The relationship between insulin resistance and colon cancer

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Abstract

Obesity and colon carcinoma are a growing health problem with colon carcinoma being the most common cancer of the alimentary tract. Risk factors for colon carcinoma, which are mediated by insulin resistance, include the so-called Western diet that is rich in high glycemic foods and beverages, a sedentary lifestyle, obesity, and others. We reviewed English papers cited on MEDLINE concerning epidemiological data and pathophysiology that link insulin, insulin growth factor-1, insulin resistance, and adipocytokines with colon cancer. Insulin resistance, a crucial mechanism that links obesity, diabetes mellitus type 2, and the metabolic syndrome, is a state in which the normal response of cells to insulin is reduced, which results in hyperglycaemia and hyperinsulinaemia. Some of the pathophysiological mechanisms have been thoroughly investigated and defined, and some are still to be discovered. Raising the awareness and subsequent prevention of the obesity–insulin resistance–metabolic syndrome cascade could influence, and thereby lower the adenoma–adenocarcinoma occurrence, that is now on a rising path.

Key words: insulin resistance, insulin, insulin growth factor-1, colon cancer, adipokines, proinflammatory cytokines

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1. Introduction

Insulin resistance, a crucial mechanism that links obesity, diabetes mellitus type 2, and the metabolic syndrome, represents a state in which the normal response of liver, muscle, and other peripheral tissue cells to insulin is reduced. In response to high plasma glucose concentrations, pancreatic beta cells secrete more insulin, thus leading to high insulin levels, namely hyperinsulinemia. Insulin is an essential hormone since it is involved in the modulation of energy metabolism, cell growth, and cancer development [1]. We now distinguish two insulin receptor (IR) isoforms, IR-A and IR-B that differ in the presence of a short exon 11 as a result of splicing in the IR coding sequence [2, 3]. It has been shown that the two isoforms exhibit different biological effects, namely, the shorter IR-A isoform shows an affinity for both insulin and insulin growth factor-1 (IGF-1) and has mitogenic effects, while the long isoform IR-B has mainly metabolic intracellular effects [4]. IR-B has a high affinity for insulin and is the major insulin receptor form in adults, found in fat, liver, and muscle tissue, while IR-A, found mostly in fetal tissue, can be overexpressed in tumors [4, 5]. IGF-1 plays an important role in the metabolic cascade of insulin resistance. Hyperinsulinemia has an effect on cell proliferation, not only through insulin receptor signaling, but also through the amplification of IGF-1 effect. IGF-1 production in the liver is influenced by growth hormone, and insulin increases the production and upregulation of growth hormone receptors in the liver, thus closing the insulin-growth hormone-IGF-1 circle [6]. Studies have shown that overproduction of growth hormone and consequently IGF-1, as found in acromegaly, leads to an elevated risk of developing both benign and malignant tumors of the colon [7, 8]. IGF-1 has autocrine, paracrine, and endocrine actions on cell proliferation and apoptosis by enhancing cell cycle progression, as well as on angiogenesis by enhancing vascular endothelial growth factor (VEGF) production [9-11]. The IGF-1 receptor, which preferentially binds IGF-1 over insulin, is responsible for part of the IGF-1 effect, and has also been extensively investigated [12, 13]. Not only are IGF-1 and insulin effects intertwined by a crosslink effect on each other’s receptors, but insulin and IGF-1 hybrid receptors (HR) have been identified in both immortalized cell lines and human tissues. These HR can be formed with both IR-A and IR-B receptors, but studies have shown that HR with IR-A isoform are activated by both insulin and IGF-1, while HR with IR-B isoform recognize only IGF-1. As IR-A receptors are overexpressed in tumors cells one can conclude that both insulin and IGF-1, through their effect on HR/IR-A, enhance cell proliferation (Figure 1) [14, 15].

