Title: Association of Adipokines and Insulin, which Have A Role in Obesity, with Colorectal Cancer

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Abstract

Obesity related diseases are an important part of public health and it is seen that obesity is related with colorectal cancers. Adipocyte hypertrophy and visceral adipose tissue accumulation can cause adipocitis related diseases and pathogenic adipocyte formation. Adipose tissue has a very important and active role in immune response formation. cytokines/adipokines which are secreted from adipose tissue have an active role in communication between adipocytes and macrophages. Thus, visceral adipocitis is related with low grade chronic sistemic inflammation. Also, adipocytes have an important role in colorectal cancer pathogenesis because of proinflammatory cytokines, growth factors and hormones

secretion. Most highlighted cytokines are adiponectine, resistine and ghrelin. Also, insulin like growth factor(IGF-1) increase, insulin resistance, plasma insulin levels, glucose and serum free fatty acids levels increase, glucose intolerance, high body mass index are seen to be related with colorectal cancer pathogenesis. Thus, in this review, we focus on the relationship between colorectal cancer and adipokines and insülin.

Key words: colorectal cancer, resistine, insülin, adipokines, adiponectin, obesity

INTRODUCTION

The term cancer describes various malignant tumors that may influence almost all organs and tissues. Incidence of cancer has been gradually increasing with changing life styles, increasing interaction with various carcinogenic agents and unfavorable changes in quality of life [1]. According to the data obtained from Global cancer statistics data base (GLOBOCAN), 14.1 million people were diagnosed with cancer in 2012. Deaths from cancers are 8.2 million worldwide and according to five-year survival data, 32.6 million people live with cancer [2]. In Turkey, cancers account for 19.7% of deaths [3]. According to the data of "Turkish Cancer Statistics" which was published by Turkish Ministry of Health in 2016, colorectal cancers are the third most common type of cancer in both female and male gender [4]. Similarly, while colorectal cancers are the third most common type of cancer among men worldwide (10% of all cancers), it ranks as the second among women (9.2% of all cancers). The rate of this type of cancer has been increasing with industrialization and urbanization, and although it is more prevalent in high-income countries, it has been increasing also in low- and moderate-income countries [2].

In epidemiological studies on correlation between obesity and cancer conducted so far, association of obesity with colon, endometrial, postmenopausal breast cancer, renal, esophageal, pancreatic, gall bladder, liver and hematological cancers has been demonstrated [5]. The underlying mechanism of the correlation between colorectal cancers and obesity has not been understood and it has been hypothesized that adipokines and the hormone insulin play a key role in this relationship. The first mechanism among these is expressed that obesity leads to insulin resistance and hyperinsulinism, causing a reduction in insulin binding protein

1 (IGFBP-1) levels. This reduction, in turn, leads to an increase in insulin-like growth factors (IGF-1) levels, promoting cell proliferation and inhibiting cell apoptosis. In the second mechanism is that obesity alters levels of adipokines secreted from adipose tissue (resistin, leptin, adiponectin and proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α). Increased level of these adipokines other than adiponectin may lead to tumor formation, progression and metastasis [6]. Summary of obesity and potential factors thought to be associated with colorectal cancers is given in Figure 1 [7]. There is obesity-associated insulin resistance, inflammation and adipokine production in mechanism of correlation of carcinogenesis of colorectal cancers and adiposity. Fat tissue macrophages that infiltrate visceral fat tissue gain anti-inflammatory, adipostatic, proinflammatory and adipogenic properties. Thus, they contribute to obesity-associated inflammation and insulin resistance [8].

Obesity results from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue. The patterns of altered levels of adipokine among obese subjects may be considered as important predictors for risk of colorectal cancer. For this reasons, the arrangements to prevent obesity will be protective against both chronic diseases and cancer.

