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RISK ESTABLISHED BETWEEN TYPE II DIABETES MELLITUS AND CANCER: A REVIEW

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Abstract:

Diabetes has become a serious and silent disease in human society reason for many abnormalities and diseases including deadly disease cancer. Mostly it occurs either due to decreased production of insulin or its irresponsiveness to receptor. Type II diabetes have alliance with increased possibility for different cancers. Diabetes and associated factors are the possible reason for creating microenvironment for cancer genesis and progression. Raised level of circulating insulin in case of non-functional IRs or C-reactive protein can help to predicts risk for colorectal, postmenopausal breast, pancreatic, bladder and endometrial cancer. IRS1 factor is considered responsible for cell proliferation and apoptosis inhibition and promoting cancer. Obesity in women increases the level of estrogen making them prone towards development of breast cancer. Obesity along with Type II diabetes directly affects insulin signaling and indirectly promotes DNA damage through production of free radicals leading to cell mutation thus cancer-biogenesis. In obesity and overweight, adipose cells produces several inflammatory cytokines including IL-6 and TNF-α which induce inflammation and regulate proto-oncogenes and related transcription factors which create insulin resistance and generate microenvironment for unchallenged cell proliferation, apoptosis inhibition and angiogenesis resulting in cancerous tumor. Obesity is also related with low level of adiponectin hormone that causes inflammatory condition for tumor development. In Hyperglycemia free radical production raises causing oxidative damage to DNA leading to mutation in proto-oncogenes and tumor suppressor genes that trigger development of cancer. Thus diabetes and cancer alliance is statistically remarkable. To avoid their connections with human being, counseling is required to change their life style in the direction of "eat healthy, think healthy, and be healthy" to decrease obesity and diabetes to prevent cancer disease.

Keywords: Type II diabetes, Cancer, Inflammation, Hormones, Cytokines

Introduction

Diabetes is a wide spread, consequential and persistent disease that arises may be due to improper production of pancreatic hormone (insulin) or lack of hormone receptor sensitization. Diabetes of all types can lead to complication in many parts of the body and can increase the overall risk of dying prematurely. Diabetes is spreading in human world in a quick fashion which is mainly a life style and food based disease. It has become a worldwide economic burden on human society because the numbers and prevalence of diabetic patient have been increasing day by day. The number of people with diabetes increased from 108 million to 422 million adults aged over 18

years, from the year 1980 to 2014 that was around four times higher [1]. WHO estimates that the largest number of diabetic patient were living in the region of South-East Asia and Western Pacific Region, contributing approximately half of the whole diabetic patient worldwide (Table 1) [2]. With population growth in every age group, diabetes prevalence is also rising, in-fact from the past 3 decades the prevalence of diabetes has increased significantly in countries at all emolument level. Eastern Mediterranean Region and South-East Asia Region were showing significant increase in diabetes prevalence from 5.9% to 13.7% and 4.1% to 8.6%, respectively from the year 1980 to 2014 (Fig. 1) [2].

