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Review Article

DIABETES AND CANCER

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ABSTRACT

Cancer and diabetes are common diseases having a big impact on health .Around 1.6 million new cases of diabetes and 1.4 million new cases of cancer are being diagnosed yearly. Evidences suggest that people with diabetes have a higher risk of getting cancer. The biological link between diabetes and cancer are complex and incompletely understood. This review article focusses on the association between diabetes and cancer.

Key words: cancer ,diabetes mellitus ,obesity

INTRODUCTION

Both diabetes and cancer have risk factors in common. The most commonly diagnosed cancers are -cancers of liver, lung, breast, colorectal regions.[1] World wide diabetes is the twelfth and cancer is the second cause of death.[2] After adjusting for age ,cancer and diabetes are associated with the same individual more frequently than can be with chance. The results of several studies [3] have shown that some cancers develop more commonly in diabetic patients(mostly type 2 diabetic patients).The relative risk imparted by diabetes is greater for cancers of liver, endometrium and pancreas and lesser for cancers of breast, colon and rectum and bladder. Other cancers are not associated with diabetes.

Non alcoholic fatty liver disease, steatosis and cirrhosis are related to diabetes and are associated with increased risk for developing liver cancers .Abnormal glucose metabolism is associated with pancreatic cancer(reverse association).Reduced testosterone levels in diabetic patients may be associated with development of prostrate cancer.(low risk).Epidemiological studies suggest that in cancer patients diabetes mellitus may significantly increase the mortality.[4]

Higher C-peptide which is a marker of insulin resistance ,is associated with a poorer disease survival in patients with colorectal [5] and prostrate [6] cancers .Risk factors common to both cancer and diabetes are ageing ,obesity ,sex ,physical activity , alcohol , smoking and diet. Prostate cancer observed with PSA is associated with lower risk in diabetic patients. Reduced testosterone levels in diabetic patients may be the cause of reduced incidence of prostrate cancer in diabetic patients. Obesity may not be directly related with prostate carcinoma but is associated with higher mortality if present.[6] Epidemiological studies suggest that there is an increased mortality in patients with diabetes and cancer.[4] .A higher pre-diagnostic C-peptide levels (marker of insulin resistance) is associated with a poor disease specific survival in patients with prostate cancer [6] and colorectal cancer [5] .

It is still unclear whether the association of diabetes with cancer is direct , whether cancer diabetic association is is due to common risk factors like obesity(indirect) or diabetes is a marker of underlying biologic factors like hyperinsulinemia, insulin resistance that alters cancer risk.

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The risk factors common to diabetes and cancer are sex, aging, obesity, diet, alcohol , smoking and physical activity .Nonmodifiable risk factors are age ,sex and ethnicity .

Modifiable risk factors are obesity ,diet, physical activity ,smoking and alcohol intake.

DISCUSSION:

OBESITY,DIET AND PHYSICAL ACTIVITY:

Overweight and obese induviduals have a higher risk for cancer than people with normal weight .The cancers mostly associated with overweight and obesity are cancers of pancreas colon ,rectum ,endometrium ,gallbladder, kidney and liver .Increase in body weight is due to increase in adipose tissue ,hence total body fat is a better measure of the risk of cancer than BMI .For Type 2 diabetic patients increased waist circumference, waist-hip ratio or measures of visceral adiposity are associated with risk of cancer independent of BMI [7]. Weight loss is associated with a lower risk of cancer.[8] Studies suggest that taking a diet high in vegetables fruits ,whole grains and less in red meat and processed meat reduced the risk of many cancers.[9,10,] Studies have suggested that increased physical activity is associated with a lower risk of postmenopausal breast cancer, colon cancer and endometrial cancer [11].In some cancers like breast and colorectal cancers, physical activity post cancer diagnosis was associated with improved survival.[12,13] .Smoking has an adverse effect on diabetes related complications like cardiovascular disease ,retinopathy[14] and also causes cancer .Moderate alcohol consumption is associated with less incidence of diabetes and excess alcohol consumption is associated with increased risk of complications like cancers of oropharynx, larynx ,liver ,colon etc.[15]

