancer risk is unknown.[82,83]

In conclusion, serious morbidity and mortality develop in the human body due to its components in the following processes. The relationship between MetS and cancer is caused by five components and these five components consist of the contents of MetS: abdominal obesity, hyperglycemia, high blood pressure, hypertriglyceridemia, and low HDL levels. As highlighted in the article, there is a positive correlation between the various components of MetS and the majority of cancer types. Some types of cancer are more common in men than in women. However, female individuals with MetS also have a higher cancer risk than healthy individuals. Many of the studies carried out support this thesis.

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