Earlier there was no established link between occurrences of different types of cancers and diabetes. Advancement of science and technology attributed development of tools and technology those aids in the area of diagnosis and prognosis of diabetes, thus offer a hint that if anyone diagnosed with diabetes would be at increased risk of various types of cancers. Diabetes is of two types, Type I and Type II. Type I diabetes also known as juvenile diabetes is primarily the result of autoimmune destruction of beta cells a chronic condition in which the pancreas produces little or no insulin whereas Type II diabetes well-known as adult onset diabetes is another chronic condition that affect the way the body processes blood sugar in the terms of insulin resistance [3]. Type II diabetes is being associated with increased risk for several cancers, including colon cancer, post-menopausal breast cancer, pancreatic cancer, liver cancer, bladder cancer etc. Increased incidence of cancer and related mortality among people suffering with diabetes clearly reflects diabetes minimize survival rate by promoting cancers. Normal cells develop into malignant cancer cells through a complex process including DNA damage, initiation of damaged cell growth and more progressive growth with angiogenesis etc. Metabolic intermediates of body in the state of overweight, obesity and Type II diabetic conditions helps in the genesis and progression of cancer by creating microenvironment for producing inflammatory cytokines [4, 5]. In addition contaminated herbicide and pesticide dietary intake and lack of physical activities also provides the environment for genesis and progression of cancers. Numerous factors related to overweight, obesity and Type II diabetes as well as adulterated food supplements with herbicides and pesticides along with lack of physical activities contribute to cancer genesis (Fig. 2) [6]. Studies conducted in developed countries like USA, United Kingdom, China, Australia, Japan etc. confirm beyond doubt that diabetes heightens the risk of several types of cancers. Research also suggests that women with diabetes appear to be more prone than male towards the development of malignant tumors. Women (27%) and men (19%) with diabetes are likelier to develop cancer, compared with healthy women and men. In contrast to men with diabetes, women struggling with diabetes have an 11% higher risk of kidney cancer, 13% higher risk of oral cancer, 14% of increased risk of stomach cancer and 15% chance for occurrence of leukemia. But in case of liver cancer men will be at 12% higher risk than women [7].

Procedure connecting Type II Diabetes and Cancer

Normal cells transform into malignant cells by following a complex mechanism, initiated by DNA damage from a carcinogen or reactive molecules, promoted by stimulation of initiated cells growth, and progression through more aggressive growth with angiogenesis and metastasis [5]. Innumerable factors are relating to metabolic condition like overweight, obesity, and Type II diabetes, as well as food supplements intake and physical inactivation appear to promote cancer development.

Factors involved in development of diabetes induced cancer

Levels of insulin or C-peptide, a biomarker of insulin production predicts risk for colorectal, postmenopausal breast, pancreatic, bladder and endometrial cancers [8]. Other factors include diabetes duration, varying levels of metabolic intermediates, different drugs used for therapeutical approach and the possible presence of chronic complications related to disease. Increased insulin level to overcome blockage of the metabolic pathway exaggerates activation of mitogenic pathway. Studies suggest that an increased concentration of insulin receptors in case of hyperinsulinemia act as mitogen [9]. Studies also suggest that IGF-1 (Insulin Growth Factor-1) is even more potent than insulin in promoting cell proliferation and inhibiting apoptosis [5]. In postmenopausal state, women become obese and body fat becomes the primary site of estrogen synthesis and thus elevated level of serum estrogen increases the risk of breast and endometrial cancers among women of this age group [10]. Adipose cells produce several pro-inflammatory cytokine by stimulating macrophages, like Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) which are involved in activation of signaling pathways that further promote cell proliferation, angiogenesis and inhibition of apoptosis [11]. Increased body fat because of insulin resistance, tend to increase leptin level resulting in hyperinsulinemia, which again promote inflammation, and induce production of aromatase enzymes that in turn raises estrogen production leading towards cancer [4]. Chronically elevated glucose levels are associated with insulin resistance and often with excess body fat; however research is not yet clear about a direct impact of hyperglycemia on cancer risk [5]. Studies reflects some facts that, hyperglycemia without hyperinsulinemia does not lead to neoplastic growth, which means that insulin receptor activation may be more important than hyperglycemia for tumor growth [12]. Thus cytokines production in adipose tissues by the increased number of activated macrophages, along with lack of production of insulin and production of aromatase enzymes leads to increase in estrogen level thus causing and promoting cancers (Fig. 3).

Diabetes care and cancer prevention

“Cancer screening and counseling on lifestyle changes should be part of preventive care in people with obesity and/or diabetes,” according to a consensus statement from the American Association of Clinical Endocrinologists and the American College of Endocrinology [8]. The American Institute for Cancer Research (AICR) and American Cancer Society (ACS) recommend that people should be lean so

that Basic Metabolic Rate (BMR) would be in normal range without being underweight [10]. Modest body weight reduces cancer risk, reasons are not explained yet and require clearance but reduced calorie consumption is one of the most effective ways to reduce the risk of cancer and this can be accomplished by consumption of more green and fibre rich diet instead of carbohydrate rich diet, hence reducing portions of foods concentrated in calories [13]. Plant based food products lowers the risk of cancer development. Plant foods supply dietary fibre, nutrients, and phytochemicals that seem to provide protection against cancer development.

