Why should the gastroenterologist bother about obesity ? An oncologic point of view

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Abstract

The incidence of obesity worldwide has increased dramatically during recent decades. As a consequence, obesity and associated co-morbidities constitute a serious threat in public health. Substantial epidemiologic evidence indicates that obesity is associated with increased risk of death, and increased incidence and progression of several cancers. Particular attention will be brought here to digestive and liver cancers. Plausible mechanisms by which obesity might participate to increased promotion and progression of cancer will be developed including hyperinsulinemia, insulin resistance and the pro-oxidative pro-inflammatory milieu characterizing the metabolic syndrome. We will focus on the specific case of hepatocellular carcinoma since the highest increase in mortality in obese individuals has been observed for this malignancy. Epidemiological evidence will be reviewed. We will next attempt to offer explanation for the higher risk of HCC in obese individuals although, at this point in time, we have insufficient knowledge to point towards the preeminence of factors directly related to obesity or more tightly linked to NASH itself, the underlying liver disease. (Acta gastroenterol. belg., **2010**, 73, **504-509**).

Key words : insulin resistance, non alcoholic steatohepatitis, heptocellular carcinoma, obesity, cancer, type 2 diabetes.

Abbreviation list

AMPK : AMP-activated protein kinase
BMI : body mass index
HCC : hepatocellular carcinoma,
IGF : insulin-like growth factor
IRS : insulin receptor substrate
MAPK : mitogen-activated protein kinase
NAFLD : non-alcoholic fatty liver disease
NASH : non-alcoholic steatohepatitis
PI3K : phosphoinositide-3 kinase

The incidence of obesity worldwide has increased dramatically during recent decades. Consequently, obesity and associated disorders now constitute a serious threat to the current and future health of all populations on Earth. The World Health Organization estimates that more than 1 billion adults worldwide are overweight, more than 300 millions of whom are clinically obese, as defined by a body mass index (BMI) equal to or greater than 30 kg/m^2. Particularly alarming is the equally marked increase in obesity among children.

Overweight and obesity are associated with an array of co-morbidities, including type 2 diabetes, cardiovascular diseases, fatty liver disease, degenerative disorders including dementia, chronic back pain, osteoarthritis, respiratory diseases, gallbladder disease and several cancers (1).

Substantial epidemiologic evidence indicates that obesity (BMI ≥ 30 kg/m^2) but also overweight are associated with an increased risk of death (2). Premature death in overweight subjects is principally due to cardiovascular diseases, hypertension and type 2 diabetes, but also to increased incidence and progression of several cancers (2). Several recent meta-analyses highlight the link between overweight or obesity and the occurrence of most types of digestive cancers, including esophageal adenocarcinoma (3), gastric adenocarcinoma (4), colorectal adenocarcinoma (5), liver cancer (6), gallbladder cancer (7) and pancreas adenocarcinoma (8). Accordingly, the risk of death from those cancers is increased in obese patients, and overweight and obesity might be responsible for approximately 14% of cancer deaths in men and 20% of cancer deaths in women in the U.S. (9). Data from the European Union are more optimistic, with 5% of all cancers being attributable to an excess body mass in the early 2000s (10). Nonetheless, 21,500 cases of colon cancer and 6,000 cases of gallbladder cancer are attributable to a high BMI each year in Europe (10).

In addition, the risk of progressive liver disease in obese patients should no longer be underestimated. Deaths from cirrhosis are reported to be higher than expected in obesity and diabetes. Obesity is increasingly recognized as a risk factor for hepatocellular carcinoma (HCC) although the relative contribution of the underlying liver disease itself versus obesity-associated factors remains difficult to establish. Pointing towards a role of obesity, the occurrence of HCC in the absence of cirrhosis is reported this setting. In addition, obesity and associated conditions are well recognized factors that participate to accelerate disease progression and fibrosis, particularly documented in chronic hepatitis C and alcohol-induced liver disease, and reduced antiviral treatment efficacy.

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In this review we will focus on the pathophysiologic processes plausibly mediating the connection between obesity and increased cancer incidence, cancer progression and death. We will focus on the specific case of liver cancer, since the highest increase in mortality in obese individuals has been observed for HCC.

The insulin resistant state : a pro-proliferative condition ?

