Review

Metabolic syndrome and colorectal cancer: a review

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The metabolic syndrome (MetS) has become one of the major public-health challenges worldwide and abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, glucose intolerance, proinflammatory state, prothrombotic state are components of the MetS. There is an accumulation of evidence that MetS with its systemic and hormonal effects may affect both the susceptibility to carcinomas and prognosis of patients diagnosed with cancer. Yet few reports have focused on the relationship between MetS and the outcomes from colorectal cancer. Studies examining cancer incidence in patients diagnosed with the MetS are generally lacking; however, studies indicate that clustering of the components of the MetS increases the risk of colorectal cancer mortality compared with the individual components alone. Colorectal cancer is one of the most common malignancies and it is one of the leading causes of cancer mortality in the world. Understanding the risk factors for colorectal cancer may guide the development of strategies targeted toward its prevention.

Key words: Colorectal cancer, insulin resistance, metabolic syndrome, obesity.

INTRODUCTION

The metabolic syndrome (MetS) has been evolving for years, but with the recognition that obesity is becoming a major global health problem [Laclaustra et al., 2007] and this syndrome is an important risk factor for the development of circulatory diseases such as ischemic heart disease or cerebrovascular diseases based on arteriosclerosis [Lakka et al., 2002]. MetS comprises various clinical conditions, such as hypertension, dyslipidemia, and impaired glucose tolerance, which are associated with abdominal obesity (Figure 1) [Ozcelik et al., 2010]. Interventions that resolve MetS are essential for preventing the subsequent circulatory diseases. Various criteria have been proposed to define MetS, but there is still no international consensus [Matsuzawa, 2005]. MetS is a major risk factor for cardiovascular disease or type 2 diabetes mellitus (DM). The idea that this syndrome could also be related to some cancers, particularly colon cancer, has been hypothesized relatively recently [Kaaks, 1996]. This hypothesis was based largely on the similarity of some risk factors, primarily central obesity and physical inactivity, for cardiovascular disease, type 2 diabetes, and colorectal cancer (CRC). The immediate factors causing MetS are dietary, genetic, and environmental, with an emphasis on dietary elements.

Colorectal cancer is one of the main causes of cancer mortality worldwide. The contribution of diet and nutrition to cancer risk, prevention and treatment have been a major focus of research in recent years due to the suggested protective role ascribed to nutrients present in vegetables [Ravasco et al., 2010; Liu et al., 2012]. Epidemiological evidence suggests that obesity is a important risk factor of many types of cancer, and the data are particularly compelling for colorectal cancer. Since the obesity epidemic shows no signs of abating and further increases in its prevalence are expected in the future, defining the underlying cellular mechanisms by which obesity enhances cancer is an important step in
the development of intelligent strategies to prevent and treat obesity-associated cancer [Louie et al., 2013; Bardou et al., 2013]. The MetS, and particularly its underlying component hyperinsulinaemia, might influence colorectal cancer risk through several plausible biological mechanisms. By suppression of hepatic secretion of insulin-like growth factors (IGF)-binding protein-1, insulin enhances the levels of bioavailable IGF-1. IGF-1 stimulates cell proliferation and differentiation, inhibits apoptosis and increases production of vascular endothelial growth factors, important in tumour angiogenesis. Further, insulin stimulated cell growth in a human colon cancer cell line in a dose-dependent manner.

The association between MetS and colorectal cancer is important. The components of MetS appear to have an additive effect on colorectal cancer development acting through different pathophysiological pathways. Understanding the pathological mechanism that links MetS and its components to carcinogenesis has a very important clinical significance. Controlling even one or two of the components of the MetS may result in a longer, healthier and cancer-free life [Pelucchi et al., 2010; Forootan et al., 2012; Yang et al., 2013]. This article will review the evidence from the studies that have examined factors related to the metabolic syndrome in relation to the risk of colorectal cancer.

**Figure 1.** Metabolic syndrome comprises various clinical conditions, such as blood pressure (BP), dyslipidemia, and impaired glucosetolerance, which are associated with abdominal obesity.

