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The relationship between obesity and the pathophysiology of gastrointestinal cancer, nutrition and the intestinal microbiota

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Authors

Hamilton Roberto M. de Oliveira Carriço[1], Jaqueline de Carvalho Ferreira[2], Giovana Casarini Yamashiro[2], Breno Freitas M. Cristino[2], Diógenes T. da Silva Oliveira[3], Délio Tiago M. Malaquias[3], Thales Corrêa de Oliveira[4], Gabriel Queiroz Sabbag[5], Laura Pontieri Biasotti[5], Alysson Corrêa A. Oliveira[5], Priscilla dos Santos D. Montalvão[6], Pâmela Christinny F.Viêra[7], Rubens Rodrigues Tudela[8], Aline Cristina C. da Silva[3], Gianluca França C. Sganzella[3], Rogério Leite dos Santos[3], Jenyffer Victoria C. Villca[3], Hannah Kamarowski Fontana[3], Lucas Fernandes T. de Syllos[3], Ana Laura Nogueira Ervilha[3], Daniella Campos Furtado[3], Giovana Rocha Victorello[3], Ana Clara Pavaneli R. De Souza[3], Luana Mara de Lima[3], Rafaela Del Grosso Reis[3], Erica Miriam Fernandes M. Vão[3], Sadrak Horácio Cassoma[3], Elisitt Escarlet V. Cabrera[3], Luiza Goulart B. Bustamante[3], Viviane Ferrari Gomes[3], Thales Corrêa de Oliveira[3], Lucimara Pigaiani[3], José Vinícius Bicho dos Reis[3], Charles do Nascimento M. Júnior[9], Pedro Dias Bezerra Neto[10], Juliana Fontes B. Paschoal[3-11] and Thiago Augusto R. Bezerra[3-12]

Affiliations

[1] UNISUL. Santa Catarina, Brazil.
[2] Nove de Julho University. São Paulo, Brazil.
[3] UNAERP, São Paulo, Brazil.
[4] UNIPTAN, Minas Gerais, Brazil.
[5] São Leopoldo Mandic, São Paulo, Brazil.
[6] UniEvangelica, Santa Casa de Misericórdia de Goiânia. Goiás, Brazil.
[7] ITPAC, Porto Nacional. Tocantins, Brazil.
[8] São Judas College. São Paulo, Brazil.
[9] UNOESTE, São Paulo, Brazil.
[10] Potiguar University. Rio grande do Norte, Brazil.
[11] University of São Paulo, São Paulo, Brazil.
[12] Faculty of Medicine from Ribeirão Preto, São Paulo, Brazil.

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ABSTRACT
Introduction: Obesity is linked to some types of cancer, such as those of the gastrointestinal tract (esophageal, liver, gallbladder, stomach, pancreas and colorectal cancer), ovary and thyroid. Objective: to describe the association of the main factors related to the relationship between obesity and the pathophysiology of gastrointestinal cancer, nutrition and the intestinal microbiota. Material and Methods: This article is a systematic review, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology. Results and Discussion: Obesity increases the concentrations of insulin, IGF1 and IGF2, which in turn reduce apoptosis and stimulate cell growth. With increased adiposity, there is also an increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), tumor necrosis factor (TNF) and C-reactive protein. Conclusion: Given the evidence presented in this study, it is observed that expanding adipose tissue may have a clinically relevant contribution to the development of gastric cancer. A greater understanding of the mechanisms of obesity-induced carcinogenesis is needed to develop methods to prevent or treat gastric cancer. A greater understanding of the molecular mechanisms present in obesity may lead to the identification of new therapeutic targets.

Keywords: Gastric Cancer and Obesity, Intestinal Microbiota, Obesity-Induced Carcinogenesis.

INTRODUCTION

A study released with data from 2022 shows that more than one billion people live with obesity in the world. Obesity among adults has more than doubled since 1990 and quadrupled among children and adolescents (5 to 19 years old). The data also shows that 43% of adults will be overweight in 2022 [1].

Obesity is a complex chronic disease. The causes, as well as the interventions needed to contain the crisis, are backed up by strong evidence. However, they are not implemented. At the World Health Assembly in 2022, member states adopted the World Health Organization's (WHO) Acceleration Plan to end obesity, which supports action at national level by 2030. So far, 31 governments are leading the way in curbing the obesity epidemic by implementing the plan [2-4].

