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Study on the Correlation between Metabolic Syndrome and Colorectal

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Abstract

Metabolic syndrome has been widely recognized in various studies as being intricately linked to the initiation and progression of colorectal adenoma. The potential pathways through which metabolic syndrome influences colorectal adenoma encompass chronic inflammation, insulin resistance, oxidative stress, and dysbiosis of the intestinal flora. This review aims to consolidate the understanding of the association between metabolic syndrome and colorectal adenoma, elucidating the interconnected mechanisms between different metabolic syndrome-related disorders and colorectal adenoma. By shedding light on these connections, this review offers valuable insights for the preventive strategies targeting colorectal adenoma.

Keywords

Metabolic Syndrome, Obesity, Hypertension, Lipid Disorders, Colorectal Adenoma, Colorectal Cancer

1. Introduction

Colorectal cancer (CRC) is a common cancer worldwide, ranking among the top three malignant tumors in terms of incidence. It is a leading cause of cancer-related deaths globally, with increasing rates year by year [1]. In China, the incidence and mortality rates of CRC have been escalating each year, correlating with the country's rapid economic growth and dietary changes. Currently, CRC is the third most prevalent malignant tumor and the fourth leading cause of cancer-related deaths in China [2]. Research indicates that 75% to 80% of colorectal cancers evolve from common colorectal adenoma (CRA) via the "adenoma-carcinoma" sequence [3]. The pathogenesis of colorectal adenoma is com-

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plex, and numerous studies have established a correlation between metabolic syndrome (MS) components and the development of adenomatous polyps [4] [5]. To aid in early detection and prevention of colorectal cancer, this review will examine the influence of adenomatous polyps and metabolic syndrome, as well as their various components, to elucidate potential mechanisms underlying their occurrence and progression and assess their clinical significance.

2. The Relationship between Metabolic Syndrome and Colorectal Adenoma

Metabolic syndrome (MS) encompasses a group of metabolic disorders characterized by abdominal obesity, abnormal glucose metabolism, hypertension, and dyslipidemia. These disorders not only involve various risk factors but are also intricately connected to the body's pathophysiological mechanisms. Key mechanisms potentially involved in MS include insulin resistance, leptin and adiponectin imbalances, alterations in intestinal flora, and a low-grade pro-inflammatory and oxidative physiological status [6]. Insulin resistance serves as a central feature of MS, modulating cell growth and differentiation via the phosphatidylinositol 3-kinase-AKT-mammaliantarget of rapamycin pathway and the Ras-Raf-MEK-mitogen-activated protein kinase pathway, thereby playing a mediating role in tumor formation [7]. Leptin has been found to promote cell proliferation, potentially impacting colorectal adenoma development, whereas adiponectin reduces insulin resistance and suppresses leptin action; diminished adiponectin levels have been associated with an increased incidence of colorectal adenoma [8]. Persistent chronic inflammation in MS patients [9], triggered by changes in intestinal flora, can lead to inflammatory responses and insulin resistance [10]. These alterations in intestinal flora and chronic inflammation are recognized risk factors for colorectal adenoma [11] [12]. Numerous studies have demonstrated the association between MS components and colorectal adenoma. For instance, Esposito K *et al.* conducted a meta-analysis in 2013, which revealed that any single component of MS, such as a high body mass index (BMI) or waist circumference (WC), or hyperglycemia, was linked to a higher risk of colorectal cancer [13]. Furthermore, a retrospective study performed by Yue Liu *et al.* on 4514 patients using univariate and multivariate logistic regression analysis confirmed that MS is an independent risk factor for colorectal polyps and adenoma [14]. In addition, a case-control study conducted by Naomi Fliss-Isakov on 828 subjects aged 40 to 70 years who underwent screening or diagnostic colonoscopy showed that abdominal obesity (OR = 1.67, 95% CI: 1.20 - 2.30), high blood pressure (OR = 1.47, 95% CI: 1.03 - 2.09), and elevated glycohemoglobin (HbA1c%) (OR = 1.57, 95% CI: 1.06 - 2.34) were independently associated with colorectal adenoma. Furthermore, the triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio was independently associated with serrated polyps (OR = 2.31, 95% CI: 1.32 - 4.03) [15]. This study highlighted that the combination of three metabolic alterations is closely associated

with colorectal polyps. Similarly, studies by Jeong Hwan Kim *et al.* found that metabolic syndrome is linked to colorectal adenoma, with abdominal obesity among the various MS components identified as a significant risk factor for colorectal adenoma [16].

