Is diabetes a causal agent for colorectal cancer? Pathophysiological and molecular mechanisms

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Abstract

The possible relationship between diabetes mellitus (DM) and colorectal cancer (CRC), concerning pathophysiological and molecular mechanisms is highlighted in this review. The most recent and complete articles and developments in this particular field were thoroughly reviewed. Common risk factors, such as obesity, sedentary lifestyle, and Western diet between DM and CRC, led to the theory that DM might be a causal agent for CRC development. Various studies have connected type 2 DM and CRC, either proximal or distal, in both sexes. Additionally, chronic insulin treatment has been linked with increased colorectal tumor risk among type 2 diabetic patients. Interestingly, elevated hemoglobin A1c has been proven to be an independent predictor of aggressive clinical behavior in CRC patients. These mechanisms include the insulin-like growth factor-hyperinsulinemia theory and the participation of oncogenic intracellular signaling pathways. Furthermore, it has been proposed that Cox-2 inhibitors might have a role in decreasing the incidence of CRC. Finally, the use of statins to reduce the risk for colon cancer in patients with diabetes has remained controversial. Diabetic patients over 50 should receive counseling regarding their elevated risk for CRC, and screening colonoscopy should be recommended before initiating insulin therapy. However, there are no current guidelines, and this strategy is not yet applicable to some countries, as the corresponding risk would not allow screening colonoscopy to be adopted. There is strong evidence to indicate that DM is a causal agent for CRC development. This conclusion provides new impetus for re-evaluating CRC screening worldwide.

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Key words: Diabetes mellitus; Colorectal cancer; Molecular oncogenic pathways; Screening

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the Western world with 655,000 deaths per year[1]. In addition, the incidence of diabetes mellitus (DM) is increasing rapidly. In 2000, at least 171 million patients suffered from diabetes worldwide, and it is estimated that by the year 2030, the number will almost double[2]. Serious long-term complications of DM include cardiovascular, retinal, and nerve disease, along with chronic renal failure and high tendency for infections. Common etiologic factors including obesity, sedentary
lifestyle, and Western diet between these two widespread diseases, led to the hypothesis that there might be a connection between diabetes and CRC, rendering diabetes a causal agent for CRC.

Diabetes has been linked with ovarian[1], pancreatic[4-5], liver[3], renal[6], breast cancer[4], melanomas[6], and cancers of the urinary tract[8], stomach[7], cervix[7], and endometri-um[7]. Patients with type 1 and type 2 diabetes might be at an increased risk for cancer, but there is more evidence available for patients with type 2 diabetes[8]. As far as CRC is concerned, type 2 DM has also been linked with the aforementioned cancer.

**RELATIONSHIP BETWEEN DIABETES MELLITUS AND COLORECTAL CANCER**

Various studies have connected diabetes with men or women suffering from CRC, with proximal or distal CRC, or with both sexes and colorectal subsites. Part of these discrepancies might be attributed to different sample sizes, follow-up duration, inclusion/exclusion criteria of the studied population, classification systems, disease heterogeneity, or interplay between biological and environmental factors. A large retrospective study conducted in 2006 reported that there is a significantly elevated risk for proximal CRC in type 2 diabetic men, but no significant increase in risk for diabetic women[8]. Cigarette smoking has been reported to positively modify diabetes-associated CRC risk[9]. Moreover, CRC has been connected with type 2 diabetic men[6,10], diabetic women[11], or both sexes[12]. Interestingly, type 2 diabetes predisposes patients to an increased risk for proximal[6] or distal CRC[9], or both proximal and distal, colonic and rectal cancers[12]. Thus, the relationship between type 2 diabetes and CRC has been proposed and reported in several studies.

Chronic insulin therapy has been associated with an increased colorectal tumor risk among type 2 diabetic patients[13-14]. Specifically, a three-fold risk increase for patients with insulin-dependent type 2 DM in comparison to the general population has been observed[13]. On the other hand, there is limited information on the short and long term outcome for diabetic patients diagnosed with CRC. An association between the control of type 2 DM, as determined by the levels of hemoglobin A1c (HbA1c), has been examined. Elevated HbA1c has been proven to be an independent predictor of aggressive clinical behavior in patients with CRC. Siddiqui et al[8] reported that patients with poorly controlled type 2 DM have more right sided and advanced colorectal cancers, a younger age of presentation, greater use of exogenous insulin, and a poorer 5-year survival. Interestingly, neoadjuvant chemotherapy in rectal cancer is less effective in diabetic patients than in non-diabetics[17]. Nevertheless, according to a Norwegian study, diabetes does not seem to affect the short-term survival or the overall cancer-specific survival in patients with CRC. Indeed, the shorter overall survival in diabetic patients suffering from colorectal cancer in comparison to non-diabetics is attributed to cardiac diseases and higher age[18].