Insulin

Although insulin is known with its metabolic effects, it also plays an important role in colorectal carcinogenesis and cancer progression. It performs this effect by increasing number of receptors of insulin-like growth factors (IGF-1) and growth hormone, stimulating synthesis of ovarian androgens and inhibiting synthesis of sex hormone binding globulin and IGF-1 binding protein [9]. Excessive energy intake, physical inactivity and obesity lead to insulin resistance. Consequently, plasma insulin concentrations tend to increase [10]. Insulin resistance has been associated with increased plasma insulin levels, glucose intolerance, increased insulin-like growth factor (IGF)-I, increased glucose and free fatty acids, increased body mass index and increased risk for colorectal cancer [9,11].

Nevertheless, when the studies in the literature are reviewed, the association between colorectal cancers and insulin levels is not clear [12-15]. While some studies reported that

hyperinsulinemia and insulin resistance led to an increase in risk of colorectal cancer [12,13]. there also are some studies reporting no association [14,15]. In a meta-analysis study, hyperinsulinism and insulin resistance were associated with an increased risk of colorectal cancer [12]. In another meta-analysis study, it was reported that in non-Asian societies, high levels of c-peptide and insulin were significantly associated with risk of colorectal cancer and there was no association in Asians [13]. No statistical significance was determined in another study in which insulin levels of the patients with colorectal cancer were evaluated based on tumor stage [16]. In conclusion, meta-analysis studies conducted also suggest that hyperinsulinism, high c-peptide levels and insulin resistance (HOMA-IR) are associated with increased risk of colorectal cancer [12,13]. As a result, insülin resistance is mainly caused by excessive energy intake leading to adiposity. Obesity related colorectal cancer, a growing health concern has been tied to the dramatic change in low physical activity level, dietary habits, the adoption of the Western diet (red and processed meats, high-fat dairy products refined grains, desserts, low intakes of vegetables, fruits, whole grains, and fish). For example, a higher fiber diet may be beneficial in hiperinsulinemi, as dietary fiber reduces postprandial hyperglycemia by delaying the digestion and absorption of carbohydrates, and increasing satiety with the effects of a resultant weight loss. This weight loss and balanced/healty food patterns as Mediterranean diet consequently the development of colorectal cancer can be prevented.

Adiponectin

Adiponectin, a large adipokine secreted from adipose tissue, attracts attention with its anti-inflammatory, anti-atherogenic, anti-angiogenic and insulin-sensitizing properties, as well as its beneficial role in glucose metabolism [6,8]. Adiponectin suppresses secretion of inflammatory cytokines like TNF-α and initiates release of anti-inflammatory cytokines like IL-10 during atherogenic process [17]. It has been reported that low adiponectin levels may be a risk factor for obesity-associated types of cancer such as colorectal and prostatic cancers [18]. Adiponectin provides suppression over cancer via various pathways. In this pathway, adenosine monophosphate-activated protein kinase (AMPK) has a central role. Adiponectin

activates AMPK and inhibits phosphaditylinositol-3-kinase / protein kinase B (PI3K/AKT), mTOR, glycogen synthase kinase 3-β, Janus kinase /signal transducer and transcription pathway activator (JAK/STAT) pathways. AMPK influences cell growth signaling via mTOR and, thus, inhibits development of carcinogenesis, it also prevents promotion of tumor cell adhesion and migration [19].

In many studies the association between circulating adiponectin levels and risk of colorectal cancer has been evaluated [20-24]. Nevertheless, there are discrepancies between results of epidemiological studies. In a study of patients with colorectal cancers with adenomatous polyps which was conducted by Kumor and colleagues [20], adiponectin levels of the patients with colorectal cancer were determined to be significantly decreased compared to both adenoma and control groups. Nakajima and colleagues [24] determined that adiponectin levels were lower in multivariate analysis in patients with adenoma compared to the control group and it was inversely related with number of adenomas but there was no association with size of adenoma and stage of cancer. In studies conducted in a similar way, adiponectin levels were determined to be lower in individuals with colorectal cancer [21,23]. Also in another study conducted in Turkey, adiponectin levels of individuals diagnosed with colon cancer and the control group were found to be similar [22]. Genetic, environmental and ethnic factors are thought to be effective in serum adiponectin levels. Although regulatory ways for these levels remain unclear, it has been emphasized that some genetic variations may also be effective [25]. It has been reported that life style habits such as alcohol consumption, eating habits, exercising, smoking etc. may influence serum adiponectin levels [25]. Dietary intakes have major role in controlling the inflammation and also weight management. For example, the consumption of fruits, vegetables, whole grain and nuts produce several nutraceuticals that have been beneficial to modified carcinogenesis via multiple pathways. Adherence to diet in fiber and complexes carbonhydrate leads to improve concentration of adiponectin stimulating insülin sensitivity. It is possible that these dietary pattern decrease risk for carsinogenesis through the elevation of adiponectin.