Obesity is due to an imbalance between energy intake and utilization resulting from a relatively high dietary intake (both in quantities and quality) not compensated for by physical expenses. It is associated with various endocrine and hormonal imbalances. But more strikingly, obesity is associated with insulin resistance, low grade chronic inflammation and altered innate immunity (11). Insulin resistance is a state of reduced insulin sensitivity of insulin-responsive tissues. Its key consequence is the impaired ability of insulin to suppress hepatic glucose production and stimulate peripheral glucose uptake. This leads to hyperglycemia and, providing β-cell function is adequate, to compensatory hyperinsulinemia, the hallmark of insulin resistance.

Epidemiological and clinical evidence that justify an in-depth consideration of insulin resistance and hyperinsulinemia as factors in carcinogenesis have been reviewed elsewhere (12-15). Experimental data also offer strong support for such a mechanism and we would like to particularly highlight the study by Tran *et al*. (16). This study stems from the observation that lifestyle risk factors for colorectal carcinoma such as diets high in calories, saturated fat, and carbohydrates with high glycemic index, as well as low levels of physical activity, are remarkably similar to those for the development of obesity, insulin resistance and diabetes. Colon cancer and precancerous aberrant crypt foci can be induced in rodents by the injection of azoxymethane. In this model, tumorigenesis is enhanced by injections of insulin and reduced by caloric restriction. Tran *et al*. demonstrated that in rats fed a low, intermediate or high saturated fat diet colorectal carcinoma promotion was most strongly correlated with direct measures of insulin sensivity by hyperinsulinemic-euglycemic clamp studies (16).

Indeed, insulin can promote cell proliferation and survival (17,18). Insulin signaling is evoked upon binding of insulin to its receptors. Subsequent events involve auto-phosphorylation of the intracellular domain of the insulin receptor and phosphorylation of insulin receptor substrate-1 (IRS-1), which transmits the insulin signal via two major cascades distinguished by 2 principal mediators : the phosphoinositide-3 kinase (PI3K) and the mitogen-activated protein kinase (MAPK) (Fig. 1). Signaling via the PI3K pathway results in activating phosphorylation of the serin/threonin kinase Akt, which in turn activates or inhibits a large array of proteins that will affect cell growth, proliferation and survival, as well as lipid and carbohydrate metabolism. The PI3K pathway is one of the most commonly altered signaling pathways in human cancers (19).

Activation of insulin receptor can also promote, via the formation of a complex between the adaptor protein Grb2 and SOS, GTP loading and consequent activation of the small GTPase Ras. Ras lies at the head of the MAPK signaling pathway and provides a point of convergence for signaling by a number of growth factors. The importance of signaling via the Ras/MAPK pathway for cell proliferation and survival is shown by the high prevalence of Ras mutations in a range of cancers (20).

If it is easily understandable that hyperinsulinemia in normally sensitive cells would increase proliferation and survival, this effect should be buffered in insulin resistant cells which are characterized by their (partial) resistance to intracellular transmission of signals evoked upon binding of insulin to its receptor. However, there is some evidence that insulin signaling via the MAPK pathway is preserved despite inhibition of the PI3K cascade in insulin resistant cells. Indeed, insulin can activate farnesyltransferase, an enzyme essential for Ras anchorage to the cell membrane and activation, by an IRS-independent mechanism. Moreover, insulin may also up-regulate expression of Ras itself. Finally, in transformed cells, increased expression of insulin receptor or loss of the ability to down–regulate its expression in response to hyperinsulinemia may occur, increasing the pro-proliferative effect of insulin signaling (17,21,22).

In addition, in conditions of insulin resistance, insulin-like growth factor (IGF) signaling gains in importance. First, a shift towards increased expression of isoform A of the insulin receptor may occur, an isoform that also binds IGF-2 (insulin-like growth factor-2) which exerts growth promoting effects (21). IGF-1 signaling via its receptor (IGF1-Receptor) promotes cell proliferation and survival stronger than insulin does. Stimulation by Growth Hormone is the principal stimulus for IGF-1 release and insulin up-regulates hepatic Growth Hormone Receptor expression. There is considerable homology between the insulin receptor and the IGF1-Receptor, and insulin (even more when in excess or when affinity for its own receptor is decreased) can bind to and activate IGF1-Receptor. By this means, insulin can enhance the growth promotion due to IGF signaling.

