SEGURIDAD y Promoción de la SALUD
Year 35 nº139 Third Quarter 2015
Fundación MAPFRE

Cancer and metabolic syndrome two convergent pathologies

Health Promotion

Over the last fifty years we have experienced breakneck changes in our environment, behaviour and lifestyle. These changes have triggered an alarming increase in the prevalence of the disorder cluster known as metabolic syndrome (MS). At present about 31 percent of the adult population suffers from this multifactorial disorder. In relatively recently times a correlation has been mooted between the components of MS and the increased incidence of some types of cancer, such as colon, pancreas, liver, prostate and breast cancer, among others. There is currently a wealth of epidemiological data suggesting a relation between obesity, endocrine-metabolic disorders, type 2 diabetes mellitus and cancer, but there is as yet no definitive data on the molecular bases of these relations, especially in cases such as pancreas, liver and colorectal cancer, which are the most frequent in these patients. Better knowledge of the common physiopathological processes of these illnesses would therefore enable us to identify targets both from the diagnostic and therapeutic point of view to forestall any tumour development among MS sufferers.

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The latest report by the Spanish Medical Oncology Society (*Sociedad Española de Oncología Médica*) called «The Situation of Cancer in Spain 2014», working from 2012 figures of the GLOBOCAN report, forecasts an increasing incidence up to 2015. It is now estimated that one out of every three males and one out of every five females will suffer from cancer in Spain.

The figures published by the Diabetes Foundation (*Fundación para la Diabetes*) are hardly more hopeful: nearly 13 percent of the adult Spanish population is now diabetic. Diabetes is also spreading much faster than WHO forecasts for this disease, and Spain is one of the countries recording the fastest increase of type 2 diabetes mellitus (DM2). A recent review of population studies, moreover, with over 24,000 persons analysed, has shown that 31 percent of the adult Spanish population now suffers from metabolic syndrome (MS), a non-causal cluster of various risk factors or disorders that increases the probability of suffering from DM2[1] and other pathologies.

Cancer represents a cost to Spain of nearly 9 billion euros a year, what with medical expenses, lost productivity and informal care (Congress of the European Society of Medical Oncology ESMO 2012). DM2 is not far behind; the most thoroughgoing studies point to a cost of between 2.4 and 2.675 billion euros a year, including hospital expenses,

consumables and the cost of insulin and oral antidiabetic drugs[2]. Cancer and MS are therefore frequent diseases with a huge healthcare impact and economic cost in Spain.

Recent epidemiological findings suggest an association between the incidence of cancer and DM2 or obesity, habitual MS pathologies

Recent epidemiological data also suggests an association between the incidence of cancer and DM2 or obesity, habitual MS pathologies. Overall, DM2 sufferers are at least twice as likely to have liver, pancreatic and endometrial cancer, and about 1.2-1.5 times as likely to have colorectal, breast and bladder cancer [3].

The aim of this study is carry out a review of the different molecular bases that relate diet, metabolic-endocrine changes and cancer, to help in the identification of a coordinated treatment for MS and cancer.

Pancreas, Liver and Colon: target organs in metabolic syndrome situations

DM or obesity sufferers are at greater risk from certain tumours; of these the most aggressive are pancreas, liver and colorectal cancer; these cancers also present the worst prognoses.

The pancreas plays a fundamental role in the control of glycaemia thanks to its cells' insulin-secretion capacity. In any MS patient there is a dysfunction of the pancreas cells, due mainly to an apoptosis-induced reduction in cell mass, together with a reduction in their regeneration, which has in turn been correlated with an increase in oxidative stress at tissue level[4]. Furthermore, a situation of prolonged hyperglycaemia produces cell fatigue; in the long run they become incapable of secreting enough insulin to reduce plasma glucose levels. Prolonged high plasma lipid levels, as often found in MS patients, are also associated with pancreas lipotoxicity, which once more tends to increase oxidative stress in the tissue. At functional level this manifests itself as the nuclear and cytoplasmic pleomorphism that is characteristic both of adenocarcinomas and pancreatic neuroendocrine tumours. This increase in free radicals at tissue level has also been correlated with a functional alteration of the pancreas and a concomitant development of tumours.