Diabetes, Hormone & Cancer

In post-menopausal women estrogen synthesis increases in adipose cells and leads to elevation in serum estrogen, thus prevailing the risk for post-menopausal breast and endometrial cancers among women who did not gone through hormone replacement therapy. Hyperinsulinemia decreases liver produced sex hormone binding globulin, which increases estrogen bioavailability [10]. Lower than normal level of testosterone is the sign and symptoms of Type II diabetes in men [14]. The increased production of estrogen from aromatase conversion sends the negative feedback response which prohibits the secretion of gonadotropins such as luteinizing hormone (LH) and subsequent decrease in testosterone secretion. Thus studies suggest that higher estrogen level with decrease in testosterone level increases the risk of colorectal cancer in men [15].

Diabetes, Inflammation & Cancer

Obesity and inactivity have long been considered as risk factors that drive towards the development of Type II diabetes. People suffering with Type II diabetes have greater chance to show elevated level of inflammatory cytokines and production of free radicals that can cause DNA damage which disrupt insulin signaling may leads to cancer genesis [16]. In such circumstances adipose cells, residing macrophages and other phagocytic cells get activated to secret several pro-inflammatory cytokines like IL-6 and TNF-α to activate signaling cascade that promote cell proliferation, inhibition of apoptosis and angiogenesis after cancer genesis and tumor formation. Researchers link elevated levels of IL-6, TNF-α, and C-reactive protein with greater risks for colorectal, breast, prostate, lung, and other cancers, but still, they are not assure by experiments and unpredictable results [4 , 17].

Diabetes, Obesity and Cancer

Adipose tissue consists of adipocytes, endothelial and immune cells. Adipose cells release cytokines such as TNF-α and IL-6 that are associated with inflammation and insulin resistance remarkably pointing towards origin of cancers. Increased body weight especially with insulin resistance tends to increase leptin production. Elevated leptin level further increase hyperinsulinemia, promote inflammation and also activate the aromatase enzyme. Studies suggest leptin also directly promotes increase in cell numbers in uncontrolled manner, angiogenesis and decreased apoptotic cell death [4]. Mass studies associate connection between elevated leptin to increased incidence of

colorectal, postmenopausal breast and other cancers. Moreover, obesity is responsible for decrease in the production of adiponectin which is considered as an adipose derived hormone. Decreased level of adiponectin may promote cancer development through changes in cell signaling that increases cell proliferation and angiogenesis [18]. Several studies have shown decrease in adiponectin level with increased cases of colon, postmenopausal breast cancer, but limited or no connection have been reported with other type of cancers.

Diabetes, Hyperglycemia and Cancer

Hyperglycemia is responsible for the production of free radicals and some other reactive molecules, which could initiate oxidative damage to DNA leading to mutation in oncogenes and tumor suppressor genes [9]. However, there is no clear link has been deciphered regarding the effects of high blood glucose level in Type II diabetes and its connection with various types of cancers. According to Giovannucci *et al*., studies related to utilization of higher circulating glucose by the malignant cancerous cells for growth and proliferation were needed to be focused [12]. Elevated level of HemoglobinA1c (HbA1c) which has been proved to be as marker for hyperglycemia, indicates higher risk for certain cancers [19, 20]. However, intervention trials on people with Type II diabetes drew no link between HbA1c and cancer risk that has been proved by meta-analysis [21]. Because chronically increased glucose level might be responsible for insulin resistance and excess body fat, but research is not yet clear about a direct impact of hyperglycemia on cancer risk [5, 8, 9]. Studies involving diabetic animal models show that hyperglycemia are not directly associated with tumor growth; rather state of hyperinsulinemia was found to be associated with neoplastic growth, suggesting that insulin receptor activation may be a potent cause of cancer genesis and tumor formation [12].