The most worrying statistic is the staggering number of obese people worldwide - approximately one in eight of the planet's inhabitants, amounting to around 12.5% of the global population. This statistic goes beyond an aesthetic concern, as it is closely linked to a series of serious illnesses, such as diabetes, cardiovascular disease, cancer and even early death [1-5].

Between 1990 and 2022, while the global population grew by 51%, the number of obese people grew by an alarming 360%, jumping from 221 million to 1.04 billion today. A crucial detail is that of this total, 159 million are children and adolescents, indicating a worrying trend of increasing obesity in this age group [2-6].

The prevalence of obesity among adults has risen in practically every country, doubling on average among women and tripling among men. This trend has also affected children and adolescents, with a fourfold increase in the 5-19 age group. At the same time, there has been a significant reduction in the number of underweight people, while overweight has emerged as the main problem of malnutrition worldwide [7].

In Brazil, there is an intermediate situation regarding obesity, although the proportion of people affected is significantly higher than the global average. In recent decades, the country has witnessed a worrying advance in weight gain, reflected in the obesity statistics for children, adolescents and adults [6].

In 1990, the rate of obese children and adolescents was 3.1% for both sexes. However, by 2022, these figures had risen to 14.3% among girls and 17.1% among boys. Among adults, the prevalence of obesity has also grown significantly, from 11.9% to 32% among women and from 5.8% to 25% among men [1-3].

Brazil is currently ranked 54th in the world for childhood obesity and 65th among countries with the highest prevalence of obesity among men and 70th among women. These figures highlight

the urgent need for policies and actions aimed at promoting healthy habits and preventing obesity in all age groups [1-3].

Science shows that obesity is linked to some types of cancer, such as those of the gastrointestinal tract (oesophageal, liver, gallbladder, stomach, pancreatic and colorectal cancer), ovary and thyroid, for example. With this concern, the WHO and the National Cancer Institute (INCA) have called attention to prevention measures [8].

This increased risk is due to abnormal cell proliferation. This cell division facilitates the appearance of compromised cells, which will become cancer in the future. In addition, there can be significant difficulties in screening patients who are overweight [8-10].

The vast scientific evidence, corroborated by the WHO's International Agency for Research on Gastric Cancer (CG), proves that excess body fat represents a risk for the development of at least 13 types of cancer, such as esophagus (adenocarcinoma), stomach (cardia), pancreas, gallbladder, liver, intestine (colon and rectum), kidneys, breast (postmenopausal women), ovary, endometrium, meningioma, thyroid and multiple myeloma [8-10].

Excess body fat causes a state of chronic inflammation and increases in the levels of certain hormones, which promote the growth of cancer cells, increasing the chances of developing the disease [9].

Obese patients have greater resistance to insulin, causing the body to produce a greater amount of the hormone, activating mechanisms that promote cell duplication, which can lead to the triggering of tumors [3].

OBJECTIVES

The aim of this study was to describe the association of the main factors related to the relationship between obesity and the pathophysiology of gastrointestinal cancer, nutrition and the intestinal microbiota.

MATERIAL AND METHODS

This article is a systematic review, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, which sought to identify the pathophysiology of obesity with the development of gastric adenocarcinoma and the nutritional impact on hospitalized patients.

A search strategy was developed based on the evaluation of an objective on the subject in question, which forms the basis of the study.

The search descriptors were selected by searching the Health Sciences Descriptors website (DeCS) and then combining them with the Boolean operator "AND".

The databases used for the search were: PubMed and the Virtual Health Library (VHL), which evaluated cross-sectional, cohort and case-control studies from 2010 to 2024, in Portuguese, English and Spanish.

In all, the result of the search in the databases using the descriptors, but without application of filters, resulted in 221 available articles. After applying the following filters, PubMed: search periods between 2010 and 2024, Portuguese, English and Spanish language and type of literature being a cross-sectional study. VHL: search periods between 2010 and 2024, Portuguese, English and Spanish language and type of literature being an observational study, a total of 65 articles were selected.

After pre-selecting the articles, a research protocol was created which clearly illustrated the aim of the study, the data collection process and the criteria involved in including the articles. After the analysis, 42 studies were excluded. Therefore, 25 articles were selected for this review.