**PATHOPHYSIOLOGICAL AND MOLECULAR MECHANISMS**

Several pathophysiological mechanisms have been proposed to explain the possible relation between DM and CRC. The insulin-like growth factor (IGF-1)-hyperinsulinemia theory implies that elevated insulin and free IGF-1 levels support the proliferation of colon cells, thereby leading to a survival benefit, resulting in CRC[19]. In patients with type 2 DM, elevated insulin levels are present in an effort to overcome peripheral insulin resistance by increased insulin production. Moreover, hyperinsulinemia is further augmented by exogenous application of insulin. The aforementioned molecular model suggests that hyperinsulinemia, IGF-1, and the relative binding proteins play important roles in metabolism, cell growth, proliferation, and the regulation of apoptotic process in colon cells[8].

Thus, normal colon cells acquire neoplastic characteristics, displaying cancerous transformation.

The aforementioned theory supports the view that not only does insulin stimulate the growth of colon cells in vitro[20], but its proliferative effect is also mediated by insulin cognate and IGF-1 receptors[21]. It has been demonstrated that the epithelium of colon carcinoma cell lines shows an increased insulin receptor density in comparison to normal colon epithelium. Furthermore, insulin leads to increased bioavailability of IGF-1[22]. Insulin and IGF-1 signaling pathways either enhance proliferation, or inhibit apoptosis of colon epithelial cells, leading to carcinogenesis.

Oncogenic intracellular pathways mainly involving kinase neoplastic proteins [mitogen activated protein kinases, extracellular signal regulated kinase, phosphatidylinositol-3-kinase, protein kinase B and mammalian target of rapamycin (mTOR)] are activated[23] (Figure 1). However, there have been conflicting results concerning the link between IGF-1 and CRC, as there are studies both supporting and disputing this link[6]. In addition, the actions of insulin and IGF-1 are mediated by the activation of Ras, which may lead to increased sensitivity of colon cells to growth factors and accelerated progression from adenoma to carcinoma[24]. The time from adenoma formation to development of CRC is believed to be between 10 and 15 years[6].

Interestingly, insulin stimulates cell proliferation and c-Myc expression in various colon cancer cell lines, in the intestinal non-cancer cell line IEC-6, and in fetal rat intestinal cell cultures (Figure 1). The effects of insulin involve activation of the mTOR signaling pathway in combination with nuclear translocation of β-catenin, an effector of Wnt signaling (Figure 1). Hence, both Wnt and mTOR pathways participate in insulin-stimulated onco gene expression in intestinal cells[22,23]. Furthermore, it has been reported that insulin stimulates the phosphorylation and activation of p-21-activated protein kinase-1 (PAK-1) in an in vitro hyperinsulinemic mouse model, indicating that PAK-1 serves as an important link between insulin and Wnt signaling pathways, promoting intestinal carcinogenesis[24]. Finally,
the peroxisome proliferators-activated receptor-γ is associated with CRC, including insulin and inflammation related mechanisms, given its association with insulin, diabetes, obesity, and inflammation[24] (Figure 1).

Another possible molecular mechanism linking diabetes and CRC involves the hormone glucagon-like peptide-1 (GLP-1), secreted by the intestinal endocrine L cells, along with the participation of the Wnt signaling pathway and the oncogenes c-Myc and cyclin D1. Specifically, in type 2 diabetic patients, GLP-1 secretion is reduced, due to insulin resistance. Reduction of GLP-1 secretion causes compensatory activation of the Wnt pathway in combination with increased expression of proto-oncogenes, such as c-Myc, resulting in intestinal cell proliferation and, plausibly, CRC development[25]. Nevertheless, cross talk exists between individual oncogenic pathways, which regulate either apoptosis or survival of colon cells. Thus, the theory defined remains controversial, with several aspects requiring thorough investigation, further complicating the relationship between DM and CRC.

Slower bowel transit time is another appealing concept connecting diabetes and CRC. Patients with diabetes are more prone to suffer constipation (bowel movements less than once a day) and slower colonic transit times, possibly because of diabetic neuropathy affecting the intestine. Certain fecal contents are cancer promoting, such as bile acids, ammonium acetate, and fecapentaene-12[6]. Nevertheless, there is no epidemiological evidence that constipation is associated with CRC.

Risk factors such as sedentary lifestyle, obesity, Western diet, and the metabolic syndrome are common in both type 2 DM and CRC[27]. Obesity has a role in increased CRC risk of the diabetic population, because of a variety of factors including insulin resistance, increased inflammatory markers [interleukin (IL)-1, IL-6, tumor necrosis factor-α], and high levels of androgens and estrogens[6,27].

**PROPHYLAXIS FOR COLORECTAL CANCER**

Given the increased CRC risk in patients with type 2 DM, it would be reasonable to postulate that these patients might benefit from any potential prophylaxis against CRC. The use of potential chemoprotective agents, such as aspirin, non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase 2 (Cox-2) inhibitors, have been considered and investigated. The basis for applying these agents is that they inhibit the production of prostaglandins, which are inflammatory mediators participating in the formation and proliferation of cancers[28].