Leptin

Leptin is one of the most commonly found adipokines which has a key role in control of hunger and satiety by being involved in regulation of food intake, energy balance and body weight [26]. Leptin is a product of the obese (ob) gene mapped to chromosome 7 and shows its activity via OB-R receptor. Stomach is the major source of leptin in gastrointestinal tract. Although leptin is produced in both endocrine and exocrine cells in gastric mucosa, exocrine cells have a greater role [27]. Leptin receptors are more predominant particularly in proximal portion of intestines and exist in basolateral margins and lumen of intestinal cells [28]. It was demonstrated that in ob-ob mice with leptin deficiency, cell proliferation decreased and apoptosis in intestinal cells increased after small intestinal resection [29]. Leptin levels may vary among women and men because it is expressed that leptin levels are higher in women due to high amount of fat tissue and an increase in leptin levels may be possible in obesity-associated cancers [30]. It was reported that, as leptin stimulates cell migration and proliferation in colorectal cancers and normal intestinal epithelial cells, leptin expression could be used as a marker for characteristics of tumor cells and prognosis [31]. In a previous study, it was determined that a significant increase occurred in proliferative activity of normal colonic epithelial cells in obese models, whereas tumor cell proliferation was significantly reduced in those with leptin deficiency, and tumor growth was inhibited in mice with leptin deficiency or leptin receptor deficiency [32]. Nevertheless, in a meta-analysis involving 13 studies, it was emphasized that there was no correlation between leptin levels and risk of colorectal cancer [33]. More studies are required to be conducted for evaluation of leptin signalization and determination of potential mechanisms on prognosis in tumor tissues [34]. However, it should be noted that diet has an important role on change the concentration of leptin. Not only the total energy intake on the concentration of leptin, but also the type and amount of fatty acid, carbohydrate consumption, carbohydrate type and glycemic load in the diet play the key roles caused by insulin resistance and leptin resistance.

Ghrelin

Ghrelin is a 28-aminoacid hormone which is principally produced in stomach, has growth hormone-secreting effect and has a role in energy balance and regulation of food intake.

Approximately 60-70% of Ghrelin is secreted from stomach and more than 30% is secreted from small intestines. Ghrelin has two important forms in stomach and plasma: acyl and deacyl forms [35]. Effects of Ghrelin are provided by ghrelin receptor, also known as growth hormone secretagogue receptor (GHSR) [36]. Ghrelin has various physiological effects in gastrointestinal, cardiovascular, pulmonary and immune systems. Additionally, it also has important roles such as promoting food intake (orexigenic effect) and influencing cell proliferation. It stimulates differentiation of pre-adipocytes and as it inhibits lipolysis, it has a principal role in process of adipogenesis [36]. It has been shown to have an anti-apoptotic or pro-apoptotic role in different cancer cells [7]. Effect of ghrelin on cancer cell proliferation among various cancers still remains controversial. Recently, it was reported to induce proliferation of colon cancer cells via GHSR, Ras, phosphadityinositol 3 kinase (PI3K), Akt and mTOR pathways [37].