IGF binding proteins (IGFBP) can oppose the effect of IGF-1 by binding IGF-1 and thus lowering its bioavailability. Most of IGF-1, more that 90% according to some papers, is bound to IGFBP-3 [12, 16]. Some authors point out the importance of the independent antiproliferative
effect of IGFBP, regardless of the IGF-1 binding activity \[17, 18\].
Williams et al. found that IGFBP-3 enhances p53-dependent apoptosis after DNA damage in colorectal cancer; therefore a loss, or down-regulation of IGFBP-3, could allow malignant cell survival and tumor formation \[19\]. Insulin also reduces secretion of IGFBP from the liver \[20, 21\].
The insulin/IGF system has been associated with tumor formation and progression in breast, ovarian, prostate, lung, and colon cancer, especially the sporadic form of colorectal carcinoma that emerges through the adenoma – carcinoma pathway \[12, 13\].
Obesity and colon carcinoma are a growing health problem with colon carcinoma being the most common cancer of the alimentary tract. The incidence of colon carcinoma varies between between developed and less developed countries. Japan, for example, which has experienced a rapid westernization of its national diet, has had a steady rise in the incidence of colorectal cancer \[22\]. Risk factors for colon carcinoma, which are mediated by insulin resistance, include the so-called Western diet that is rich in high glycemic foods and beverages, a sedentary lifestyle, obesity, and others. A meta-analysis by Larsson et al., stated that a 5–unit increase in body mass index (BMI), as well as increased waist circumference, was directly proportional to an increased risk of colon cancer in men and women, and a similar conclusion was made by Robsahm et al. \[23, 24\].
In this review we will focus on epidemiological studies that evaluated the influence of obesity, insulin resistance, and type 2 diabetes mellitus on the occurrence and progression of colon carcinoma, as well as the underlying pathophysiological mechanisms and role of adipocytokines.

2. Epidemiology

2.1 Obesity

A number of studies have addressed the issue of obesity and colon cancer risk. One of the first studies, by Lee et al., prospectively followed 17 595 college alumni for 25 years and found that increased BMI in young adulthood correlated with a higher risk of colon cancer later in life \[25\]. Since then, numerous studies have drawn the same conclusions in different parts of the world \[26-28\]. A large prospective study of almost one million adults during a follow up period of 16 years found that the relative risk for colorectal cancer varied from 1.34 (95% CI: 0.94-1.34) in patients with a BMI 25-29.9 and 4.52 (95% CI: 2.94-6.94) in patients with a BMI between 30-35 \[29\]. In the European Prospective Investigation into Cancer and Nutrition trial (EPIC), during 6 years of follow up, weight and BMI were significantly associated with colon cancer risk in men for the highest vs. the lowest quintile, and there was also a positive relationship with waist circumference and waist to hip ratio (WHR) \[30\]. This result was concurrent with the result of an earlier study by Moore et al., a retrospective analysis from the Framingham cohort, which demonstrated a two-fold increase risk of colorectal cancer for a waist circumference more than 99 cm in women and 101 cm in men \[31\]. Interestingly, the cardiovascular health study that followed around 6000 men and women older than 65 over a period of 7 years found that waist circumference and WHR were risk factors for colorectal carcinoma, whereas BMI had a statistically nonsignificant positive association \[32\]. This coincides with the fact that BMI is not an ideal representative measure of body composition, and that visceral adiposity is undoubtedly connected with insulin resistance, the metabolic syndrome, and subsequent cancer risk. Another interesting finding is that in most of these studies the association between BMI and colon cancer was stronger for men than for women, but this changed when taking the women's age into account. This observation suggests that the effect of obesity may be influenced by the hormonal status \[33-35\]. It is important to point out that the positive correlation of BMI and colon adenoma incidence was reported in obese men, and waist circumference and WHR were also found to be significant factors of adenoma occurrence \[36-39\].
A recent study by Kantor et al. reported that late adolescent obesity compared with normal weight was associated with future colon carcinoma risk. This points out the importance of early prevention of colon carcinoma by implementing adequate dietary measures \[40\]. Bordonaro reported, based on preliminary analyses of data obtained from The Cancer Genome Atlas, that cancer genomes of obese, microsatellite stable, colon cancer patients exhibit fewer somatic mutations, and correspondingly lower numbers of mutations in driver genes (P = 0.026). They also reported of a lower number of K-ras mutations in patients with high BMI. These intriguing reports, although requiring further
validation, impose that obesity lowers the threshold for mutations needed for neoplastic progressions of colon cancer cells [41].