3. The Link Mechanism of Metabolic Syndrome Diseases and Colorectal Adenoma

3.1. Linkage Mechanism between Obesity and Colorectal Adenoma

Obesity, (particularly central obesity), has been associated with an increased risk of colorectal adenoma development [17]. Domestic studies by Liu Yang *et al.* have reported that obese individuals are more likely to develop colon polyps and face a higher risk of cancer [18]. In a study conducted by Comstock *et al.*, colonoscopies performed on 128 asymptomatic men revealed that those with a BMI of 25 kg/m^2 were 6.5 times more likely to detect three or more polyps compared to men with a BMI of less than 25 kg/m^2. Additionally, obese individuals were found to have a higher prevalence of polyp-type adenomas [19]. Several mechanisms have been proposed to explain the increased risk of colorectal adenoma among obese individuals. Firstly, obesity is often accompanied by insulin resistance, manifesting as hyperinsulinemia. When insulin and its analogues bind to their corresponding receptors, they can promote colorectal epithelial proliferation and differentiation while inhibiting apoptosis. This process can induce the formation of adenomatous polyps, which may further progress to carcinogenesis [20]. Secondly, obesity is associated with a chronic inflammatory response. Long-term stimulation from this chronic inflammation can elevate the risk of developing colorectal adenomas [21]. Thirdly, increased adipose tissue in obese individuals has endocrine functions, secreting inflammatory factors and protein hormones, including tumor necrosis factor and leptin. These secretions create a favorable environment for precancerous lesions [22]. Research has specifically highlighted the role of leptin in promoting intestinal mucosal hyperplasia, which over time can contribute to the transformation of colorectal polyps into adenomas [23].

3.2. Linkage Mechanism between Type 2 Diabetes and Colorectal Adenoma

Type 2 diabetes, a prevalent chronic metabolic disease, not only affects large blood vessels, microvascular, and nervous system lesions but also significantly increases the risk of tumors [24]. Meta-analytic studies indicate a consensus that diabetes serves as an independent risk factor for the progression of colorectal polyps to colorectal cancer, increasing the risk of intestinal polyps by approximately 30% [25]. The development of colorectal adenomas in the context of high blood sugar levels is primarily associated with insulin resistance and hyperinsulinemia, which are critical elements in both type 2 diabetes and colo-

rectal cancer pathogenesis. Elevated insulin levels promote intestinal cell proliferation, differentiation, and migration through several signaling pathways, following the "hyperplasia-adenoma-cancer" sequence, thereby facilitating carcinogenesis [26]. During insulin resistance, there is a compensatory increase in the body's insulin level, leading to an enhanced synthesis of insulin-like growth factor binding protein (IGFBP) in vivo. Consequently, the content of insulin-like growth factor (IGF-1) increases. Upon the binding of IGF-1 to IGFBP, tyrosine kinase receptors are activated, ultimately participating in cell proliferation and differentiation through two signaling pathways: the PI3K/Akt pathway and MAPK/Ras pathway. Notably, heightened insulin levels not only impact metabolic pathways but also lead to the overstimulation of the pro-mitotic pathway, thereby promoting the excessive proliferation of tumor cells within the digestive system. The proliferative effect on epithelial cells is a critical factor in the development of colorectal malignancy [27]. Additionally, high insulin and IGF-1 levels activate the Ras system, which subsequently stimulates the mTOR and Wnt signaling pathways. This activation heightens the sensitivity of colorectal cells to growth factors, accelerating the transition from adenoma to carcinoma [28]. Furthermore, type 2 diabetes can induce gastrointestinal dysfunction, resulting in symptoms such as delayed gastric emptying, diarrhea, and constipation, which can prolong the exposure of colonic mucosa to potential carcinogens [29]. The compromised immune surveillance in patients with type 2 diabetes further elevates their susceptibility to developing colorectal adenomas [30]. Collectively, these factors underscore the heightened risk of colorectal cancer development in individuals with type 2 diabetes.