Data from two large randomized trials (the British Doctors Aspirin Trial and the UK-TIA Aspirin Trial) show that the use of high-dose aspirin (1200-300 mg/dL) for a minimum period of five years reduces the incidence of CRC[28]. However, applying both high-dose aspirin and...
NSAIDs over the long term is associated with gastrointestinal complications. Therefore, benefits and risks have to be considered on an individual basis. It would also be helpful to establish if smaller doses of aspirin could be effective for chemoprevention.

The association between Cox-2 expression, adenomatous polyps, and CRC has generated much interest. Specific Cox-2 inhibition might have a role, because colorectal adenomas and cancers show a higher than normal Cox-2 expression, which has been associated with worse survival.[28] Thus, Cox-2 inhibitors have been shown to decrease the incidence of CRC. The effects of Cox-2 inhibitors are regulated by inhibition of prostaglandin synthesis. Cox-2 and prostaglandins mediate resistance to apoptosis, modulate tumor angiogenesis, and increase metastatic potential in the intestine. These effects are controlled through prostaglandin E2 and the epidermal growth factor receptor. Although there is some evidence that Cox-2 inhibitors might reduce the incidence of CRC, the cardiovascular risk (acute myocardial infarction) outweighs the potential benefit.[29]

An interesting theory has been proposed recently, implicating homocysteine as the missing link between type 2 DM and CRC.[29]. Recent findings indicate that a high homocysteine level is a risk factor for developing DM. In addition, hyperhomocysteinemia is associated with aberrant methylation of DNA, which might lead to inactivation of tumor suppressor genes and CRC growth.[29]

Moreover, the use of statins has been associated with a small reduction in the risk for colon cancer in diabetic patients. However, the causal link is not clear[30]. There are also studies, which do not connect statins with a reduced risk of CRC in large cohorts of patients, indicating that long-term regular use of statins does not protect against CRC[31-34]. Nevertheless, the application of statins has been linked with a relative reduction in the CRC risk[30], along with a reduced risk for stage IV CRC[35]. Interestingly, simvastatin therapy results in inhibition of the release of IL-8 and IL-6 from colorectal cell lines. Hence, CRC risk is reduced because of decreased synthesis and release of the aforementioned proinflammatory cytokines by the tumor cells[36]. Thus, the conflicting results necessitate further investigation to elucidate this controversial topic.

PREVENTING COLORECTAL CANCER

A large number of epidemiological studies have demonstrated that the risk for CRC is increased in patients with type 2 DM. A recent meta-analysis showed that patients with type 2 DM have a 30% increased risk for CRC versus the general population and that this risk is doubled in patients treated with insulin. The increased risk correlates with the duration of insulin therapy and might be due to increased levels of insulin and free IGF-1. The increased risk in patients with type 2 DM treated with insulin is comparable to a positive family history.

A better way to prevent CRC in patients with type 2 DM is screening. Over the past decade, tests generally offered in screening guidelines include colonoscopy every 10 years, fecal occult blood testing (FOBT) annually, double contrast barium enema every five years, or flexible sigmoidoscopy every 5-10 years. Current guidelines in most Western countries recommend colonoscopy every 10 years, beginning at the age of 50 years for people with average risk, or alternatively screening with FOBT every year combined with flexible sigmoidoscopy every five years.

Most patients with type 2 DM will be over 50 at diagnosis and are eligible for screening according to screening guidelines. Diabetic patients over 50 should receive counseling regarding their elevated risk for CRC and screening colonoscopy should be recommended before initiating insulin therapy. In younger diabetic patients, the decision should be made individually and be based on the presence of other risk factors, such as smoking or previous insulin therapy. Bearing in mind that the action of insulin and IGF-1 is partly mediated by the activation of Ras, which might lead to accelerated progression from adenoma to carcinoma, screening intervals concerning the population with a positive family history should not exceed five years, especially in patients under insulin treatment. However, there are no current guidelines for this group of patients, and these recommendations only reflect the opinion of some experts. Hence, this strategy may not be applicable to some countries, as the corresponding risk would not allow screening colonoscopy to be adopted. Unfortunately, patients are often reluctant to undergo screening for CRC, and a high percentage of colorectal cancers could have been prevented; the disease is often diagnosed at advanced stages. Thus, the duty of the medical community is to inform the patients concisely, accurately, and clearly, convincing them to be checked regularly.

In conclusion, more clinical trials are required to elucidate not only the relationship between type 2 DM and CRC, but also CRC outcome in diabetic patients. Furthermore, the precise molecular mechanisms should be determined, which will lead to targeted therapy for CRC in diabetic patients.

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