### 2.2 Insulin resistance

Obesity cannot be regarded as an independent factor that aggravates the risk of colon cancer without addressing the issue of hyperinsulinaemia and insulin resistance. As mentioned in the introduction, while analyzing a state characterized by hyperinsulinemia and elevated levels of growth hormone, such as acromegaly, numerous studies have evaluated the subsequent risk of colon cancer. The United Kingdom Acromegaly Study Group that evaluated 1,362 acromegalic patients found an elevated colon cancer mortality rate (mortality SR 2.47; 95% CI 1.31 - 4.22) [42]. This was confirmed by other smaller studies, that not only found an increased relative risk for colon cancer, but also for adenoma incidence and adenoma recurrence as well [43, 44]. Jenkins et al., reported an odds ratio for adenoma incidence of 4.2 (95% CI 2.5 - 6.8) in acromegalic patients, what was later confirmed in the extension of that study [45, 46].

The previously mentioned Cardiovascular health study reported that fasting and 2 h postchallenge glucose were significantly and linearly related to a higher risk of colon cancer (P = 0.02), as well as 2h postchallenge insulin (RR 2.0; 95% CI 1.0 - 3.8), while fasting insulin was not related to a higher cancer risk (RR 1.2; 95% CI 0.8 - 2.5) [32]. This confirmed that postprandial insulin, which encompasses insulin resistance, was a stronger predictor of colon cancer risk than fasting insulin [6]. Trevisan et al., extracting data from the Risk Factors and Life Expectancy study that included 37,302 men and women, found a relative risk of colorectal cancer from 1.8 to 2.8 which positively correlated with C-peptide levels, 2h postchallenge insulin, and glucose, as well as glycosylated hemoglobin levels (HbA1c) [47]. The association between C-peptide levels, a marker of hyperinsulinemia, and the risk of colon cancer was evaluated in other studies [48, 49]. In the Physicians Health study, a statistically significant association was found between C-peptide levels and an increased risk of colorectal cancer in men (PP for the highest vs. lowest quintile of C-peptide 2.7, 95% CI 1.2 - 6.2 P = 0.047) regarding age, smoking, fasting, BMI, and alcohol consumption [48]. Khaw et al. reported that HbA1c levels predicted the incidence of colon cancer independently of diabetes, and that an increase in HbA1c of 1% was associated with a 33% increase in colorectal cancer risk [50]. The importance of HbA1c was stressed in a study by Aleksandrova et al., that suggested the increased risk of colorectal cancer in diabetics was due to elevated HbA1c levels. In that study, the lowest incidence of colorectal cancer was reported in the patient group that had HbA1c levels lower than 5% [51]. A similar conclusion was reached by analysis of results obtained from the earlier mentioned EPIC study and CLUE II cohort [50, 52]. On the other hand, Huang et al., in a recent study on 6,348 participants, reported that diabetes, but not prediabetes, was associated with a higher risk of advanced adenomatous polyps, but both diabetes and pre-diabetes were important for the occurrence of non-advanced adenomatous polyps [53].

### 2.3 Diabetes mellitus

Accumulating epidemiological evidence over several decades has established a clear connection between diabetes mellitus and colorectal cancer. All evidence that was previously stated in the chapter of insulin resistance represents a part of the puzzle because of the inevitable correlation of insulin resistance and type 2 diabetes mellitus, but several studies have addressed the importance of type 2 diabetes mellitus independently. A large prospective Cancer Prevention Study which enrolled almost 900,000 participants, with and without diabetes mellitus, reported an increased risk of colorectal cancer in men with type 2 diabetes mellitus (RR 1.3; 95% CI 1.03 - 1.65), and a positive, but statistically nonsignificant, elevation for women (RR 1.16; 95% CI 1.17 - 2.18) [54]. Similar results were obtained by other case-control studies, after controlling for BMI and other covariates [26, 55]. A large meta-analysis by Deng L et al., analyzing 24 studies including eight case-control and 16 cohort studies, with a total of 3,659,341 participants, indicated that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes (summary RR of colorectal cancer incidence of 1.26, 95% CI 1.20 - 1.31), without heterogeneity between studies (P for heterogeneity = 0.296) thus confirming the results of earlier mentioned studies [56].