RESULTS AND DISCUSSION

There is indisputable evidence that obesity increases the risk of cancer of the stomach, colon, rectum, bile ducts, pancreas, esophagus, breast, endometrium, ovary, kidney and multiple myeloma. In men, for every 5 kg/m2 increase in BMI, the risk of rectal cancer rises by 9% and biliary cancer by 56% [10].

Adipose tissue is an active endocrine organ and modulator of immune function, and is no longer considered an inert repository of stored fat. The main activities related to this tissue partly explain the relationship between obesity, metabolic syndrome, gastrointestinal disorders and cardiovascular disease. We can also highlight the role of adipose tissue in the homeostasis of the redox balance and inflammatory processes, and it can help produce pro-and anti-inflammatory cytokines [10].

Mesenteric adipose tissue, due to its recurrent association with gastrointestinal disorders, has a high correlation with hepatic steatosis, acute pancreatitis, gastrointestinal cancer and Crohn's disease [11].

Some authors suggest that the initial link between obesity and gastrointestinal disorders may be directly linked to insulin resistance [11].

It is known that the accumulation of intra-abdominal fat (central obesity) has a greater relationship with various diseases when compared to total body fat [11]. In addition,

computed tomography and magnetic resonance imaging are used as the gold standard for quantifying intraperitoneal fat and determining the waist-to-hip ratio used in clinical studies [12-14].

Gastric cancer (GC) is the fifth most common neoplasm and the third leading cause of cancer death worldwide. The most common histological type, accounting for around 90% of cases, is adenocarcinoma [12-14].

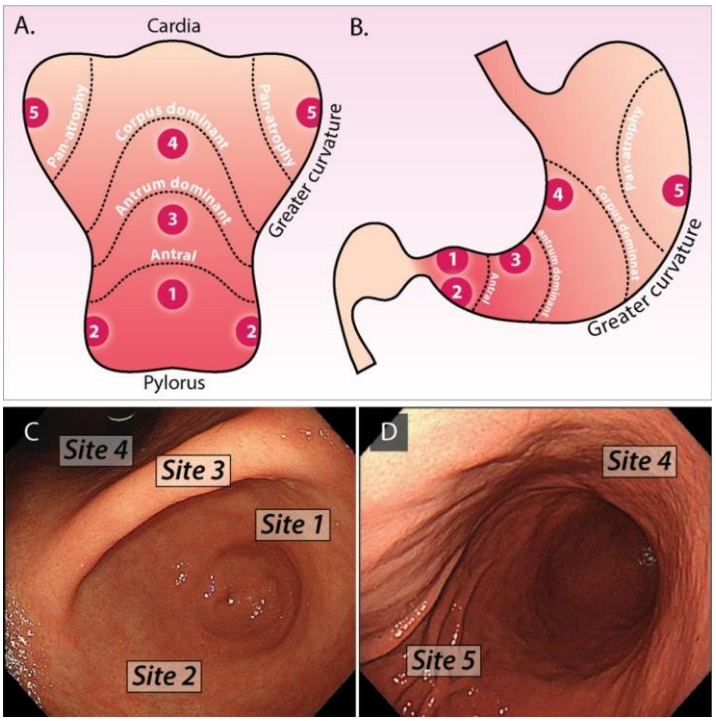
Gastric lymphomas, sarcomas, neuroendocrine tumors and other rarer tumors have different evolutionary potentials and treatments. Stomach cancer has a prognosis and treatment defined by the location and staging of the tumor and the number of resected and affected lymph nodes. Several studies have shown that more than 50% of patients with early cancer can be cured when they are completely resected [12-14].

The peak incidence of stomach cancer is predominantly in men, around the age of 60 to 70 [10].

Gastric cancer is diagnosed by histopathology through biopsy, but in most cases the disease is diagnosed late. This is due to the confusion of its symptoms with other diseases, which ends up compromising the prognosis [13].

The Kimura-Takemot classification is one of the most widely used for modified staging involving only the antrum (antral), antrum to incisure (dominant antral), antrum to minor curve (dominant body) and antrum, minor curve and major curve (pan-atrophy). This staging system integrates the biopsy system (FIGURE 1) [15].