The liver is the biggest organ in the body and one of the most important due to its metabolic activity. Non-alcoholic steatohepatitis (NASH) is a fatty inflammation of the liver caused, among other factors, by obesity, DM2 and hyperlipidaemia, all present in the MS cluster. This build-up of fat in the liver cells is associated with hepatic inflammation and fibrosis, and could lead to chronic liver damage or cirrhosis, which is a very big risk factor for the onset of liver cancer. Some studies report a direct relationship between obesity and the incidence of liver cancer[5]. Some researchers also report a positive association between excess body weight measured as body mass index (BMI) and liver cancer onset[6]. Functional, histological and inflammatory alterations that might appear in this organ as a result of MS could bear a direct relationship with the likelihood of suffering from hepatocellular carcinomas.

The gastrointestinal tract or GI tract basically carries out three functions: processing of food, defence against pathogenic agents and secretion of various substances, including both paracrine and endocrine factors. Different MS-associated situations have been brought into relation with the GI tract, including altered gastrointestinal motility[7] and increased permeability of the intestinal barrier[8]. Alterations of the motor function are accompanied with autonomic neuropathy, also affecting the enteric nervous system[9]; this could be the underlying cause of cancer onset at GI tract level. An increase in epithelial permeability could be the forerunner of chronic intestinal inflammation[10], affecting homeostasis between microbiota and host[11]; this could also increase the colonic tissue's proneness to tumour development. Other studies have also shown that very high fat diets increase the number of preneoplastic lesions in the colonic tissue[12]; it is also known from experimental studies that diets of this type increase triglyceride precursors that are deposited on the tip of small intestine villi, producing oxidative stress and favouring polyp development[13].

Molecular bases that relate metabolic syndrome and cancer

As already pointed out there is as yet little to go on in terms of whether the molecular or physiopathological bases relating MS and cancer (mainly pancreas, liver or colorectal) are the same as those impinging on MS independently. This section therefore looks at some of the bases proposed up to now.

The importance of adipose tissue

Leptin serves as an appetite-inhibiting, base-metabolism-boosting metabolic signal that promotes the use of accumulated fat. Although its main action is exerted at the level of the central nervous system, this hormone is also known to act at peripheral level, existence of its receptors having been demonstrated at this level[14]. Epidemiological studies have related high plasma leptin levels with cancer; the expression of leptin receptors in different types of cancer has been described[15]. Leptin, when joining up with its receptors, triggers a series of intracellular mechanisms involving mediators like ERK and

STAT3 and the MAPK pathway; this enables it to act as a growth factor, contributing to the initiation or proliferation of the tumour[16]. Leptin is in fact capable of stimulating the growth of epithelial cells of the colon[17]. Experimental studies have also shown leptin's role in carcinogenesis. The increase of circulating leptin levels in obese mice increases these animals' proneness to induced colorectal cancer[18].

Within MS a leptin resistance is developed, thereby increasing plasma leptin levels and hence the possibility of this hormone exercising proliferative effects

Within MS a leptin resistance is developed, thereby increasing plasma leptin levels [19] and hence the possibility of this hormone exercising proliferative effects. It is not yet known if the expression of leptin receptors is increased in tissues like pancreas, liver or colon in MS situations; if so, this would make these tissues more sensitive to leptin's proliferative activity.

Adiponectin is another one of the hormones released by adipose tissue. It has an insulin-sensitizing effect, reducing resistance to insulin and the development of DM2. Adiponectin also reduces the plasma levels of free fatty acids and has anti-inflammatory and antiatherosclerotic properties [20]. Several epidemiological studies have suggested that adiponectin has anti-carcinogenic effects in colon, endometrial, kidney or breast cancer[21]. The mechanisms that might account for adiponectin's anti-carcinogenic effect are not yet well known but the following have been suggested: a "downwards" regulation of its receptors[22], increasing activity of the cAMP-dependent kinase, which is a key factor in regulation of the proliferation in response to the nutritional state[23], an increase in ceramidase activity and an alteration of sphingolipid metabolism[24].

Adiponectin levels are reduced in MS situations[25]; this might drive an increase in cell proliferation processes in these patients. It is not yet known whether the expression of adiponectin receptors is reduced in tissues like the pancreas, liver or colon in MS situations; if so, this would «unprotect» these tissues from the anti-proliferative action of the adiponectin.

