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REVIEW

Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients

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Abstract Cancer incidence and mortality are higher among diabetic patients. This review examines the mechanisms, both general and site-specific, for this increase.

Hyperglycemia and hyperinsulinemia, which are the major abnormalities that characterize diabetes, can promote cancer via both independent and synergic mechanisms. Insulin is both a metabolic hormone and a growth factor that promotes cell proliferation. When insulin levels are increased due to either insulin resistance or insulin treatment, their mitogenic effect is more marked in malignant cells that frequently overexpress the insulin receptor and, more specifically, its A isoform that has predominant mitogenic activity. Hyperglycemia provides energy for malignant cell proliferation and, via the peculiar energy utilization of cancer cells, favors cancer growth and neoangiogenesis.

Additionally, diabetes-associated obesity has cancer-promoting effects due to mechanisms that are specific to excess fat cells (such as increased peripheral estrogens, increased promitogen cytokines and growth factors). Also fat-associated chronic inflammation can favor cancer via the cell damage caused by reactive oxygen species (ROS) and via the production of inflammatory cytokines and transcription factors that stimulate cancer growth and invasiveness. Finally, the multiple drugs involved in the treatment of diabetes can also play a role.

Diabetes-associated comorbidities, tissue-specific inflammation, and organ-specific dysfunctions can explain why the risk of cancer can differ by tissue type among diabetic patients.

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The increased risk of cancer-related mortality is moderate among individual patients with diabetes (RR = 1.25), but the pandemic nature of the disease means that a considerable number of lives could be spared through a better understanding of the factors associating diabetes and cancer.

Clinical studies and meta-analyses indicate that diabetes is associated with an increased risk of several types of cancer, including cancers of the liver, pancreas, colorectum, bladder, endometrium and breast. The relative risk ranges from 1.2 to 1.5 for breast, colon and bladder cancers to 2.0—2.5 for liver, endometrial and pancreatic cancers [1]. Additionally, cancer mortality is increased among diabetic patients; therefore, diabetic patients not only have more cancers but also a shorter overall survival with cancer [2]. Only few reports do not confirm this association except for prostate cancer that is reduced in diabetic patients [3,4].

Because diabetes mellitus is a pandemic disease and a growing health problem worldwide, even a small increase in cancer incidence and mortality among these patients may have important consequences at the population level. Therefore, a better understanding of the mechanisms that favor cancer in diabetic patients would prevent many cancer deaths and reduce the social and economic burdens of cancer.

The major obstacle to a better understanding of the association between diabetes and cancer is the complex and chronic nature of diabetes, nearly always accompanied by comorbidities. Moreover, cancer is also a very heterogeneous disease, with tumors of the same histotype having important genetic and molecular differences that markedly affect the clinical course of the cancer and its responsiveness to treatment.

The association between diabetes and cancer is based on both general mechanisms acting through the metabolic, hormonal and inflammatory characteristics of diabetes and also, in an independent or additive manner, on site-specific mechanisms related to organ comorbidities that affect most diabetic patients.

General mechanisms

Hyperinsulinemia

Hyperinsulinemia is a chronic condition that is present in the large majority of diabetic patients. Both type 1 diabetic patients (having an absolute requirement for exogenous insulin, with peripheral tissue hyper-insulinization and liver relative hypo-insulinization) and type 2 diabetic patients (with insulin resistance and compensatory endogenous hyperinsulinemia) are exposed to elevated insulin concentrations for decades.

The role of insulin in promoting cancer growth was first recognized in experimental animals [5], and later confirmed in a number of in vitro studies in cancer cells [6,7]. The evidence in diabetic patients remains circumstantial because prospective, randomized, long-term trials are difficult in a complex disease with multiple and changing treatments. For insulin analogs in vitro data suggest an increased pro-cancer effect of long-acting analogs [8] but data in vivo are limited and controversial, mainly based on observational, retrospective studies that were criticized for both analysis and statistical procedures [9]. Also the recent study, which suggests that glargine insulin treatment has neutral effects on cancer incidence and mortality has not resolved the issue [10,11]. Cancer, in fact, was not a primary endpoint of glargine treatment and several factors, critical for cancerogenesis, were not considered. These include the type of patients (not all diabetic), the treatment with additional medications such as sulfonylureas (potential cancer promoters) and metformin (potential cancer antagonizer), the inaccurate cancer identification (definite, probable, or possible) the short observation period for carcinogenesis and the low dose of glargine (median, 0.3—0.4 U per kilogram of body weight) [12]. Recent retrospective clinical studies seem to confirm that in diabetic patients the cancer risk is related to the dose and the length of insulin treatment [13,14].

Insulin has both metabolic and mitogenic effects via its own receptor and the cognate type I IGF receptor (IGF-IR). Insulin activates the insulin receptor (IR) and post-receptor signaling by engaging on the IR binding site [15], causing conformational changes and tyrosine phosphorylation of the receptor β-subunit, recruitment of intracellular molecules and post-receptor signaling via a complex network of redundant signals. In a simplified model, the mitogenic activity of insulin mainly occurs via the post-receptor MAPK pathway, while the PI3K/Akt pathway primarily stimulates glucose uptake and metabolic processes. Insulin resistance predominantly affects the metabolic pathway [16]; therefore, compensatory hyperinsulinemia due to the metabolic pathway resistance, over-stimulates the mitogenic pathway and promotes cell proliferation. When very elevated, insulin can also activate the IGF-I receptor, further stimulating cell growth through this mechanism.

The deleterious mitogenic effect of hyperinsulinemia is more marked in cancer cells that often overexpress the IR [17,18]. This receptor can be expressed as (fetal) isoform A or (mature) isoform B by alternative splicing of the transcript. Malignant cells not only over-express the insulin receptor but, in comparison with normal cells, predominantly express the A isoform, which has more marked mitogenic effects and is also a high-affinity receptor for IGF-2 (Table 1) [18]. This can explain why in response to insulin cancer cells grow more than non-transformed cognate cells.

Hyperinsulinemia also causes leptin overexpression through upregulation of the hypoxia-inducible factor-1α (HIF-1α), a transcription factor considered a master