Figure 1. Modified Kimura staging system divides the extent of atrophy into antrum only (antral), antrum to notch (antral dominant), antrum to lesser curve (body dominant) and antrum, lesser curve and greater curve (pan-atrophy). This system integrates biopsies from the Sydney protocol that must be taken from the antrum (sites 1 and 2), notch (site 3), lesser curve (site 4) and greater curve (site 5). The anatomical boundaries of the CAG and the biopsy sites can be seen in the open (A) and cross-sectional (B) drawing of the stomach. The biopsy sites defined in the endoscopic retroflex (C) and frontal (D) view Source: (BANKS et.al, 2019).



With regard to gastric cancer, 75% of the articles emphasized the various factors considered to be modifiable in the process of gastric carcinogenesis, including smoking, alcohol abuse, obesity, high sodium intake, a sedentary lifestyle, a low intake of vegetables and fruit and a high intake of red meat. These risk factors often occur together, aggravating the situation. On the other hand, maintaining a healthy lifestyle has a lower risk of developing this malignancy [9-19].

One study found a strong association between smoking and gastric cancer. Current smokers have an approximately 60% higher chance of developing gastric cancer than those who have never smoked. This is because tobacco carcinogens both directly attack the gastric mucosa and favor the persistence of H. pylori, reducing the effectiveness of eradication therapy[14].

A more recent analysis carried out by the International Agency for Research on Cancer (IARC) in 2017 identified smoking as a group I carcinogen, i.e. highly potential. A cigarette not only contains more than 70 known carcinogens, including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons, but also a high level of nicotine. It is known that nicotine is responsible for activating nicotinic acetylcholine receptors and inducing cell proliferation in gastric cancer lines by positively regulating cyclooxygenase [16].

GC is still a challenging disease, as it remains one of the main causes of death from neoplasms. The presence of insidious or even asymptomatic lesions contributes to the high number of diagnoses in advanced stages of the disease, compromising treatment [13].

Obesity is a pathological condition in which adipose tissue undergoes massive expansion, mainly due to adipocyte hypertrophy which impairs tissue blood circulation, leading to hypoxia, inflammation and fibrosis. In addition, the pathological accumulation of tissue fat is associated with increased cellular oxidative metabolism and malfunctioning of the protein unfolding response, which impairs the main functions of adipocytes in regulating lipid storage and the secretion of adipokines [5].

The possible pathophysiological mechanisms responsible for the association between obesity and cancer include the distribution of body fat, the inflammatory process, immunological alterations, cellular oxidative stress, nutritional alterations, dysbiosis and alterations in hormonal patterns, involving the Insulin-IGF axis and steroid hormones, adipokines produced in visceral adipose tissue. This set of factors promotes insulin resistance and increased insulin production by the pancreas to compensate for glucose metabolism [16].

Endocrine, immunological and metabolic alterations favor tumor growth through their mitogenic, anti-apoptotic and angiogenic effects, acting directly on tissues or indirectly through changes in body metabolism [17].

However, explanations of these associations and pathophysiological mechanisms are still scarce. It is important to note that hyperinsulinemia reduces the production of IGFBP-1 (Insulin-like Growth Factor Binding Pro-teins) and IGFBP-2, which normally bind to Insulin-like Growth Factor-1 (IGF-1-Insulin-like Growth Factor-1) inhibiting its action, thus increasing the levels of free, bioactive IGF-1. This somatomedin, together with insulin, binds to its receptors, resulting in the phosphorylation of IRS proteins, which activate the intracellular signaling cascade, represented by the phosphoinositol-3-kinase (PI3K-Akt) and mitogen-activated protein kinase (MAP kinase or MAPK) pathways, both involved in the process of carcinogenesis [15].

However, obesity is known to increase the risk of gastroesophageal reflux and peripheral insulin resistance. It also has high levels of adiponectin and leptin, sex steroids, glucocorticoids, inflammatory mediators and the presence of insulin-like growth factors[19]. The result is oxidative stress and neoplastic transformation of gastric cells[14].