### 3. Pathophysiology

In the introduction we pointed out the key players in the obesity–insulin resistance/diabetes–colon carcinoma
pathway. Insulin resistance is the most important mechanism that affects the proliferation and neoplastic transformation of normal epithelial cells directly, or through its effect on IGF-1 and IGFBP. This is all possible due to the fact that both normal colorectal epithelium and colon cancer cells have IR and IGF-1 receptors. Tissue homeostasis relies, therefore, on the balance of proliferative and antineoplastic signaling that occurs on the top of colonic crypts and is influenced by insulin/IGF-1 pathways [57]. Abbruzzese and al., found a high positive staining for phosphorylated IR (activated IR) during the malignant transition of normal colorectal cells to adenomas and adenocarcinomas, suggesting that the early activation of insulin–IR pathway is crucial in colorectal carcinogenesis [58]. Furthermore, insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) were positively correlated with advanced transition of normal colorectal epithelium to adenoma and subsequently adenocarcinoma. Overexpression of IRS-2 activates the oncogenic PI3 kinase pathway, leading to Akt phosphorylation and reduced cell adhesion, both characteristics of invasive colorectal carcinoma [59, 60]. Insulin also stimulates the farnesilation of the ras protein, which determines the localization of ras in the plasma membrane, and by that modulates the cellular response to various proliferative factors (IGF-1, epithelial growth factor and platelet-derived growth factor) that use the ras pathway [61, 62].

The role of IGF-1 in colon cancer has been extensively researched, since the observation of several earlier mentioned studies on acromegalic patients that established the link [7, 8, 42, 45, 46]. An overexpression of IGF receptors was found in human colon cancer cells, which was later associated with Akt activation and up-regulation of the anti-apoptotic protein Bcl-xL, as well as activation of β catenin and its translocation into the nucleus, and subsequent promotion of cell proliferation gene transcription [63-65]. Giovannucci et al., in a study on 32,826 women from the Nurses Health Study, concluded that high levels of circulating IGF-1 and particularly low levels of IGFBP-3, are independently associated with an elevated risk of large, or tubulovillous/villous colorectal adenoma and cancer [66]. Results from the Flexi-Scop trial found that high IGF-1 and low IGFBP-3 levels increased the risk of high-risk adenomas, defined as at least one adenoma more than 1 cm in diameter, tubulovillous or villous morphology, severe dysplasia, or the presence of three or more adenomas. These findings suggest that circulating IGF-1 and IGFBP-3 levels are related to future colorectal cancer risk, and may predict adenoma progression [67]. A similar conclusion was obtained from a large cohort of 14,275 patients that was assessed for IGF-1 and IGFBP. Higher levels of bioavailable IGF-1 were associated with an increased risk of cancer, whereas higher levels of IGFBP-1 and 2 with a decreased risk [68]. Insulin and IGF-1 signal transduction, control the cell cycle by activation of the ras protein, which occurs in about half of colonic cancer, and may enhance growth of adenomas into cancers [69-72].

4. Adipocytokines

Adipose tissue is not only a source of lipids, but also an endocrine organ, since it produces adipokines and cytokines that have local, peripheral, and central effects [73]. Obesity, which is associated with insulin resistance, is often regarded as chronic systemic low-grade inflammation, and is therefore linked with the neoplastic transformation of colon cells. The role of inflammation in colon cancer has been investigated in patients with inflammatory bowel disease, and this continuous mucosal inflammation has been recognized as a risk factor for cancer development [74]. Poullis et al., assessed 320 healthy patients for stool calprotectin levels and lifestyle factors, and found that fecal calprotectin levels were associated with typical lifestyle risk factors for colorectal cancer. This pointed out that low-level asymptomatic bowel inflammation may be the link between lifestyle factors and the pathogenesis of colorectal cancer, and that circulating proinflammatory cytokines may play a role in this mechanism [75].

4.1 Cytokines

Crucial inflammatory cells of the adipose tissue in obese individuals are macrophages, which secrete various proinflammatory cytokines [76]. These proinflammatory cytokines and reactive oxygen species (ROS) have been characterized as tumor-promoting signaling molecules, that promote cancer cell proliferation [77, 78]. Tumor necrosis factor alpha (TNF-α), one of the proinflammatory cytokines, through activation of NF-kB, increases the production of nitric oxide (NO), a substrate for ROS formation. ROS formation is an important step in DNA damage, since it can cause DNA base modification, deletions, frame shifts, and other rearrangements that can trigger cancer progression [79]. By
this we can conclude that TNF-α, through activation of NF-kB, supports cancer cell proliferation, angiogenesis, and metastasis [80-82]. TNF-α by induction of oxidative stress exacerbates pathological processes leading to oxidation of low-density lipoprotein, dyslipidemia, glucose intolerance, and insulin resistance [83]. It is important to state that, abnormally high levels of TNF-α and IL-6, whose secretion is promoted by TNF-α, were found in the plasma of obese individuals and were associated with the development of insulin resistance [84]. Furthermore, exposure of colorectal cancer cells to insulin, IGF-1, and TNF-α in vitro, leads to increased rates of proliferation and impaired apoptosis [6]. The role of IL-6 in tumorigenesis has been demonstrated in IL-6-deficient animal models that do not develop tumors [85].