Diabetes, IRS1 and Cancer

When glucose level increases, it sensitizes Insulin Receptor (IR) which in turn causes multiple tyrosine phosphorylations of Insulin Receptor Substrate1 (IRS1) and signaling cascade. IRS1 is involved in several metabolic pathways and especially in insulin regulated Receptor Tyrosine Kinase signal transduction pathway (RTK pathway). Insulin in bound state with its IR, further activates intrinsic tyrosine kinase activity of the receptor which leads to its auto-phosphorylation as well as multiple phosphorylation of tyrosine residues present on IRS1 proteins [22]. Eventually, the phosphorylated motifs present on these membrane associated proteins, recruit signaling proteins (intermediates) and initiate intracellular pathways PI3K/Akt and Erk MAP kinase pathways that ultimately affect glucose metabolism. Several metabolically important cellular pathways including insulin/IGF signaling (RTK) pathway might be activated in hepatocellular carcinoma (HCC) [23].

Conclusion

Diabetes and its rigorous day by day increase in population mostly in urban people has become a serious problem worldwide. Till now people were only concerned

to tackle diabetes as a problem of endocrinological metabolism but recent researches have pointed the needle towards the correlation of diabetes with various cancers. There are other backgrounds which could be inter-related with the problem of diabetes and its role in promoting cancer genesis and progression. Therefore, many factors simultaneously become responsible for the change in cellular microenvironment on molecular level. Diabetes itself and along with increasing cases of "diabetes induced" cancer has become global economic burden on society. Hence there is need to get change in our life style, diet, working habits, for which we should go for healthy diet, continuous physical exercise that sufficiently oxygenate our body to decrease obesity, thus risk of diabetes and deadly disease cancers.

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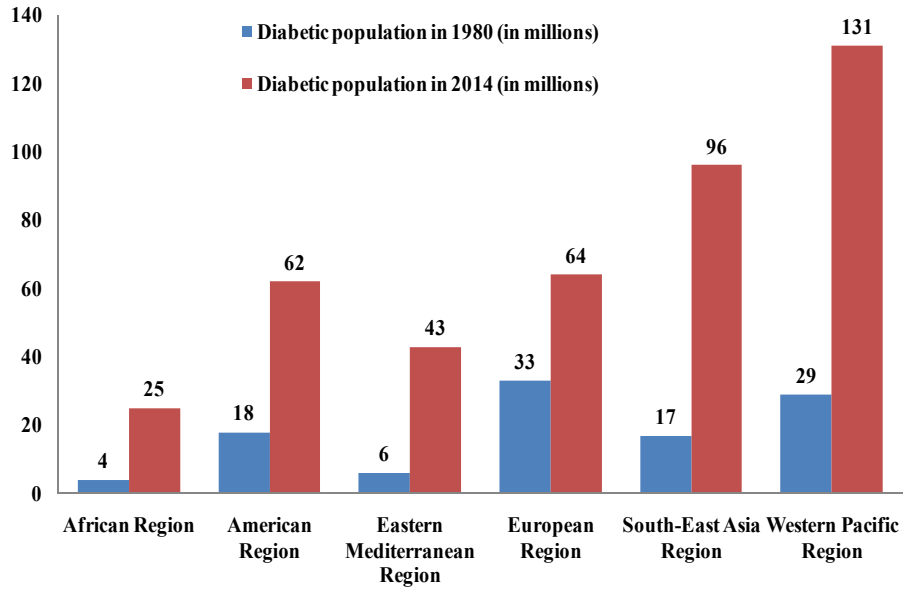

Fig. 1: Estimated number (in millions) of people with diabetes (adults 18+ years).