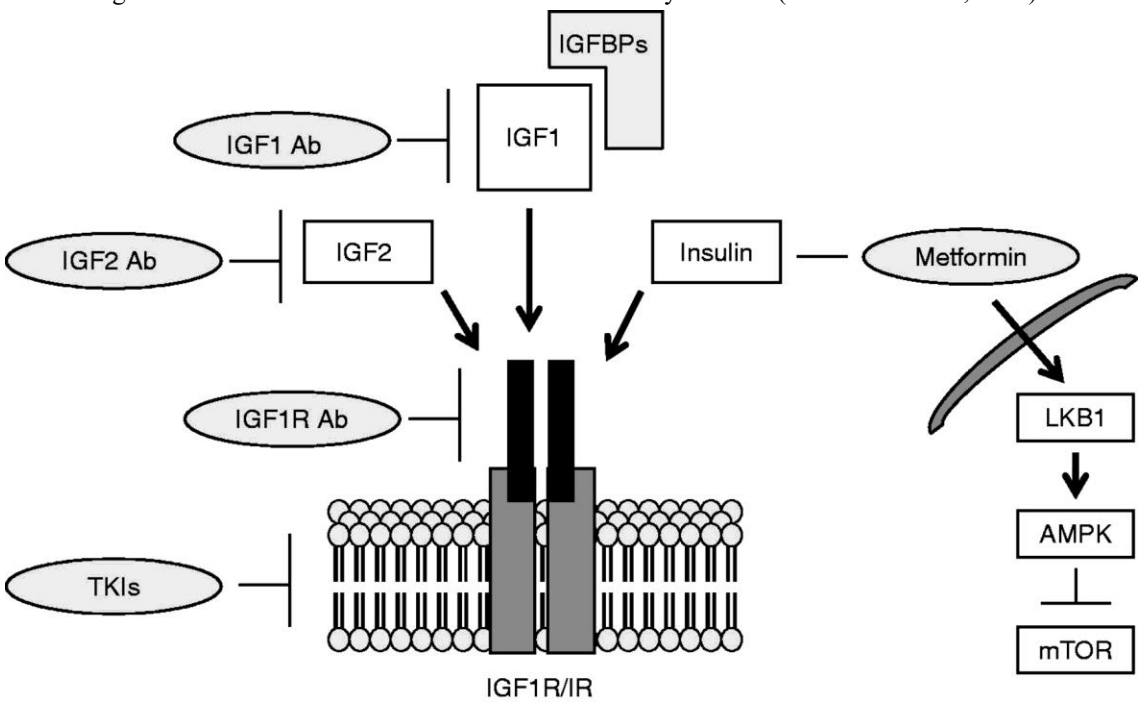
Adipose tissue is the main site of peripheral estrogen synthesis. Obesity causes an increase in the production and circulation of active free estrogens, mainly estradiol, androgens and

testosterone, and a reduction in levels of sex hormone-binding globulin. Estradiol increases sensitivity to insulin receptors and insulin-like growth factor (IGF)[20].

Obesity increases concentrations of insulin, IGF1 and IGF2, which in turn reduce apoptosis and stimulate cell growth. Increased adiposity also increases the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), tumor necrosis factor (TNF) and C-reactive protein [21].

A Schematic representation of anticancer therapies targeting insulin and IGF1 signaling. IGF1 and IGF2 bind to IGF1R (FIGURE 2). Monoclonal antibodies targeting IGF1 and IGF2 have been developed and prevent IGFs from interacting with IGF1R. Monoclonal antibodies have also been developed that block IGF1R, thus preventing the binding of insulin and IGF1 [21].

Figure 2. Metabolic endocrine factors related to obesity. Source: (ALIMOVA et.al, 2019).



Therefore, the adipocytes of visceral fat form an active endocrine organ that secretes adipokines such as adiponectin. Adiponectin increases insulin sensitivity and can have an anti-inflammatory and anti-cancer effect. It also has antiproliferative and angiogenic effects. Many cancers express adiponectin receptors, including gastric tumors [22].