**UNDERSTANDING METABOLIC SYNDROME**

The metabolic syndrome has become one of the major public-health challenges worldwide and this syndrome is called the insulin resistance syndrome. Some individuals are genetically predisposed to insulin resistance and physical inactivity and obesity can elicit insulin resistance in these individuals. However, most people with insulin resistance have abdominal obesity. Poorly understood complex biological mechanisms at the cellular level appear to link insulin resistance with other metabolic risk factors [Sakkinen et al., 2000].

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines suggest that a diagnosis of metabolic syndrome is made where three or more of the following risk factors are present: central obesity, elevated triglycerides, low high-density lipoprotein (HDL), raised blood pressure and raised fasting plasma glucose [Expert Panel on Detection, 2001]. Central obesity is more highly correlated with metabolic risk factors than body mass index (BMI) and, therefore, measurement of the waist circumference (WC) is recommended to identify the bodyweight component of MetS. Several other definitions exist for MetS, as published by the International Diabetes Federation (IDF) [Alberti et al., 2005]. Table 1 illustrates the main differences between these definitions. The NCEP and
IDF definitions of metabolic syndrome are very similar and it can be expected that they will identify many of the same individuals as having metabolic syndrome. The two differences are that IDF excludes any subject without increased WC, whereas in the NCEP definition MetS can be diagnosed based on other criteria; and the IDF uses geography-specific cut-off points for WC, whereas the NCEP uses only one set of thresholds for WC regardless of geography. These two definitions are much closer to each other than the original NCEP and World Health Organisation (WHO) definitions [Braga-Basaria et al., 2006].

**WHAT CAUSES THE METABOLIC SYNDROME?**

The syndrome becomes a disease when causal mechanisms are identified. Abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, glucose intolerance, proinflammatory state, prothrombotic state are components of the MetS and these components are major and emerging risk factors for cardiovascular diseases [Third report of the National Cholesterol Education Program (NCEP), 2002], however patients with MetS show increased risk for vascular and metabolic disorders. Because of the high incidence of glucose intolerance shown in this population, patients with MetS also have great risk for DM [Kanbak et al., 2011]. This syndrome develops as a result of poor eating habits and/or sedentary lifestyles, which are associated with insulin resistance and obesity. As indicated by the elements in the clinical definitions of the MetS, insulin resistance is thought to be the prime underlying factor. Insulin resistance occurs when there is a decrease in the responsiveness of peripheral tissues to the effect of insulin, with a concomitant hyperinsulinemia responsible for insulin like growth factor 1 (IGF-1) production in the liver [Kanbak et al., 2011]. Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis and insulin resistance or hyperinsulinemia, directly causes other metabolic risk factor [Scott et al., 2004]. Insulin resistance generally improves with increasing body fat content and some studies showed that hyperinsulinemia may enhance output of very low-density lipoprotein (VLDL) triglycerides and raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver. Finally, insulin resistance may raise blood pressure by a variety of mechanisms. The pathophysiological mechanisms underlying the development of the MetS are multi-factorial and incompletely understood [Miranda et al., 2005; Grundy et al., 2004]; however, obesity has a fundamental role. The effect of obesity is thought to be mediated, at least in part by the role of the adipocyte in controlling circulating free fatty acids and the development of insulin resistance [Miranda et al., 2005; Bergman et al., 2006].