AMPK is another intracellular intermediate potentially implicated in increased carcinogensis associated with hyperinsulinemia. AMPK acts as a metabolic sensor. Its activation results in inhibition of hepatic glucose production and lipid synthesis and in inceased muscle glucose uptake. AMPK activation can inhibit protein synthesis, cell growth and proliferation via inhibition of the mammalian target of rapamycin (mTOR) complex 1 (19). Metformin, a glucose lowering therapy, augments signaling via AMPK. In diabetic patients, metformin treatment is associated with the lowest risk of cancer those treated with insulin or insulin secretagogues (15). It is, however, difficult to evaluate the relative contribution of metformin's intracellular actions (activation of AMPK

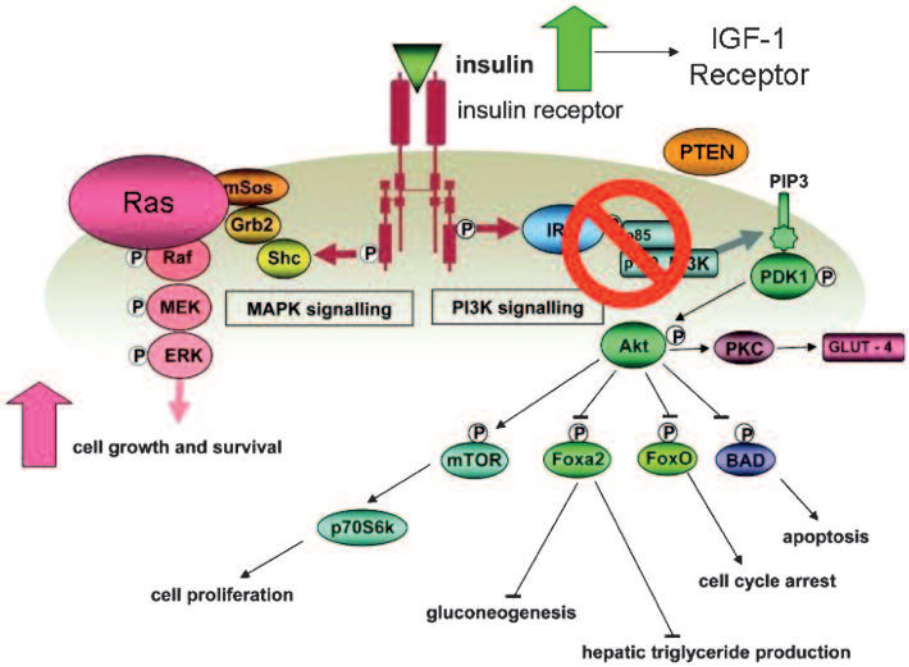

Fig. 1. — Principal signaling pathways activated by the insulin receptor and hypothetical scheme for enhanced cell growth and survival in insulin resistance.
In uncompensated insulin resistance, signaling via the PI3K pathway is diminished, glucose uptake by cells via GLUT-4 glucose transporter is reduced, suppression of gluconeogenesis is reduced and glucose levels rise. In compensated insulin resistance, the pancreas responds by increasing insulin secretion : signaling through PI3K pathway might be at least partially restored. However, increased insulin concentrations enhance signaling via the kinase of the MAPK pathway principally through increased activation of Ras. This occurs in an insulin receptor-dependent manner as well as via stimulation by insulin itself or hyperresponsiveness of the IGF-1 receptor pathway.
Adapted from (17), reproduced with permission.

and inhibition of mTOR) or consequences of lowering of glucose and thereby of insulin levels.

Obesity, insulin resistance and type 2 diabetes are closely associated with chronic inflammation characterized by abnormal cytokine production (in particular by the inflamed adipose tissue and known as adipocytokines) and also by activation of a network of inflammatory signaling pathways. Some of those pathways are mechanistically related to the induction of insulin resistance as it is the case for the NF-κB or the JNK pathways (18). Inflammation is also a key factor in tumorigenesis and cancer progression. ROS production by activated immune cells or induced by the insulin resistant state, participates to oxidative damage, in particular to DNA, a key factor in the somatic mutations that underlies tumorigenesis. The importance of NF-κB as well as other pro-inflammatory signaling responses in the promotion of carcinogenesis is now well recognized (23). Among the adipocytokines, leptin appears to have pro-oncogenic properties. Moreover, leptin induces the adipose tissue aromatase enzyme complex, which is expected to increase concentrations of the mitogenic sex hormone oestradiol. By contrast, obesity and insulin resistance are associated with reduced levels of anti-inflammatory (anti-NF-κB) and pro-apoptotic adiponectin. Importantly, as adiponectin signals via AMPK which inhibit cell growth and proliferation at least partly as a result of the inhibition of mTOR complex 1, reduced adiponectin might naturally decrease the pro-proliferative threshold.