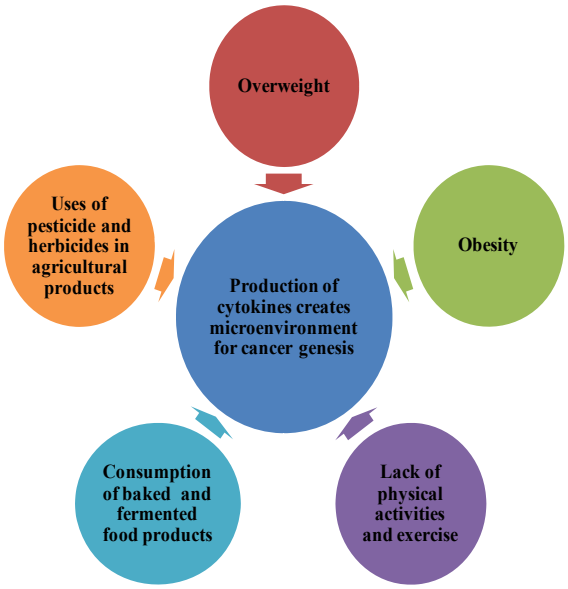

Fig. 2: Factors involved in creation of microenvironment for cancer genesis.

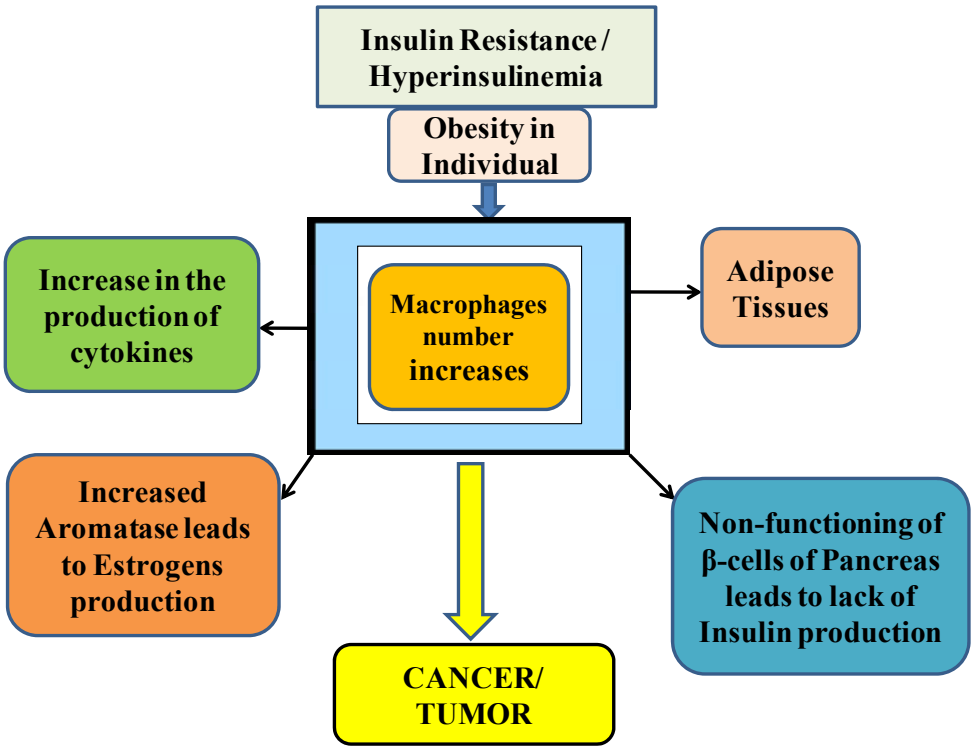

Fig. 3: Elements involved in development of diabetes induced cancer.

TABLE 1: Estimated prevalence of diabetic people (adults 18+ years) according to Global Report on Diabetes (WHO 2016).

WHO Regions	% of Diabetic Population Prevalence in 1980	% of Diabetic Population Prevalence in 2014
African Region	3.1	7.1
America Region	5	8.3
Eastern Mediterranean Region	5.9	13.7
European Region	5.3	7.3
South-East Asia Region	4.1	8.6
Western Pacific Region	4.4	8.4

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