Diabetes and cancer: a short review for internists

Diabetes e cancro: uma revisao breve para internistas

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Abstract

The risk of developing a range of cancers is moderately increased in type 1 and type 2 diabetes. Obesity, insulin resistance, hyperinsulinemia, and diabetes therapy with insulin, insulin analogues and sulfonylureas may be responsible for this fact. Metformin seems to have a protective effect. We examined all these aspects, and believe that the current aetiopathogenic link among diabetes, diabetes treatment and cancer is tenuous, further studies are necessary.

Key words: diabetes, cancer, insulin, insulin analogues, sulfonylureas, metformin.

Resumo

A diabetes tipo 1 e a diabetes tipo 2 são um risco moderadamente elevado para o desenvolvimento de uma série de cancros. A obesidade, a insulinoresistência, a hiperinsulinemia, e o tratamento da diabetes com insulina, análogos de insulin e sulfonilureias sao provavelmente responsáveis para este facto. A metformina parece ter um efeito protector. Nós examinámos todos estes aspectos, e achamos que a associaçao etiopatogénica actual entre a diabetes, o tratamento da diabetes e o cancro é escassa, são necessários mais estudos.

Palavras chave: diabetes, cancro, insulina, análogos de insulina, sulfonilureias, metformina.

INTRODUCTION

Numerous papers have been published about the risk of cancer for type 2 diabetes. This disease is associated with three of the five leading causes of cancer mortality in the USA, i.e., carcinoma of the colon, pancreas and breast (postmenopausal). The excess risk for carcinoma of the colon is ~30 %, for carcinoma of pancreas ~50 % and carcinoma of breast ~20 %.[1]

There are a few publications, concerning the risk of cancer for subjects with type 1 diabetes. Type 1 diabetes carries an excess cancer risk of ~20 %, and involves a different range of tumours, such as cancers of the stomach and skin (squamous cell carcinoma), and cancer of the cervix and endometrium. Significant excess has also been observed for leukaemia; increased risk of acute lymphatic leukaemia accounted for most of the variation of leukaemia risk; this risk is higher in females compared with males, and higher at the age over 10 years compared with younger subjects.[2,3]

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We aim to briefly analyse some factors, possibly involved in this modest increase of cancer risk in type 1 and type 2 diabetes.

Obesity, type 2 diabetes, insulin, and cancer

Overweight or obesity is found in most of type 2 diabetics. The major cancers linked with type 2 diabetes are associated with obesity or insulin resistance. Insulin resistance leads to hyperinsulinaemia, and to an elevation in the availability of insulin-like-growth-factor (IGF-1) – another known tumour growth factor-. IGF is mediated by a reduction in IGF binding protein 1 (IGFBP-1) levels. It may be that these changes in the insulin-IGF-1 axis provoke the survival and progression of early malignant foci.[1,4,5]

The insulin-IGF-1 axis, type 2 and type 1 diabetes, and cancer

Insulin and IGF-1 are considered as sister molecules which share a common descent but diverged early in vertebrate evolution. They have co-evolved with their receptors to subserve different metabolic or trophic functions. The ability of insulin to potenciate the action of IGF-1 has been observed in a variety of tissues. This insulin action has been found in response to endogenous (secondary to insulin resistance, mainly in type 2 diabetes) or exogenous hyperinsulinaemia (secondary to iatrogenic overinsulinisation, mainly in type 1 diabetes).[1,5,6]

Other growth factors, insulin, and cancer

Insulin resistance and endogenous or exogenous hyperinsulinaemia can also increase cellular mitogenic responsiveness to other growth factors than IGF-1. The diminished strength of insulin signaling along the canonical phosphatidylinositol 3-kinase (PI3K) pathway and reduction of its action is due to insulin resistance. The hyperinsulinaemia leads to overstimulation of the mitogen-activated protein kinase (MAP kinase) and activation of farnesyltransferase and increase of farnesylated Ras. Thus, the mitogenicity will be enhanced. Hyperinsulinaemia decreases the hepatic synthesis and blood levels of sex hormone-binding globulin. Therefore, it comes to an increase of bioavailable estrogen in both men and women and elevated levels of bioavailable testosterone in women but not in men. Hyperinsulinaemia leads to an increase of androgen synthesis in the ovaries and possibly the adrenal glands in premenopausal women. Augmented endogenous sex steroid levels are associated with a higher risk of postmenopausal breast, endometrial, and possibly other cancers.[1,5,6]