Thus although insulin resistance can not be considered as a stand alone cancer risk factor, the pro-inflammatory, metabolic, and oxidative stress context related to obesity, insulin-resistance and metabolic syndrome is to be considered as favoring cancer genesis and progression. Yet, the link between obesity and cancer is not straightforward, and different pathophysiological mechanisms might be involved depending on the type of cancer. For instance, a large body of evidence points to an important role of insulin resistance in the development of obesity-related colon cancer (24) whereas, although obesity might stimulate their progression, chronic irritation due to gallstones or acid reflux is thought to be the main causal mechanism of gallbladder

cancer and esophageal adenocarcinoma, respectively (12,17).

Obesity and hepatocellular carcinoma : what is the connection ?

HCC accounts for the majority of primary cancer in the liver (the fifth most common cause of cancer and the third most common cause of cancer death worldwide). Most of the cases of HCC are typically associated with chronic hepatitis B and hepatitis C but the etiology of 15-50% of new cases, principally in developed countries where the incidence has increased in the last 2 decades, remains unclear and can not be related to a viral origin. This suggests that other risk factor(s) likely account for this increase.

NAFLD/NASH, associated with obesity and insulin resistance is becoming the most common etiology of chronic liver disease in most developed countries. Despite the lack of long-term prospective data, it is believed that a proportion of patients with NASH (25-35%) demonstrate progression of fibrosis with 8-10% progressing to cirrhosis. Among those patients, a majority develop a complication of cirrhosis including HCC. Retrospective data suggest that as many as 4-27% of cases of NASH will develop HCC after cirrhosis arises, although the overall occurrence of HCC in the setting of NAFLD remains a rare situation. Longitudinal outcome studies report the prevalence of HCC in NAFLD to be 0-0.5% and the prevalence of HCC in NASH to be 0-2.8% over a time period of 20 years (reviewed in (25,26)). Given the high prevalence of NAFLD/NASH, those small percentages represent a significant number of patients.

Cirrhosis is the most important single risk factor for HCC and is present in about 80% of patients with HCC, regardless the underlying liver disease. NASH likely accounts for a large proportion of idiopathic (cryptogenic) cirrhosis that represents 7-50% of underlying liver disease in patients with HCC in developed countries. This is further supported by evidence of common risk factors for NASH and HCC. In particular, as mentioned above, obesity has been established as a significant risk factor for the development of various malignancies, including liver cancer. In a large prospective mortality study, compared to subjects with normal BMI, the relative risk of mortality from liver cancer was respectively 1.68 and 4.52 times higher in women and men with BMI >35 kg/m^2 (9). Importantly, the presence of hepatic steatosis, along with obesity and diabetes mellitus has also been shown to increase the risk of HCC in patients with chronic HCV. The presence of steatosis in HCV, which correlates with BMI, increases the risk of HCC by 2.8 times compared with no steatosis.

In addition, multiple case reports of HCC in the context of NASH have been published in the recent years. Those occur at an older age compared to viral or alcohol related HCC, in patients that have (or have had for a prolonged time) underlying diabetes, obesity or other manifestations of the metabolic syndrome. In some cases (up to 30% in some small series), HCC is seen in the absence of cirrhosis raising the possibility that carcinogenesis in NASH may occur in the absence of advanced liver disease.

Altogether, this higher risk of HCC in obese individuals is likely to be related to either or both (and at this stage, we have insufficient knowledge to point towards the preeminence of one of those) the increased risk for NAFLD and subsequent NASH and the carcinogenic potential of obesity in itself, which in turn might be attributable to insulin resistance, oxidative stress and chronic inflammation. A recent work studying the occurrence of HCC in mice fed with a high fat diet highlighted the importance of the latter (27).