BIOLOGIC LINKS BETWEEN DIABETES AND CANCER:

Cancerogenesis is complex .Cells have to undergo a lot of changes before they get transformed into cancer cells. Diabetes could cause cancer by many mechanisms like hyperinsulinemia ,chronic inflammation and hyperglycemia. Many cancer cells express insulin and IGF-1 (mostly A isoform) receptors. The A receptor stimulates insulin mediated mitogenesis in normal as well as IGF receptor deficient cells. This receptor stimulates cancer cell proliferation and also metastasis.[16] Hyperglycemia causes IGF-I to stimulate vascular smooth muscle cells to undergo proliferation and migration.[17] .When IGF-1 receptors interact with their ligands ,multiple signalling pathways are activated which causes cell proliferation invasion ,metastasis ,protection from apoptosis which promotes cancer progression .Hence high insulin receptor and IGF-1 receptor is associated with adverse prognosis.

a)HYPERINSULINEMIA:

Hyperinsulinemia has a number of indirect effects like

1) a reduction in the hepatic synthesis and blood levels of sex hormone binding globulin, causing an increase in bioavailable estrogen in both men and women and also increased levels of bioavailable testosterone in women ,not in men [18].
2) increased synthesis of androgens from the ovaries and possibly the adrenals in premenopausal women.

Higher level of endogenous sex steroid levels are associated with a higher risk of postmenopausal endometrial,breast and other cancers.

b) INFLAMATORY CYTOKINES AND DIABETES AND CANCER:

Diet induces changes in IL-6 and/or insulin.Specific signaling pathways determine the extent to which diet influences tumor behavior [19]

Adipose tissue is an active endocrine organ producing interleukin-6 (IL-6),free fatty acids, monocyte chemoattractant protein,adiponectin, leptin, , plasminogen activator inhibitor-1 (PAI-1) and tumor necrosis factor-α[20] .The plasminogen

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system has been linked to cancer. PAI-1 expression is linked to poor outcome in breast cancer .[21] Cytokines like IL-6 causes cancer pro Activation of signal transducer and activator of transcription protein (STAT) signaling, which enhances cancer cell proliferation, invasion and also suppresses host anti-tumor immunity[22].

HYPERGLYCEMIA AND CANCER:

Warburg hypothesis and cancer energetics[23] emphasizes that many cancers depend on glycolysis for energy .ATP generation by glycolysis requires more glucose than oxidative phosphorylation. Untreated hyperglycemia could facilitates neoplastic proliferation byfollowing mechanisms:

1) hyperglycemia may serve as a surrogate for hyperinsulinemia.
2) Insulin receptor activation which could cause cancer.

In vivo models have shown reduced tumor growth in the setting of type 1 diabetes[24] suggesting that increased neoplastic growth in the setting of insulin deficiencyis not due to hyperglycemia. Hence hyperglycemia causes tumor growth and appropriate therapy for diabetes limits tumor growth.

ANTIDIABETIC DRUGS AND CANCER:

1) METFORMIN:

Metformin is the most commonly used drug in the treatment of Type 2 diabetes. The mode of action is mainly to reduce hyperglcemia by reducing hepatic glucose output .

Metformin has been shown in laboratory studies to reduce colony formation,inhibit cell proliferation and cause partial cell cycle arrest in cancer cell lines[25] .Studies suggest that metformin-induced activation of AMP-activated protein kinase (AMPK) in tumor cells by inhibiting protein synthesis inhibit tumor growth[25].Metformin acts better in supressing tumor growth when there is hyperinsulinemia. Metformin has reduced mammary tumor growth in rodent models [26].

Observational data suggest that metformin might improve cancer prognosis. Metformin treatment among early-stage breast cancer patients receiving neoadjuvant therapy[27] was associated with better pathological response.