Hyperglycaemia and cancer

Most cancers have highly effective insulin-independent glucose uptake mechanisms. The adenosinetriphosphoric acid (ATP) generation by glycolysis needs far more glucose than oxidative phosphorylation. This is the basis for ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), which is used for detecting tissues with high rates of glucose uptake like cancer tissues. Therefore, the possibility that untreated hyperglycaemia facilitates neoplastic proliferation deserves consideration. However, clinical data regarding this aspect are sparse and controversial.[1,5,6]

Cytokines, type 2 diabetes, and cancer

Type 2 diabetes is mostly related with obesity. Adipose tissue produces interleukin-6 (IL-6), monocyte chemoattractant protein, fatty acids, plasminogen activator inhibitor-I (PAI-I), leptin, adiponectin, and tumour necrosis factor-alpha; all these factors may lead to malignant transformation or cancer progression; cytokine IL-6 may enhance cancer cell proliferation by activation of signal transducer and activator of transcription protein (STAT) signaling; the expression of PAI-I may link to breast cancer; changes in cytokine IL-6 and insulin levels induced by hypercaloric diets may lead to the development of neoplasia.[1,5,6]

Insulin analogues and cancer

First all all, we have to consider two potentially relevant observations, providing the essential background for any discussion, concerning insulin therapy and cancer: 1) the insulin levels within the physiological or therapeutic range are associated with the rate of tumour diagnosis; and 2) the intrinsic mitogenicity of insulin may vary according to the functional plasticity of the insulin-IGF-1 signalling network, particularly in tumour cells.[1,5]

The short-acting and long-acting biosynthetic human insulin analogues in current clinical use result from the modification of structure of insulin molecule, and might be associated with an increased risk of tumour progression. Therefore, they have been subjected to the mandatory preclinical testing procedures. A variety of systems, including human osteosarcoma cells and human mammary epithelial cells, has been used to demonstrate receptor affinities and mitogenic potencies of these insulin analogues (lispro, aspart, glulisine, detemir and glargine). The three short-acting insulin analogues (lispro, aspart and glulisine) showed a slight increase in IGF-1 receptor affinity compared with that of human insulin. The long-acting insulin analogue (detemir) seems to show reduced metabolic and mitotic potencies in vitro compared with human insulin. The long-acting insulin analogue (glargine) has a six- to eightfold increase in receptor affinity and mitogenic potency compared with human insulin.[1,5]

Otherwise, a pancreatic cancer cell line responded similarly to insulin glargine and human insulin. An other experiment demonstrated proliferative alterations and increased resistance to apoptosis in breast, colorectal and prostate cell lines under pharmacological doses of insulin analogues lispro, detemir and glargine, but not in response to human insulin.[1,5,6]

The first of the insulin analogues to be developed, insulin B10Asp, was based on a single amino acid substitution. It had a tenfold increase in mitogenicity, compared with human insulin. After 2 year carcinogenicity studies in rodents, this insulin analogue was withdrawn when mammary tumours appeared in rats.[1]

Recent studies about insulin glargine and cancer risk in humans, and protective effect of metformin

The recent four publications[1,5,7-11] of data extracted from population registries in Germany, Sweden, UK

and Scotland included more than thousand type 2 diabetics.

In the German study, after an average of 1.6 years of follow-up the incidence of cancer per 100 person-years was 2.5 in subjects using human insulin, 2.2 in those using insulin aspart, 2.1 in those using insulin lispro and 2.1 in those using insulin glargine. The risk of cancer increased with higher average doses of human insulin; the incidence values per 100 person-years were 1.7, 2.4 and 3.1 for <20, 20-40 and >40 U, respectively; the corresponding incidence values for insulin glargine were 1.9, 2.0 and 5.3; the adjusted hazard ratio (HR) for insulin glargine vs human insulin was 1.6 within doses >40 U, but around 1 for lower dose strata. However, treatment groups were not directly comparable: subjects had different distributions of age, sex, history of hospital stay, concomitant medications, including oral hypoglycaemic agents, and geographic region.[1,5,7]

In the Swedish study with an average of 2 years of follow-up, there were no differences among the insulin users for cancer overall, nor any statistically significant increased risk with increasing daily defined doses of insulin glargine. For breast cancer, compared with users of insulin alone other than insulin glargine, the HR was 2.0, 95 % confidence interval (CI) 1.3-3.0 for users of insulin glargine only and 1.2, 95 % CI 0.8-1.7 for users of insulin glargine in combination with other insulins. The HR was 0.8, 95 % CI 0.6-1.0 for myocardial infarction and 0.8, 95 % CI 0.7-1.0 for mortality of women, using insulin glargine alone. Treatment groups were not comparable, considering the age and other subjects data. The cancer risk was not dependent on insulin dose. Gastrointestinal and prostate cancers were not associated with type of insulin.[1,5,8]