In literature, the association between serum ghrelin levels and colorectal cancer has not become clear and results differ. No difference was determined between plasma ghrelin levels of 78 patients who are diagnosed with gastric or colorectal cancer and those in the control group. Furthermore, ghrelin levels were reported not to be influenced by tumor localization and levels of other hormones (growth hormone, glucagon and cortisol) [38]. In another study involving individuals with gastrointestinal tract cancers, it was determined that while ghrelin and adiponectin levels of individuals both with colon and rectum cancers were lower compared to the control group and leptin levels were higher, there was no difference in levels of these hormones by gender [39]. Nevertheless, in another study, when 95 individuals with colon cancer and 39 health controls were compared by age, BMI and gender, total serum ghrelin levels were determined to be higher compared to the healthy control group. Additionally, while it was determined to show a positive correlation with tumor size and advanced stage tumors (compared to initial stage), it exhibited an inverse relationship with tumor differentiation and it was not associated with tumor localization, demographical/clinical characteristics and survival [40].

Large-scale prospective clinical studies are required in order to shed further light on effects of ghrelin on general activity in tumors and various types of cancer including colorectal cancers and to reliability and benefits of treatment with ghrelin/ghrelin receptor agonist in patients with cancer [41].

Resistin

Resistin is a recently discovered member of cysteine-rich protein family, so called "resistin-like molecule". It is produced from peripheral blood monocytes and stromavascular portion of adipose tissue [42]. Leptin, adiponectin and resistin have physiological roles in reduction of food intake, energy balance and regulation of body weight [20]. Insulin resistance, as well as alterations in hormones secreted by adipose tissue such as adiponectin, leptin and resistin have been determined to be directly associated with colorectal cancers and inflammatory bowel diseases [43].

Role of resistin in colorectal carcinogenesis has not been managed to be explained. However, it is also expressed that serum resistin concentration might be a factor that contributes increased risk of colorectal cancer. Activation of monocytes, as a part of the inflammatory process, has been associated with increased resistin levels in patients with colorectal cancer. Chronic inflammation plays an important role in pathogenesis of cancer and there is a close relationship between resisting and inflammatory markers [44]. In a study, resistin levels of individuals with colon cancer were determined to be higher compared to the control group and high resistin levels were reported to be associated with the chronic inflammation-associated cancer [45]. Although the role of resistin in colorectal cancers has not been completely clarified, various mechanisms are thought to be effective on these results. In vitro studies report that resistin induces a proinflammatory effect via TLR4 receptor stimulation and NF-κB pathway [46,47]. Furthermore, resistin is also told to show its effects by execution of release of vascular endothelial growth factor, which supports tumor invasion, and of production of matrix metalloproteins [48].

In a study, resistin levels of individuals with colorectal cancer were determined to be higher compared to the control group [21]. Sălăgeanu and colleagues [45]. determined that resistin

levels were higher in patients with colon cancer compared to the control group but there was no correlation between tumor grade, stage and tumor localization, and resistin levels. Nakajima and colleagues [24]. concluded that resistin levels were higher compared to the control group, independently of BMI, but resistin levels increased proportionally to tumor stage. However, in another study, no difference was determined in plasma resistin levels when patients with colorectal cancer were compared to the control group [49].

In a meta-analysis study, it was emphasized that resistin levels were higher in individuals with colorectal cancer compared to the healthy control group but more randomized and experimental studies that may confirm effect of resistin on development of colorectal cancers are required [50].

In conclusion, obesity is a well-defined risk factor for various diseases including metabolic, cardiovascular and several cancer types. Especially, the epidemiological evidence clearly indicates common factors linking obesity and colon cancer. This can be explained by several changes in hormonal and cytokine profiles that stimulate cell growth, inhibit apoptosis, and promote angioneogenesis. Cancer and obesity can be associated with consumption of high-energy diets, a sedentary lifestyle, increased age, processed red meat, and reduced consumption of fruit, vegetables and fiber. All these factors influence adipose tissue. These factors have the potential to influence the production of adipose-derived hormones as adiponectin, leptin, resistine and ghrelin. Considering that alterations in adipokine levels are closely related with colorectal cancers. In terms of weight management and control of inflammation, it is necessary to take into account that dietary intake of individuals has an important role.

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