4.2 Adipokines

Aside from cytokine secretion, adipose tissue is the major endocrine organ synthesizing and secreting adipokines. Obesity alters adipokine secretion, and through that, their role in energy metabolism and tumor development. Adipokines represent a heterogeneous group of mediators such as adiponectin, leptin, resistin, visfatin, ghrelin, and RBP4, but more than 50 others have been described so far. Although adiponectin is only secreted from adipose tissue, plasma concentrations of adiponectin were found to be significantly lower in obese subjects (visceral fat predomination) [86, 87]. Serum levels of adiponectin were also reduced in patients with type 2 diabetes mellitus and insulin resistance [88, 89]. In vivo studies showed that low serum levels of adiponectin were associated with insulin resistance and tumor formation [90, 91]. It has been proposed that adiponectin could have a protective effect in several malignancies, including colorectal cancer, through its anti-atherogenic, anti-angiogenic, and anti-proliferative functions [92-96].

Leptin is a peptide hormone secreted mainly by adipocytes of white adipose tissue (WAT), and higher levels of leptin are found in obese individuals, particularly those with central obesity [97-99]. Leptin downregulates the transcription of the preproinsulin gene and insulin excretion, which could be connected with high leptin levels in insulin resistance [98, 100]. Leptin acts as a potent mitogen, and antiapoptotic adipokine in the development of colorectal carcinoma [101, 102]. A study by Koda, found that leptin was overexpressed in colorectal carcinoma. Moreover, low levels of leptin were present in normal mucosa and significantly correlated with tumor grade (P = 0.002), as well as with histological type [103]. This points out the crucial role of leptin in the progression of adenoma–adenocarcinoma pathway [104].

Ghrelin has to be regarded in the light of its two forms, acyl-ghrelin and des-acyl ghrelin. Ghrelin stimulates liver gluconeogenesis and prevents insulin glucose lowering; however, des-acyl ghrelin inhibits liver glucose production [105]. Studies have shown that obese individuals have lower concentrations of des-acyl ghrelin and no difference in acyl-ghrelin concentrations, so it seems that obesity leads to a relative acyl-ghrelin excess and des-acyl ghrelin deficiency, which contributes to obesity-associated insulin resistance [106, 107]. Ghrelin is a potent stimulator and regulator of the GH/IGF-1 pathway, whose influence on the pathogenesis of colon cancer has been explained earlier. A dysregulation of acyl-ghrelin and des-acyl ghrelin functions could be involved in colon cancer promotion [108]. More studies are needed to elucidate the influence of ghrelin, since there are only scarce data that represent the relationship regarding acyl-ghrelin and des-acyl ghrelin expression and colon cancer occurrence.

5. Conclusion

Insulin resistance, a state inevitably connected with obesity, type 2 diabetes mellitus, and metabolic syndrome, has been recognized as a risk factor for numerous conditions including tumor development. Colon carcinoma, a growing health concern has been tied to the dramatic change in dietary habits and the adoption of the Western lifestyle. We can say that the Western diet has caused an epidemic of obesity, insulin resistance, metabolic syndrome, and cardiovascular disease, and is now causing an epidemic of colon cancer. The pathogenesis that underlies the obesity-insulin resistance adenoma-adenocarcinoma pathway connects and intertwines numerous modulators, hormones, growth factors, adipokines, and cytokines. Some of the pathophysiological mechanisms have been thoroughly investigated and defined, and some are still to be discovered. The ones that have been confirmed in large studies and meta-analysis are the insulin/IGF-1 pathways, proinflammatory cytokines and adipokines, which were mentioned in this review. Many other studies that have not been cited in
this review, also address these important questions, and are therefore not less valuable, but from our standpoint should be the subject of future research. In conclusion, we believe that raising the awareness and subsequent prevention of the obesity- insulin resistance- metabolic syndrome cascade could influence, and thereby lower the adenoma-adenocarcinoma occurrence, that is now on a rising path.

Author contributions

SS, LVJ and DR are responsible for the conception and design of the paper, acquisition of data, analysis and interpretation of data and gave the final aproval. MD has revised the paper and gave the final approval.

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