Obesity is characterized by storage of fat in the body and it is a result of positive ‘energy balance’ and prevails.
in conditions of energy excess. As a result of major economic, social and technological changes, many populations find themselves in environments characterized by abundant calorie-rich food and low physical activity requirements and this situation is spreading across the world [Gunter and Leitzmann, 2006]. Obesity plays a key role in the MetS and our previous study showed that abdominal fat tissue elevation characterized by increase in waist diameter plays a key role in MetS pathogenesis and also contributes to development of insulin resistance [Ozcelik et al., 2010]. Obesity contributes to hypertension, high serum cholesterol, low HDL and hyperglycaemia [Hu et al., 2004]. The risk of serious health consequences in the form of DM, coronary heart disease (CHD) and a range of other conditions, including some forms of cancer, has been shown to rise with an increase in body mass index. Insulin resistance is common, and is present in almost all obese patients. When insulin resistance is accompanied by dysfunction of pancreatic islet β-cells - the cells that release insulin - failure to control blood glucose levels results and obese patients end up becoming diabetic, and abnormalities in β-cell function are therefore critical in defining the risk and development of DM [Steven et al., 2006]. Obesity is in conjunction with by high levels of non esterified fatty acids released from adipose tissue that cause insulin resistance. If free fatty acids are elevated quite a while, inadequate insulin may be released for the degree of insulin resistance, resulting in hyperglycemia. The increased free fatty acids associated with obesity are metabolized to triglycerides, which accounts in part for the associated hypertriglyceridemia [Ruotolo and Howard, 2002; Defronzo and Ferrannini, 1991]. This is also associated with decline in lipoprotein lipase action in peripheral tissues and the liver and leads to decreased clearance of VLDL and hypertriglyceridemia [Avramidou et al., 2003]. The mechanism for the decreased HDL is less well understood but is thought to be secondary to the related metabolism of triglyceride rich lipoproteins. The increased low-density lipoprotein (LDL) is quickly lipolyzed by hepatic lipase to small, dense LDL, and increases in small, dense LDL particles are observed [Ruotolo and Howard, 2002] and several mechanisms have been proposed for the link between insulin resistance and hypertension [Reaven, 2007].

Hypertension is a very common condition which frequently remains undiagnosed until relatively late in its course, leading to a variety of other life-threatening conditions like kidney damage and heart failure. It is a very prominent feature of the MetS. The association of elevated blood pressure and metabolic abnormalities with poor cerebrovascular outcome had been recognized long before the concept of the MetS became popular [Kannel, 1996]. Studying hypertension in the context of the MetS has provided significant insights into the etiology of the condition, known to be complex and multifactorial [Shirai, 2004] and insulin resistance and obesity have been recognized as the main factors involved in cause of hypertension in the MetS. Multiple studies were performed in order to elucidate the mechanisms of this association. These studies have shown that all of the elements of the syndrome contribute to increased blood pressure, which further promotes vascular damage in cardiac, renal and brain tissue [Khan et al., 2007]. Insulin resistance induce blood pressure elevation by activation of the sympathetic nervous system and renin-angiotensinaldosterone system (RAAS) with consequential sodium retention and volume expansion, endothelial dysfunction and alteration in renal function [Low et al., 2004; Sowers and Fronlich, 2004].

Increased visceral fat accumulation is a strong predictor of arterial hypertension. One of the proposed mechanisms by which hypertension is linked with central obesity includes sympathetic nervous system overactivation. Chronic sympathetic stimulation facilitates energy balance and weight stabilization in chronic overeating, but at the cost of adverse consequences such as elevated blood pressure. It has also been suggested that chronic increases in portal venous fatty acid levels may be responsible for hypertension that accompanies visceral obesity. As a result hypertension is more than just elevated blood pressure, it is intimately associated with the MetS [Duvnjak et al., 2008].

In summary, MetS is a cluster of metabolic abnormalities and related clinical syndromes most important of which are coronary artery disease and DM and cancer. In-depth knowledge of the markers of MetS will help in better understanding of the condition.