In metabolic syndrome situations there is an underlying state of inflammation largely triggered by the adipose tissue; this could be favourable to the development of tumours

Various proinflammatory cytokines like TNF-., interleukins (IL-6, IL-8, IL-10), macrophage inflammatory protein (MIP-1), chemotactic factors, etc.[26], are also released from adipose tissue. Inflammatory situations or processes have been related with many types of cancer (stomach, pancreas, prostate, liver, bladder and even colorectal); this is so because inflammatory cytokines impinge on growth, apoptosis and cell proliferation[27]. In obesity situations this inflammatory state is accompanied with macrophage infiltration into various tissues, contributing to invasion of the tissue, angiogenesis and metastasis[28].

In MS situations there is a state of underlying inflammation largely driven by adipose tissue; this could be favourable to the development of tumours in the pancreas, liver and colon in these cases.

The importance of hyperglycaemia and hyperinsulinemia

One of the characteristic features of MS is the presence of high blood levels of glucose. This hyperglycaemia might be very favourable to tumour growth and development since the cancerous cells have a boosted metabolism and high glucose demand. Epidemiological studies have associated hyperglycaemia with a higher cancer risk[3], although the mechanisms involved in this relation are not yet known with any precision. It is known that cancer cells, to adapt to this high glucose demand, overexpress glucose transporter proteins like GLUT1, GLUT3 or GLUT12[29], and that the metabolic increase of tumour cells is associated with a higher ATP demand, whereby all glycolysis-associated enzymes are also increased in the tumours[30]. A recent study[31] has shown that, in tumour cell lines of the colon, breast, pancreas or liver, high glucose levels in the medium drive an overproduction of Wnt and thereby of beta-catenin with consequent transport to the nucleus and activation of transcription factors.

All these hyperglycaemia-associated pro-tumour processes could contribute towards a higher cancer incidence among MS sufferers, but there is as yet no conclusive data on the matter.

Most obesity and DM2 situations promote insulin resistance to a lesser or greater degree; in the case of DM2, moreover, this is usually associated with an increase in circulating insulin levels[32]. This insulin resistance and hyperinsulinemia are also frequently observed in MS situations[33]. Under normal conditions insulin released from pancreas cells favours the cells' glucose takeup and keeps glycaemia within a normal range. In situations of insulin resistance and hyperinsulinemia, however (MS), other anabolic functions of this hormone come to the fore, such as cell proliferation. Various experimental studies have shown that insulin administration several times a week increases the development of colon cancer[34]. It is also known that the expression of insulin-like receptors (INR) is increased in colon and breast tumours[35].

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colon in MS situations; if so, this could be associated with a greater likelihood of tumour development.

As well as insulin, the so-called insulin-like growth factors (IGF type 1 and 2) have also been related at experimental level with the development or growth of different types of tumour[36]. Hyperinsulinemia also increases liver secretion of IGF-1 and IGF-2 and also in neoplastic tissues[37]. IGF-1 and IGF-2 act through their membrane receptors. The receptor IGF-1 is overexpressed in various solid tumours[38]. Activation of these receptors activates in turn the intracellular signalling pathways RASMAPK and PI3K-AKT, the second of which activates mTOR, promoting translocation of proteins and tumour growth[39]. Experimental obesity models have described high circulating levels of IGF-1 and IGF-2[40]. Circulating levels of these growth factors have been related with the incidence of prostate cancer in humans[41].

There have as yet been no studies into plasma or tissue levels of IGF-1 and IGF-2 and their corresponding receptors in MS situations and their relation with the increase in tumour incidence in these situations.

The importance of dyslipidemia and oxidative stress

An important consequence of high levels of free fatty acids is their lipotoxic effects, as a result of their build-up outside adipose tissue. This situation is typical of obesity and MS situations, where the accumulation of fats in tissues like the pancreas or liver, together with an underlying inflammation, might drive the production of reactive oxygen species[45], highly correlated with processes of mutagenesis and carcinogenesis[44].