In the UK study, after an average of 2 years of follow-up, the incidence of cancer per 100 person-years was 0.9 for metformin only, 1.6 for sulfonylurea only, 1.1 for metformin plus sulfonylurea and 1.3 for insulin initiators. However, metformin users had better compliance and metabolic control than other groups. Compared with metformin only, the adjusted HRs were 1.1, 95 % CI 1.0-1.2 for metformin plus sulfonylurea, 1.4, 95 % CI 1.2-1.5 for sulonylurea only, 1.4, 95 % CI 1.3-1.6 for insulin and 1.1, 95 % CI 1.0-1.3 for non-pharmacological therapy. The risk for insulin regimens was specifically elevated for colorectal cancers (HR 1.7) and pancreatic cancers (HR 4.6), but not for breast or prostate cancers. Cancer rates were similar for all insulins including insulin glargine; any relation between insulin dose and cancer risk was not found. Metformin addition to insulin was associated with HR 0.54, 95 % CI 0.43-0.66. These findings point to a protective effect of metformin on cancer risk.[1,5,9]

The patients were followed about 4 years in the Scottish study. Individuals on insulin glargine with rapid-acting insulin had a lower rate of cancer progression than those on human insulin, HR 0.8, 95 % CI 0.55-1.17. Subjects on insulin glargine alone had a higher overall rate, HR 1.55, 95 % CI 1.01-2.37. The number of site-specific cancers was small, but there were more cases of breast cancer in those on insulin glargine alone, compared with those on non-glargine insulins, HR 3.39, 95 % CI 1.46-7.85.[1,5,10]

In summary, the German study showed an overall elevated risk of cancer dependent on dose for any type of insulin; the cancer risk increased with higher average doses of any insulin. In the Swedish and Scottish studies, individuals on insulin glargine only had a higher risk of breast cancer than users of other insulins. An association between insulin, and paticularly insulin glargine, and increased risk of cancer was not found in the UK study; the most striking finding of the UK study is the probable protective effect of metformin: the UK study has shown that the risk of cancer in subjects on metformin is equivalent to those prior to diabetes medication; the combination with metformin reduces the rate of progression of cancer associated with sulfonylurea or insulin; metformin decreases the rate of cancer of the colon or pancreas; a reduction for cancer of the breast or prostate has not been found. The potential strengths and weaknesses of these studies have been broadly debated; the complete data of diabetics have been rarely accounted; all this precludes the use of comparator medications; the studies are retrospective, therefore statistically not relevant; they included only type 2 diabetes subjects, therefore, any statement concerning type 1 diabetes is not possible.

We have to mention one more recent study using the manufacturer's (sanofi-aventis) pharmacovigilance database for all randomized clinical trials comparing insulin glargine with any comparator in type 1 or type 2 diabetes.[12] The database included 31 studies, 12 in type 1 diabetes and 19 in type 2 diabetes with 10,880 persons, overall (insulin glargine,

5,657; comparator, 5,223). Twenty studies compared insulin glargin with NPH insulin, 29 were parallel-group studies and two had a crossover design. Studies were of around 6 months duration, except one with a duration of 5 years. In this retrospective study, insulin glargine was not associated with an increased incidence of cancer, including breast cancer, compared with the comparator group.

It has recently been published randomized clinical trial data from an open-label, 5-year trial of insulin glargine vs NPH insulin; an evidence of excess cancer risk was not found in the insulin glargine group; among the approximately 1,000 type 2 diabetics randomized, there were 57 cancer cases in the insulin glargine group and 62 cases in the NPH insulin group.[1,5]

Metformin and cancer

The above observations suggest that metformin may come to play a major role in cancer prevention in diabetes. Furtheremore, it has been demonstrated that metformin abrogates sitagliptin-induced pancreatic ductal metaplasia, a precursor of carcinoma, in a rat model of type 2 diabetes. Laboratory studies have demonstrated that metformin inhibits cell proliferation, reduces colony formation, and causes partial cell cycle arrest in cancer cell lines. The reason for this fact is possibly the partial inhibition of protein synthesis and tumour growth inhibition due to metformin-induced activation of 5'adenosine monophosphate-activated protein (AMP)-activated protein kinase (AMPK) in tumour cells. Metformin may have lesser antineoplastic activity in mice receiving a control diet than in mice receiving a high-energy diet associated with hyperinsulinaemia and accelerated tumour growth. The insulin-lowering action of metformin leads possibly to its antineoplastic activity. In less hyperinsulinaemic subjects, there is no effect of metformin on cancer development or progression. The effect of metformin on breast cancer cell proliferation is currently being evaluated, and other clinical trials of metformin therapy in patients with breast cancer are planned.[1,5,9]