**METABOLIC SYNDROME AND CANCER RISK**

Metabolic syndrome has attracted interest as a new risk factor for the circulatory diseases. Epidemiological studies conducted in Western countries show that MetS is an independent risk factor for hospitalization, or for death due to heart disease and cerebral infarction, and the hazard ratio was approximately [McNeill et al., 2005]. Several studies have shown that MetS is a risk factor for the incidence of cancer, and therefore MetS may be an important clinical factor also for preventing cancers. The relationship between the site-specific occurrence of cancer and MetS have not yet reached consistent conclusions [Lund et al., 2006]; however, several types of cancer - such as colon, prostate, and pancreatic cancers - have a positive association with MetS according to many studies [Tande, 2006; Cowey and Hardy, 2006]. Various mechanisms have been proposed to explain the relationship between MetS and cancer development [Cowey and Hardy, 2006] and studies support that the MetS, or its components, might play an important role in the etiology and progression of certain cancer types and a worse prognosis for some cancers [Pothiwala et al., 2009]. Zhanlong et al. addressed the their study of
whether cancer prognosis is impacted by MetS, as defined by 3 or more of the following indicators: central obesity, hypertension, abnormal blood lipid levels, and high blood glucose levels. If confirmed, these results showing a dramatically worse prognosis including worse survival, tumor recurrence, and liver metastasis of patients with MetS could have important implications for lifestyle intervention to prevent or to slow down cancer progression [Zhanlong et al., 2010]. Osaki et al. has demonstrated that MetS increased the risk of cancers at several sites. The hazard ratio of MetS was statistically significant, and it increased in the order of pre-MetS, MetS for liver cancer in males and females, total cancer in males, and female breast cancer [Osaki et al., 2012]. Studies have suggested that overweight and obesity are related to increased risk of several cancer types, including colon cancer, adenocarcinoma of the esophagus, breast cancer, endometrial cancer and kidney cancer [Calle et al., 2003; Gallagher et al., 2010]. Worldwide there are 1.1 billion overweight people with a BMI between 25 kg/m$^2$ and 30 kg/m$^2$ and 312 million with a BMI > 30 kg/m$^2$. Within the last four decades the prevalence of obese people in the world increased [Haslam and James, 2005]. The American Cancer Society calculates that currently new cancer cases are in the order of 1.5 million with half a million cancer deaths per year, nearly one in five due to obesity [Gallagher et al., 2010].

Obesity is a state of increased body fat mass caused by a prolonged positive energy balance. This is accompanied by a wide range of physiological and biological alterations. Several possible mechanisms have been suggested to explain the association of obesity with increased risk of certain cancers. Increased energy intake, decreased energy output, increased adipose tissue mass and endogenous hormones can explain the association between obesity with cancer risk [Percik and Stumvoll, 2009]. Excess body weight, increased plasma triglyceride levels, low levels of physical activity and certain dietary patterns can all favor elevated circulating insulin levels [Giovannucci, 2003]. Insulin is included as a hormone that is markedly increased in conditions of obesity and is therefore not an adipokine by definition; however, obesity is known to cause insulin resistance, thereby leading to an increase in serum levels of insulin as a compensatory response to the resistance [Jenifer et al., 2010]. Insulin resistance increases risk for many types of cancer. It is unclear whether this risk is due to the direct effect of insulin on cell proliferation or the indirect effect of insulin growth factor (IGF) and other hormones [Hursting et al., 2008]. In addition to its role in the metabolism of glucose, insulin also increases serum levels of the structurally similar but more potent IGF, thereby acting indirectly through the IGF system that is present on most cells throughout the body, which may also explain in part the relationship between obesity-related hyperinsulinemia and cancer risk [Boyd, 2003]. The individual components of MetS that may contribute to tumorigenesis, including insulin resistance, adipokine production, angiogenesis and oxidative stress/DNA damage; factors that can work synergistically to increase cancer risk beyond that of the individual components alone [Chan et al., 2000]. Hyperinsulinemia resulting from a high intake of refined carbohydrates would lead to more rapid growth of tumours [Venkateswaran et al., 2007]. Studies showed that high carbohydrate/high fat or low carbohydrate/high fat diets increased tumour growth and an increase in serum insulin and IGF-1 levels. Therefore, a diet high in refined carbohydrates was associated with increased tumour growth and with activation of signalling pathways distal to the insulin receptor [Nobes et al., 2009].