THIAZOLIDINEDIONES:

Thiazolidinediones (TZDs) are peroxisome proliferator–activated receptor (PPAR)γ agonists and are insulin sensitisors.

PPARγ agonists have several anti-cancer activities like inhibiting growth, inducing apoptosis and cell differentiation [28] . Recent in vitro studies indicate that the effects of PPARγ agonists on cell growth are often independent of the presence of PPARγ [29].Rodent studies indicate that PPAR agonists can potentiate tumorigenesis.[30]. TZDs may increase, decrease, or have a neutral effect on the risk of cancer in humans.

Three epidemiologic studies conducted among patients with diabetes focused on all cancers combined showed inconsistent results [31](104–106). Only a few clinical trials of TZDs for cancer treatment have been conducted, and results have largely been negative [32].

INSULIN SECRETAGOGUES

Secretagogues, like sulfonylureas and the rapid-acting glinides, stimulate β-cells to release insulin by binding to specific cell receptors, β-cell depolarization and release of insulin from stores. Sulfonylureas (e.g., glyburide, glipizide, glimepiride) cause hypoglycemia and weight gain. A small number of observational studies found a higher risk of cancer or cancer death among individuals with diabetes treated with sulfonylureas compared with those treated with metformin or other diabetes medications [33].

The mechanism involved in causing cancer in diabetic patients on secretogogues are the direct actions of the agents on cells at risk for carcinogenesis and indirect effects mediated by higher insulin levels. Glinide secretagogues and cancer risk-there are no data suggestive of association with cancer.

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INCRETIN-BASED THERAPIES

Incretins mimic the effect of gut-derived incretin hormones .Incretins improve glucose-dependent insulin secretion, delay gastric emptying and suppress post prandial glucagon levels . Liraglutide and exenitide bind to the GLP-1 receptor and exert agonist activity. The oral dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit the action of DPP-4 enzyme that rapidly degrades endogenous GLP-1.

Liraglutide was associated with a mild increase in serum calcitonin in human trials and increased risk of medullary thyroid cancer in rats. Liraglutide, exenatide and DPP-4 inhibitors increased β-cell proliferation in animal studies. A small study suggested that DPP-4 inhibitor sitagliptin was associated with increase in pancreatic ductal hyperplasia [34].

INSULIN AND INSULIN ANALOGS

Insulin is the mainstay in the mainstay in treatment of Type 1 Diabetes and in many Type 2 Diabetes patients. Studies have shown increased risk of cancer in patients treated with glargine. Insulin glargine may cause cancer through its binding to IGF-1 receptors[35]. Possible mechanisms for the link between exogenous insulin, insulin analogs, and cancer

Insulin causes cancer by two ways a)direct actions -interactions of the administered ligands or their metabolites with cancer cells or cells at risk for transformation ,b)indirect mechanisms- interactions of signaling molecules whose activities are influenced by administered insulin.

Insulin receptor is present on neoplastic cells and may itself produce neoplastic activity when triggered appropriately .

CONCLUSION:

There are several limitations in human studies on diabetes treatment and cancer risk .Most diabetic patients are treated with one or more anti-diabetic drugs. Diabetes treatment needs constant change and adjustment of medications. It is thus extremely difficult to associate a specific medication with cancer risk.Newer drugs have come in the market to treat diabetes and only short term studies are available regarding their association with cancer .

Male sex, older age, obesity , intake of diet high in glycemic index ,excessive alcohol intake, decreased physical activity and tobacco smoking are associated with inceased risk of cancer and as well as diabetes .Hyperinsulinemia, obesity and insulin resistance are all associated with increased insulin like growth factor 1(IGF 1) activity which has an important role in carcinogenesis.

Multiple larger clinical studies are necessary to get more insight in this topic as the link between cancer and diabetes is complex .

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ISSN 2319-1082

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