Diet strategies designed to modulate microbiota composition, based on functional ingredients, could help to control MS-associated disorders

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Moreover, the production of reactive oxygen species with mutagenic capacity might also arise from hyperglycaemia situations, which, as already pointed out, are part of the MS cluster. In hyperglycaemia the excess of glucose is transformed into sorbitol by aldose reductase. This reaction consumes NADPH, which is necessary for the regeneration of reduced glutathione, increasing oxidative stress. For its part non-enzymatic glycosylation of proteins, which occurs during hyperglycaemia, generates products that then link up with their corresponding receptors in macrophages or endothelial cells producing more reactive oxygen species and also activating intracellular signalling pathways that then activate the transcription factor NFk,[47]. These receptors seem to play an important role in intestinal tumour processes and have been associated with the production, metastasis and worsening of colorectal cancer in clinical studies [48].

Table 1. Summary table of endocrine-metabolic mediators involved in cancer onset and possible mechanisms involved.

Mediators	Type of cancer	Mechanism
Leptin (LEP) and leptin receptor (LEPR)	Breast, colon, prostate[15]	• ERK and STAT3 pathway. MAP Kinase pathway[16,17,18]
Adiponectin	Colon, endometrial, kidney, breast[21]	• Downward regulation of its receptors[22] • Increase in cAMP dependent protein kinase activity[23] • Alteration of sphingolipid metabolism[24]
Proinflammatory cytokines: TNF-α, IL-6, IL-8, IL-10, MIP-1	Stomach, pancreas, prostate, liver, bladder and colorectal[27, 28]	• Impinge on growth, apoptosis and cell proliferation[27, 28]
Glucose transporter proteins: GLUT1, GLUT3 or GLUT12 and glycolysis proteins	Colon, breast, pancreas or liver[3]	• Overexpression of glucose transporter proteins[29] • Alteration of glycolytic enzymes [30]

Mediators	Type of cancer	Mechanism
		• Boosted production of Wnt and ß-catenin, activating transcription factors[31]
Insulin and insulin-like receptor (INR)	Colon and breast[34, 35]	Unknown
IGF 1 and 2 (insulin-like growth factors)	Breast, colon, prostate [36, 38, 41]	• Activation of intracellular pathways RAS-MAPK and PI3K-AKT - mTOR producing translocation of proteins and tumour growth[39]
Fatty acids and molecules involved in their synthesis	Prostate, breast[43]	• Increase in lipid synthesis and expression of fatty acid synthase (FAS)[43] • Increase in monoacylglycerol lipase, (MAGL)[44]
Reactive oxygen species (ROS)	Colorectal [48]	• Non-regeneration of reduced glutathione • Non-enzymatic glycosylation activates intracellular signalling pathways that in turn activate the transcription factor NFk[47]

All these factors could suggest that in MS situations, where dyslipidemia, hyperglycaemia and an underlying inflammatory state occur jointly, there is an increase in the formation of free fatty acids and final products of protein glycosylation, which could increase the tumour risk in the pancreas, liver or colon.

The importance of microbiota

In recent years gut microbiota have been considered to be a new factor that might have a key influence on the regulation of body weight and MS cluster diseases[49]. Imbalances in the gut ecosystem (dysbiosis) and endotoxemia could be inflammatory factors responsible for the development of insulin resistance and an increase in body weight. Alterations of this ecosystem, moreover, have been related with the onset or development of certain types of cancer[50]. Diet strategies designed to modulate microbiota composition, based on functional ingredients, could help to control the most frequent MS-associated disorders more effectively, thus reducing the incidence or prevalence of certain types of cancer.

There is little to go on at present in terms of MS-induced alteration of microbiota, the integrity of the gut epithelium and the proneness of this tissue to develop a tumour process.

Conclusions

There are hardly any studies clearly establishing the physiopathological or molecular bases relating MS with the proneness to suffer certain types of cancer, particularly of the pancreas, liver and colon. The aim of this review has been to delve into the knowledge of these bases. The analysis of tissue or plasma tumour markers or urine and faeces markers as mentioned in this review could lay down the bases for including new tumour markers conducive to early diagnosis of tumour proneness in MS patients.

Acknowledgements

This work has been financed by a FUNDACIÓN MAPFRE research grant.

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