3.3. The Linkage Mechanism between Hypertension and Colorectal Adenoma

Many studies have shown that the sympathetic nervous system is a crucial factor in promoting the occurrence of hypertension. Activation of the β-adrenergic receptor (β-AR) signaling pathway leads to increased adrenaline levels and cellular sensitivity, which are believed to contribute to the progression and infiltration of various malignant tumors. Research indicates that the activation of the β-AR pathway is significant in the onset and advancement of colon cancer and breast cancer malignancy [31]. According to an animal experiment, catecholamine release can enhance tumor propensity in mice. This effect may be linked to catecholamines' ability to induce an oxidative stress response [32] [33]. Studies have also revealed that hypertension triggers a chronic inflammatory process by activating the renin-angiotensin system. In recent years, inflammation has been recognized as a key player in the development of colorectal adenomas and tumors [34]. Chronic inflammatory cells and factors are not only critical for the prognosis of colorectal malignant tumors but also closely associated with tumor cell proliferation, apoptosis, and metastasis in colorectal cancers [35]. Aspirin is commonly used as a prophylactic drug for precancerous lesions, with its an-

ti-inflammatory properties believed to be pivotal in its pharmacological action against tumors [36].

3.4. Mechanisms Linking Dyslipidemia with Colorectal Adenomas

The association mechanism between dyslipidemia and colorectal adenoma indicates that hyperlipidemia can increase the risk of colorectal adenoma. One potential factor is the elevation of blood lipid levels, which can raise bile acid levels in the body. These primary bile acids are converted to secondary bile acids by intestinal bacteria, and these secondary bile acids can activate proteins such as α-protein kinase C. The activation of α-protein kinase C may lead to the hyperplasia of intestinal mucosal cells, potentially progressing to polyp formation [37]. Additionally, hyperlipidemia, particularly elevated triglyceride levels, can enhance inflammation and increase peroxidation levels within the body [38]. This inflammation activates oxidative stress and reactive oxygen species, which may cause DNA structural damage, gene mutations, and chromosomal abnormalities, thereby impacting the growth, proliferation, and apoptosis of colorectal epithelial cells, potentially resulting in polyp formation. Rajnadas *et al.* have also suggested that abnormalities in apolipoprotein metabolism and the function of lipid metabolism enzymes such as COX and PLA2 can disrupt the differentiation balance of intestinal epithelial cells, leading to excessive hyperplasia and an increased incidence of polyps [39]. Furthermore, some scholars posit that insulin-like growth factor-1 (IGF-1), a cytokine that inhibits cell apoptosis and promotes cell proliferation, can stimulate the transition from adenoma to adenocarcinoma by upregulating the activity of the K-ras protein. Elevated triglycerides can promote the secretion of IGF-1, thereby contributing to this process [40].

4. Conclusion

Recent studies have increasingly shown a strong correlation between the metabolic syndrome and the development of colorectal adenomas. The underlying mechanisms by which metabolic syndrome affects colorectal adenoma progression include chronic inflammation, insulin resistance, oxidative stress and gut dysbiosis. These findings highlight the importance of lifestyle modifications such as a low-fat diet and regulation of gut microbiota in reducing colorectal adenomagenesis [41]. Furthermore, regular colonoscopy screening in high-risk groups is essential for the prevention and treatment of colorectal adenomas and tumors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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