The state of hyperinsulinism could be responsible for the stimulation of β-catenin, an early signaling pathway in neoplasms, which promotes the inhibition of glycogen synthase 3β and the activation of Ras-MAPK oncogenes, as well as inducing the proteolysis of IGFBP-3, which could

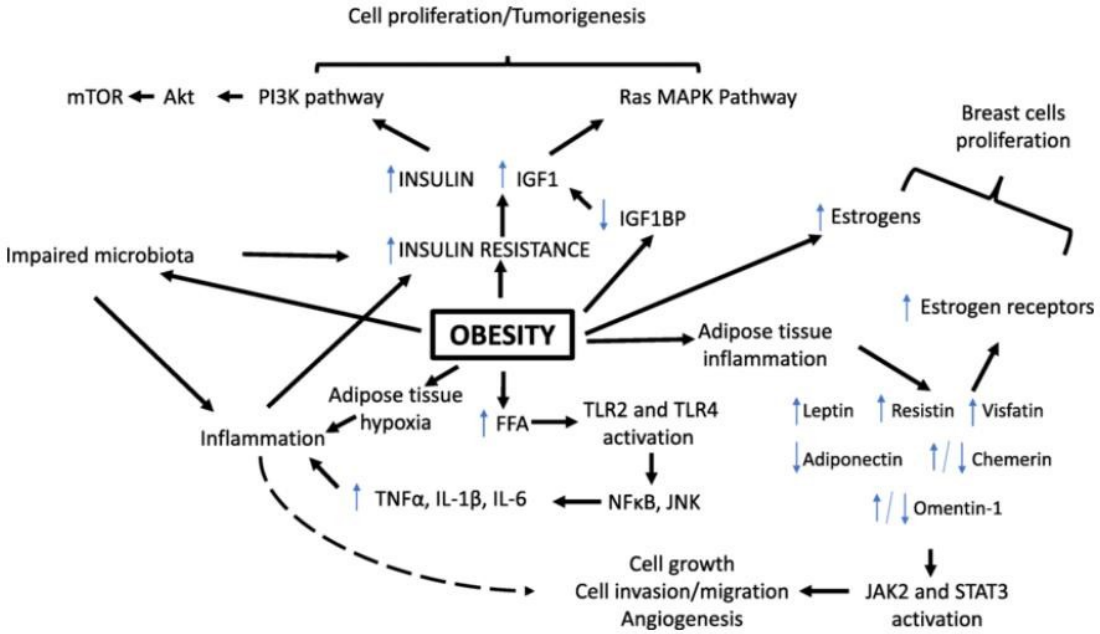
reduce the affinity of IGF-1 to IGFBP-3 fragments, increasing the release of free IGF-11. Exogenous stimulation of gastric cancer cells related to IGF1 and IGF2 leads to cell proliferation, indicating that the IGF system is active and may play a significant role in the pathophysiology and tumorigenesis of gastric neoplasia [17-19].

The IGF-IGFR-IGFBP axis consists of ligands, IGF1 insulin or IGF2 binds to IGF1R (a receptor tyrosine kinase) and activates signaling through the insulin receptor substrate (IRS) to regulate cell proliferation or cell cycle survival and progression. Most of the known actions of IGFs are exerted through their binding to the type 1 receptor (IGF-1R), while the physiological role of the type 2 receptor (IGF-2R) is still unclear. There are indications that the IGF-2R may participate in the removal of IGF-2 from the extracellular environment. Thus, multiple signaling pathways, including the phosphoinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAP kinase) pathways, are activated by the interaction between IGFs and their receptors. These pathways are involved in glucose transportation, regulation of glycogen synthesis and a variety of cell survival regulators, as well as inhibition of apoptosis [24].

IGF1 stimulates cell division and inhibits apoptosis, and may therefore contribute to the development and metastasis of cancer [25].

The main pathophysiological mechanisms of the association between obesity and gastric cancer are diagrammed below in FIGURE 3.

Figure 3. Pathophysiological mechanisms linking obesity and cancer. Source: (GALLO et.al, 2021).



Obesity is associated with chronic low-grade inflammation (also called meta-inflammation), characterized by abnormal cytokine production, immune activation and increased inflammatory signalling [2].

The pro-inflammatory cytokines expressed in obesity are considered to be the link between obesity and inflammation. Adipose tissue responds to the stimulation of extra nutrients via hyperplasia and hypertrophy of adipocytes. With adipocyte hypertrophy, adipose tissue becomes hypoperfused, which creates areas of microhypoxia, activating immune cells, especially through the NFkB nuclear transcription factor pathway, increasing the expression of genes involved in inflammation with greater release of cytokines and recruitment of macrophages to the damaged tissue [25].