**METABOLIC SYNDROME AND RISK OF COLORECTAL CANCER**

Colorectal cancer is the third most common cancer and the third leading cause for cancer mortality in the world [Jemal et al., 2007]. There is an accumulation of evidence that MetS with its systemic and hormonal effects may affect both the susceptibility to carcinomas and prognosis of patients diagnosed with cancer [Jemal et al., 2007; Colangelo et al., 2002]. Yet few reports have focused on the relationship between MetS and the outcomes from colorectal cancer. Some studies have now examined standard definitions of the MetS in relation to colorectal cancer risk [Marrero et al., 2005]. Studies examining cancer incidence in patients diagnosed with the MetS are generally lacking; however, studies indicate that clustering of the components of the MetS increases the risk of colorectal cancer mortality compared with the individual components alone. Colangelo et al. [2002] reported a modest association of postload plasma glucose and insulin resistance syndrome with colorectal cancer mortality and in another study, Stümmer and colleagues found that overweight and diabetes are risk factors for colorectal cancer [Stümmer et al., 2006].

Recent studies also provide information concerning the association between colorectal cancer incidence and the number of metabolic syndrome components, especially BMI, WC, lipid levels and plasma glucose. In an analysis of 14109 participants from the Atherosclerosis Risk in Communities (ARIC) study, 194 incident colorectal cancers were identified. In this study baseline metabolic syndrome had a positive association with age-adjusted and gender-adjusted colorectal cancer incidence. The ARIC study has shown an association between colorectal cancer incidence and the number of metabolic syndrome components [Ahmed et al., 2006]. In another study, Stocks et al., evaluated the association between metabolic syndrome and colorectal cancer in 306 individuals with known colorectal cancer. The results of this study suggest that the presence of hypertension,
obesity and hyperglycemia, correlated with colorectal cancer [Stocks et al., 2008]. Subjects with MetS have increased risk of developing colorectal adenoma and, however abdominal obesity is the component of the highest predictive value [Hu et al., 2011]. In industrialised countries where the eating habits of people, as well as their extent of exercise, have changed distinctly over the last decades, obesity has emerged as one of the leading health burdens [Augustin, 2007]. Obesity is frequently associated with diabetes, hypertension, hyperlipidemia, coronary heart disease, stroke and cancer. At the same time obesity is a complex, multifactorial disease that develops from the interaction between genotype and the environment [Janssen et al., 2002].

There is evidence that body composition and hormonal factors contribute to colorectal cancer etiology [Calle et al., 2003]. Cohort and case-control studies have consistently demonstrated a positive relation between body size and colorectal cancer. A report published in 2002 evaluated all available studies on obesity and colorectal cancer risk and found elevated risks in men and women with risks being stronger for men than women [IARC, 2002]. Similarly, for the 10 prospective cohort investigations, all reported a positive association between BMI and colorectal cancer [Ferrante, 2006]. In general, body size also seems to influence early stages of colorectal carcinogenesis: BMI has been associated with colorectal adenoma and, in particular, large adenomas of the distal colorectum in seven epidemiological studies [Zih-Jie et al., 2011].

Obesity induced changes in hormonal metabolism may be a link to cancer risk. Circulating levels of insulin are increased in obesity, and insulin has been postulated to be such a link. The anabolic signals of insulin can promote tumor development by inhibiting apoptosis and by stimulating cell proliferation [Stattin et al., 2004]. The term insulin resistance refers to a state of prevent the cellular response to the effects of insulin with higher levels of insulin required to normalize plasma glucose. Insulin resistance is believed to underlie a cluster of metabolic disturbances, including elevated levels of blood triglycerides and glucose, low levels of HDL and high blood pressure. It was noted some years ago that many of the risk factors for becoming insulin resistant coincide with those for colorectal cancer, particularly high BMI, a sedentary lifestyle, a diet rich in energy, red meat and saturated fat, and low in fiber and fruits and vegetables. At the same time, there is observational and experimental evidence for a direct link between insulin resistance and colorectal neoplasia. Several metabolic consequences of the insulin-resistant state, including hyperinsulinemia, hyperglycemia, hypertriglyceridemia and increased plasma levels of nonesterified fatty acids (NEFAs), have been positively associated with colorectal cancer among fasting subjects in prospective studies [Yamada et al., 1998; Schoen et al., 1999]. At least three mechanisms exist through which insulin resistance potentially causes colorectal cancer. The elevated concentrations of plasma insulin, triglycerides, NEFA and glucose associated with insulin resistance lead to increased insulin exposure of nonclassical insulin target tissues that express insulin receptors, such as the colon. This can potentially have a number of results. First, insulin is known to have growth as well as metabolic effects, and data from a variety of sources suggest that insulin is functionally involved in colorectal carcinogenesis [Giovannucci, 2001]. Specifically, insulin stimulates proliferation and reduces apoptosis in colorectal cancer cell lines, and it promotes colorectal tumor growth in animal models [Gunter and Leitzmann, 2006].