The mechanisms that mediate the interaction between NAFLD, NASH and HCC have not yet been elucidated completely. As it applies for other malignancies and developed above, the insulin resistant, oxidative and pro-inflammatory milieu is likely to participate to HCC promotion and progression. Some of the metabolic changes due to obesity and insulin resistance might be particularly salient in the liver and might offer plausible mechanistic explanation to this association. Indeed, the liver is an insulin sensitive organ, key in the regulation of lipid and glucid homeostasis and at the cross road between metabolic fluxes from the digestive tract (and therefore exquisitely exposed to dietary influences) and from the adipose tissue which, in conditions of insulin resistance, releases increased amounts of free fatty acid. As a consequence of its anatomic position, the liver directly collects the blood drained from intra-abdominal organs, including visceral adipose tissue, the adipose depot mostly incriminated in the metabolic syndrome. Therefore, free fatty acids and deleterious pro-inflammatory cytokines are readily transported to the liver, where their concentration will be higher than in other organs. Relevantly, AMPK activation is reduced in the insulin-resistant and NASH liver, partially due to decreased adiponectin. This in turns stimulates the activation of mTOR which constitute a pressure for protein synthesis and cell proliferation. Moreover, it has been demonstrated that leptin levels are increased in patients with NASH and that leptin might be produced ectopically in the liver of those patients, pointing out to a possible role for increased angiogenesis and invasiveness in HCC in the setting of the metabolic syndrome.

Second, in NASH, the innate immunity is altered and the inflammatory reaction is chronically activated. Particularly relevance, are the activation of NF-$\varkappa$B and JNK pathways that both participate to insulin resistance and cancer promotion.

Third, oxidative stress is prominent and a key pathogenic feature in NAFLD/NASH. It likely results from addition of several mechanisms such as increased fatty acid oxidation (β, ω and microsomal), decreased antioxidant defense mechanisms, mitochondrial dysfunction,

chronic inflammation, and evidence of macromolecule transformation by oxidative stress is part of NASH diagnosis. Oxidative stress may favor tumorigenesis through inflammation and cell proliferation or it may induce cancer-promoting mutation directly.

Fourth, NASH is characterized by hepatocellular injury and cell death, and indeed, ballooning and apoptosis are part of NASH diagnosis. This represents a stimulus for proliferation with possible fixation and amplification of DNA damages resulting from oxidative stress. Moreover, amplification of liver progenitor cells occurs in NASH, a cell compartment believed to stem cancer cells in the liver (28).

Evidence thus suggests a complex molecular interplay related to metabolic alterations, inflammatory cytokines and pathways, that leads to cell death, compensatory proliferation and ultimately carcinogenesis.

Concluding comments

Insulin *per se* can surely not be considered as a carcinogen. Rather, a complex interacting network of disturbances found associated with insulin resistance and that includes hypersulinemia, pro-inflammatory pathways, oxidative stress and metabolic alterations, likely favor cancer promotion and progression.

Some authors estimate that the global health burden of overweight and obesity may exceed that of cigarette smoking, at least in the U.S. (29), and gastroenterologists are facing part of this burden. An increasing amount of convincing data, part of which has been presented in this review, underlines the link between obesity and digestive cancers. These studies pave the way to exciting fundamental and clinical research, with the potential to discover new therapeutic targets for these dreadful diseases.

From a holistic point of view, the pro-proliferative effect of insulin might be seen a compensatory mechanism to adequately deal with elevated nutrient flux as it stimulates cell proliferation in pancreatic β-cells and fat cells. This mechanism ensures additional insulin secretion and additional fat storage capacity. This may have substantial advantages because it provides cells that can hold on to ingested fat and prevent its ectopic distribution elsewhere in the body and in particular prevent lipotoxicity in the liver. It is noteworthy that some ethnic groups such as African Americans, that have elevated insulin in obesity and increased cancer risk, have decreased risk of developing fatty liver (30). Interestingly, some variation in susceptibility to fatty liver has been traced to polymorphic variation in the adiponutrin gene *PLPLA3*, a gene linked to insulin secretion (31,32). This is important because it suggests that reducing levels of insulin in obesity as a strategy to prevent obesity-related cancers may have the unwanted side effect of reducing fat cell proliferation promoting fatty liver disease and possibly liver cancer.

The results of studies performed in bariatric patients suggest a reduction in the risk for cancer death after a large weight loss induced by bariatric surgery. However, it is not known whether weight loss in less severely obese or overweight individuals decreases the risk of cancer occurrence. Also nothing is known about strategies for weight loss that will most effectively reduce cancer risk. At this point in time, the common sense is to actively promote, in all patients, a balanced diet and a regular physical activity because such strategy has a positive impact on health and well-being and, in overweight patients it will more likely to be sustainable in the long run compared to more drastic strategies for weight loss.

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