Regarding nutritional aspects, the hormone ghrelin plays a role in appetite regulation, fatty acid metabolism and promotes fat storage. It has been found to be closely associated with the risk of gastric cancer and esophageal adenocarcinoma [22].

Resistin (RES) is a peptide found in high levels in obese people and is considered a pro-inflammatory molecule that is related to diabetes complications, and is also involved in adipocyte proliferation and angiogenesis. Thus, ghrelin is involved in the inflammatory process as it is a strong regulator of the cellular secretion of IL-6 and TNF-α through the activation of nuclear factor kappa B (NF- kB) [20].

There is a correlation between the carcinogenic potential of carbohydrate-rich foods and the exposure of the gastric mucosa to these foods, which can induce a stage of chronic gastritis. When chronic gastritis is left untreated, nitrosamines are formed, which have carcinogenic activity and can progress to the development of gastric carcinoma. These are the main nutritional risk factors that can contribute to the development of gastric cancer [25].

Several factors can trigger the inflammatory response in adipose tissue under conditions of nutritional overload, including hypoxia, cellular oxidative stress and cellular activation by saturated fatty acids, through a mechanism dependent on the activation of Toll-like receptor 4 (TLR4) [25].

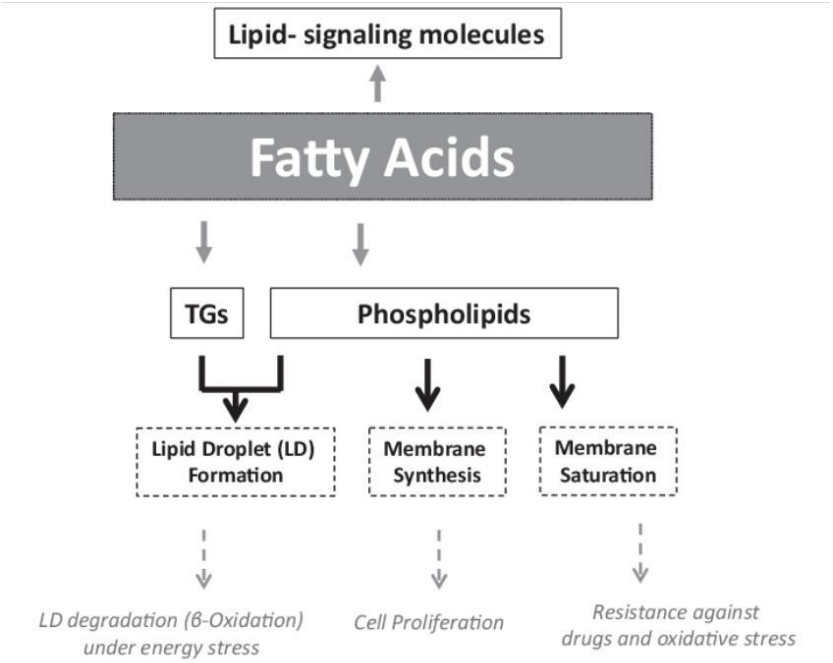
TLR4 is a member of a family of antigenic molecular pattern recognition receptors present in different human cells and tissues and involved in the innate immune response. Studies have shown that saturated fatty acids can also activate TLR4. Thus, this activation mechanism has been considered an important link between inflammation and insulin resistance in conditions of obesity and nutritional overload [25].

Thus, the activation of the inflammatory response by nutritional overload can become a promoting factor for the development of insulin resistance and, consequently, adipose tissue dysfunction [5-10].

Fatty acids modulate the growth of cells in the gastrointestinal mucosa and can induce DNA damage46 and contribute to the initiation and progression of the development of various types of cancer4. The main contributions of fatty acids to the development of gastric cancer [5-10].

On the other hand, N-3 polyunsaturated fatty acids (FIGURE 4) have the ability to suppress the production of pro-inflammatory cytokines in GC patients. Another protective aspect is the Mediterranean diet, characterized by increased consumption of olive oil, which can prevent gastric cancer [17].

Figure 4. Fatty acids promote several aspects of tumor cell development, progression, and survival. Fatty acids provide cancer cells with membrane building blocks, signaling molecules, and energy sources that support their rapid proliferation and survival. Source: (NOUSHEEN et.al, 2013).