Upon binding to its receptor, insulin initiates a signal transduction cascade, which results in not only translocation of the glucose transporter type 4 (GLUT4) receptor to the cell surface, but also increased proliferation and decreased apoptosis via the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3-K) pathways, respectively [Saltiel and Kahn, 2001]. Because the colon does not represent a classical insulin-target tissue, the colonocyte may lack a specific mechanism through which the mitogenic actions of insulin are regulated, as is the case in classical insulin target tissues such as skeletal muscle, adipose tissue and liver. Thus, elevated insulin signaling in the colonocyte may engender an enhanced proliferative state with tumorigenic consequences.

Second, in conjunction with the metabolic effects of insulin, the increased concentrations of convenient energy substrates such as glucose, triglycerides and NEFA may provide increased energy for transformed colonocytes as well as induce changes in cell signaling pathways. Elevated intracellular levels of triglycerides and their metabolites such as diacylglycerol may activate the protein kinase-C pathway with potentially mitogenic and carcinogenic effects [Prentki et al., 2002]. Third, insulin resistance causes alterations in the IGF system with accompaniment effects on cellular growth pathways. Insulin and IGF are representative of energy availability and stimulate anabolic pathways, leading to cell growth and differentiation. In the hyperinsulinemic state, IGF-binding protein (IGFBP) levels decrease, whereas free IGF-1 levels. The colon expresses IGF receptors, and following activation by IGF binding, colonocyte apoptosis is inhibited and cell cycle progression ensues. Elevated levels of IGF may therefore provide a selective growth stimulus, causing clonal expansion of epithelial cells with abnormal growth regulation. High circulating levels of IGF-1 have been positively associated with colorectal cancer risk, whereas high IGFBP-3 levels are associated with reduced risk rise [Giovannucci et al., 2000].

Obesity has also been associated with discomforts in the bioavailability of plasma androgens and estrogens mediated by several mechanisms. In response to insulin resistance, enhanced IGF-1 activity in the liver inhibits hepatic sex hormone binding globulin synthesis leading
to increasing levels of circulating sex hormones such as estrogen and testosterone. In addition, insulin and IGF-1 stimulate sex hormone synthesis by the gonads and adrenal glands. Observed gender differences in the relation of body size and colorectal cancer may be explained, in part, by alterations in sex hormone levels [Ann et al., 2007]. Colorectal cancer is one of the most common malignancies and it is one of the leading causes of cancer mortality in the world. Understanding the risk factors for colorectal cancer may guide the development of strategies targeted toward its prevention. Several clinical characteristics comprised in MetS, including obesity, dyslipidemia, and impaired glucose tolerance, have been linked to an increased risk for colorectal cancer.

CONCLUSION

The incidence of MetS has been increasing every year with urbanization, aging, and changes in diet structure and lifestyle. The clusters of the metabolic syndrome components are predictors for developing colorectal cancer and for colorectal cancer mortality. The understanding of the underlying physiopathology that links the MetS and colorectal cancer can play a key role in developing new strategies for prevention and treatment. The components of MetS appear to have an additive effect on colorectal cancer development acting through different pathophysiological pathways. Understanding the pathological mechanism that links MetS and its components to carcinogenesis has a very important clinical significance. Controlling even one or two of the components of the MetS can result in a longer, healthier and cancer-free life. Public health efforts aimed at reducing lifestyle patterns and dietary habits associated with this imbalance on insulin metabolism may have profound health benefits on a number of diseases including cancer, that represent major causes of mortality and morbidity in the world.

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