Thiazolidinediones and cancer

These substances do not increase insulin secretion. They decrease insulin resistance and hyperinsulinaemia in diabetic subjects, and reduce levels of both circulating glucose and insulin. It has been demonstrated in vitro studies that these substances inhibit growth and induce apoptosis and cell differentiation. Based on these anticancer activities, thiazolidinediones are currently considered a potential target for chemoprevention and cancer therapy. On the other hand, rodent studies have shown that these drugs can potentiate tumourigenesis. It may be that these insulin-sensitizers increase, decrease, or have a neutral effect on the risk of cancer or cancer progression in humans. Therefore, the use of these substances for cancer prophylaxis or treatment is very questionable. The results of a few clinical trials are largely negative; other studies in humans are in progress, or planned. At present, definitive human data regarding the cancer risk and thiazolidinediones are not available.[5]

Sulfonylureas, glinides, and cancer

This drugs increase endogenous insulin levels. A few observational studies found a higher risk of cancer or cancer death among diabetic subjects on sulfonylureas compared with those on metformin or other diabetic medications. However, these studies are not sufficient to examine associations with specific cancer sites because of very low cancer cases in the sulfonylurea groups. Studies considering dose, duration, recency , and persistence of use are limited.[5]

There are no published data to date, regarding an association between the glinide and cancer risk. The use of these substances is newer and less common. This may be the reason for this fact. More detailed long-term studies are necessary to examine a possible association between the sulfonylureas, glinides and cancer risk.[5]

Incretin-based diabetes medication and cancer

Following substances of this group are used for the therapy of type 2 diabetes: exenatide, liraglutide, sitagliptine and vildagliptine. All these agents augmented beta-cell proliferation in animal studies. Sitagliptine increased pancreatic ductal hyperplasia in one small study of a transgenic rodent model. Liraglutide was found to increase the risk of medullary thyroid cancer in rats and mice and was associated with slight elevations in serum calcitonin in human trials. No impact of incretin-based drugs on human cancer incidence has been reported, perhaps because these drugs are newer, more experience and further investigations are necessary.[5]

COMMENT AND CONCLUSION

Type 1 and type 2 diabetes are associated with a modest excess risk of several of the more common cancers; the cancers found in subjects with type 1 diabetes differ from those associated with type 2 diabetes; patients with type 1 diabetes may have a different cancer risk pattern than patients with type 2 diabetes.

Carcinogenesis is a complex process. A critical question is whether the association between diabetes and the risk of certain cancers is largely due to shared risk factors, or whether diabetes itself with its typical metabolic alterations increases the risk of some types of cancer.

Diabetes and cancer may be associated simply because they share common predisposing risk factors such as obesity; however, we have to consider several plausible biologic mechanisms related to diabetes like insulin resistance, hyperinsulinaemia, hyperglycaemia, and adipose tissue cytokines and hormones which may mediate malignancy or cancer progression.

Regarding diabetes therapy and cancer risk, studies in humans up to the present have a limited relevance. Only a few clinical trials with sulfonylureas, glinides and thiazolidinediones have been conducted; however, definitive human data are not available. No impact of incretin-based agents on human cancer incidence has been reported, likely because these drugs are newer. Observational human studies suggest that metformin is associated with a reduced risk of cancer. Recently, some retrospective clinical studies examined a possible association between the use of the long-acting insulin analogue glargine and/or the use of other insulins and an increased risk of cancer; there is no evidence that insulin causes cancer; there is no evidence of an overall increase in the rate of cancer development in patients on insulin glargine; it has not proved possible to place the other long-acting insulin analogue detemir under similar scrutiny, but it would be prudent for this insulin analogue to be investigated in more detail; the short-acting insulin analogues do not appear to present a possible cancer risk; these data are insufficient to confirm or refute a carcinogenic effect of specific insulins on specific cancers.

Investigations are necessary to provide a clearer understanding, concerning a possible association between different factors and biologic mechanisms related to diabetes and the risk of cancer. It is difficult to assess an independent association between specific treatment of diabetes and cancer risk; further prospective and appropriately designed studies are needed. ■

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