It is a fact that the preservatives added to sausages contribute to the appearance of gastrointestinal malignancies, because when they reach the stomach they are transformed into nitrosamines, carcinogenic substances responsible for cellular alterations that can lead to the development of cancer. Smoked meats contain polycyclic aromatic hydrocarbons and tar, which are known carcinogens[14-17].

It is known that nutrition can affect the gut microbiota and microbiome, which largely contributes to systemic diseases. Thus, dysbiosis, an imbalance of the microbiome induced by diet, especially by high-fat foods, is associated with gastrointestinal malignancy [12].

Very little is known about the contribution of the intestinal microbiota to the development of digestive neoplasms. Enteric microorganisms can promote carcinogenesis by different mechanisms: 1) inducing inflammation; 2) increasing cell proliferation; 3) altering stem cell dynamics; 4) producing certain substances such as butyrate, which can affect DNA integrity and immune regulation [21-25].

The pathophysiology of obesity has been a key factor in understanding its relationship with various types of disease. It has already been shown that obesity is related to gastrointestinal diseases such as diarrhea, celiac disease, Crohn's disease, esophagitis and liver diseases (liver stones and non-alcoholic fatty liver disease) [21-25].

In addition, adiposity, diabetes mellitus and certain lifestyle factors have been shown to be associated with gastroesophageal reflux disease [21-25].

The state of tissue inflammation, known as lipoinflammation, releases inflammatory factors into the circulation that can migrate to other tissues, generating alterations in them and giving rise to a low-grade systemic inflammatory condition. At the same time as altering angiogenesis, it represents a scenario of hypoxia and alteration of the extracellular matrix (inflammatory fibrosis), which further aggravates the condition[25].

Obesity is considered a significant risk factor in the development of reflux esophagitis and gallstones [21-25].

The organs that make up the gastrointestinal system, such as the esophagus, stomach, intestines and liver, suffer more acutely from the chemical and cellular changes that occur in obese patients. The esophageal transit time is significantly prolonged in obese individuals, compared to lean individuals, and these changes can be attributed to increased gastric and gastroesophageal junction resistance and intra-abdominal pressure [20].

Obesity is associated with gastroesophageal reflux disease (GERD) and its complications, including reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma. These associations have been attributed to the mechanical effect of abdominal fat in increasing intra-abdominal pressure, thus promoting gastroesophageal reflux and causing disruption of the anti-reflux mechanisms at the esophagogastric junction[20].

It is also suggested that visceral adipose tissue produces numerous cytokines that can cause esophageal inflammation and impair the integrity of the esophageal mucosal barrier through

reflux-independent mechanisms that make the esophageal mucosa especially susceptible to GERD-induced lesions[20].

CONCLUSION

It is extremely important to know the risk factors related to lifestyle and their mechanisms in the process of gastric carcinogenesis, most of which can be modified. The study showed that there is a close relationship between bad habits and customs, as well as the intake of some types of food, with the development and worse prognosis of gastric cancer.

Obesity is among the fastest growing diseases in the world, treatment is inadequate and associated disorders, including gastric cancer, have high morbidity and mortality. The possible mechanisms responsible for the association between obesity and cancer include the distribution of body fat and changes in hormonal patterns, involving the Insulin-IGF axis, estrogens and progesterone, adipokines and cytokines produced in visceral adipose tissue.

Given the evidence presented in this study, it is observed that expanding adipose tissue may have a clinically relevant contribution to the development of gastric cancer. A greater understanding of the mechanisms of obesity-induced carcinogenesis is needed to develop methods to prevent or treat gastric cancer. A greater understanding of the molecular mechanisms present in obesity may lead to the identification of new therapeutic targets.

The study of the factors that relate obesity to the carcinogenesis of this neoplasm can provide future support for more effective therapies for GC, as well as providing new measures aimed at prevention to modify the natural history of gastric adenocarcinoma, as this neoplasm still presents high morbidity and mortality rates, due to its absent or non-specific clinical features and late diagnosis.

Therefore, greater attention is needed to prevent risk factors, especially obesity. Given the lack of current effective therapies for weight control or reduction other than bariatric surgery, research and clinical efforts will focus on the connections between increased adipose cell mass and gastrointestinal carcinogenesis. Additional studies of the hormonal, inflammatory, genetic, and dietary factors that contribute to the development and progression of gastric cancer will help us understand the role of obesity in these processes.

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