

## "Molecular Association of Cancer and Diabetes Mellitus with Combinational Therapy"

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### Undertaking:

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### Abstract:

Million people die of diabetes and different types of cancer every year. Current study include effects of major risk factors, as hyperglycemia and obesity are novel risk factors contributing both cancer and diabetes and biochemical pathways in association with these two diseases. Diabetes mellitus can enhance risk of a varied range of tumors, for instance pancreas, liver, early gastric, lung, prostate, breast, acute myeloid leukemia and colorectal cancer. Scientists have substantiated the link of diabetes with increased prevalence, augmented progression & improved cancer aggression. Up to 16% of breast cancer patients have diabetes, and breast cancer is also associated with two major risk factors for type 2 diabetes i.e. old age and obesity. A meta-analysis showed that probability of pancreatic cancer for people having diabetes is 82% greater compared to non-diabetics. This study reports identification of ways to lower incidence of cancer by giving anti-diabetic drugs in the local population and by controlling obesity which is the major risk factor leading to diabetes and cancers. Type II diabetes mellitus (DM) occurs due to insulin resistance in obese people, a compensatory mechanism for elevated levels of blood glucose. As the prevalence of obesity increases, there is also an elevated risk of diabetes mellitus.

### Introduction:

“Cancer is a group of diseases that are characterized by uncontrolled growth and abnormal cell propagation. It can result in death if the spread is not controlled” <sup>(1)</sup>. According to World Health Organization, cancer is a generic word that can influence any portion of the body for a wide range of illnesses. A significant characteristic of cancer is the fast growth of abnormal cells that develop beyond their normal limits and then enter adjacent sections of the body and spread to different organs, the latter procedure is called metastasis <sup>(2)</sup>.

### Cancer Tumors

**Benign tumors** are not life-threatening and cancerous. They tend to grow quite slowly; they don't spread to other parts of the body and usually consist of cells that are quite similar to normal or healthy cells. They

will only cause a problem if they grow very large, become uncomfortable, or press other organ for instance, a brain tumor within the skull.

**Malignant tumors** grow fast as compared to benign tumors and are capable of spreading and killing neighboring tissue. Growth of malignant tumor cells break away from the main (primary) tumor and spread through a process known as metastasis to other parts of the body. They continue to divide and grow when they invade healthy tissue at the new site. These secondary sites are referred to as metastases and this condition is called metastatic cancer. Precancerous (pre-malignant) is a description of the condition that involves abnormal cells that may turn into cancer <sup>(3)</sup>.

### **Risk Factors of Cancer**

To raise the chance of cancer at least four of the following diabetes symptoms are hypothesized: hyperinsulinemia (including insulin resistance), hyperglycemia, sex hormone down-regulation – binding globulin, chronic Inflammation <sup>(4)</sup>.

Tobacco is very significant cancer risk factor and is responsible for about 22% deaths worldwide. World Health Organization facts on cancer state that by avoiding these factors we can minimize cancer burden and can overcome 30-50% cancers by pursuing prevention strategies <sup>(5, 6)</sup>.

### **Incidence of Cancer**

WHO defines cancer as one of the world's major causes of death, with an estimated 9.6 million fatalities in 2018. The most frequent cancers are:

Lung (2.09 million)

Breast (2.09 million)

Colorectal (1.80 million)

Prostate (1.28 million)

Skin cancer (non-melanoma) (1.04 million)

Stomach (1.03 million)

Two complicated, varied, chronic and possibly deadly illnesses are diabetes and cancer. Cancer is the 2<sup>nd</sup> main cause of death, while the 7<sup>th</sup> major cause of demise is diabetes <sup>(7, 8)</sup>.

### **Diabetes Mellitus**

Diabetes mellitus is a debilitating, long-term disease that occurs when a person's blood has elevated glucose levels because their bodies are unable to produce insulin hormone or don't utilize it properly. Diabetes can be characterized as a metabolic disorder that contributes to hyperglycemia and the potential for diabetic patients to develop multiple serious and deadly health issues has been steadily increasing. Many with T2DM have relative insulin deficiency and early in the disease absolute insulin levels increase with resistance to the action of insulin. Most people with T2DM are overweight or obese, which either causes or aggravates insulin resistance <sup>(9, 10)</sup>.

### **Complications of Diabetes**

Diabetes raises the chance of severe health issues. Many individuals suffering from diabetes can inhibit the occurrence of complications with right therapy and suggested lifestyle modifications. Macrovascular complications are a significant danger in people with type II diabetes. There are several problems related to type II diabetes.

**Skin complication:** One should be aware of the symptoms of skin infections and other skin disorders among people having diabetes.

**Eye infection:** Diabetes has risk of glaucoma, cataracts and other eye problems which can be prevented by routine check-ups.

**Neuropathy:** Nerve damage caused by diabetes is known as diabetic neuropathy. Approximately 50% of individuals with diabetes have some type of nerve damage.

**Foot disease:** Neuropathy leads to numbness in the feet.

**Ketoacidosis (DKA) & ketones:** It is important to have knowledge of the warning signs of ketoacidosis and also look for ketones in urine, particularly when feel ill.

**Nephropathy (Kidney disease):** It is also referred to as End stage renal disease. The chance of getting kidney disease can be minimized by maintaining diabetes and blood pressure normal.

**High blood pressure:** Another name for high blood pressure is hypertension that increases menace for heart attack, stroke, eye and kidney problems.

**Stroke:** By sustaining target levels for blood pressure, cholesterol and blood glucose risk of stroke can be reduced.

Irrespective of the pathophysiology of diabetes, chronic high blood glucose levels linked to microvascular and macrovascular complications increase mortality of people having diabetes. Genetic and environmental factors influence  $\beta$ -cell mass in such a way that insulin concentrations are ultimately unable to react adequately to insulin requirements, resulting in adequate rates of hyperglycemia to treat diabetes<sup>(11)</sup>.

### **Epidemiology of Diabetes**

Over the previous three centuries, the proportion of individuals with diabetes mellitus has increased fourfold, and diabetes mellitus is the ninth leading cause of death. Universally around 1 in 11 grown persons now have diabetes mellitus, out of which 90% have type 2 diabetes mellitus (T2DM). Asia is a major area of the fast-growing global epidemics of diabetes<sup>(12, 13)</sup>.

According to IDF 2019, incidence of diabetes was projected around 9.3% i.e. 463 million people in 2019 worldwide, increasing 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. In urban areas (10.8%) the frequency is higher than in rural areas (7.2%) and likewise in high-income (10.4%) as compare to low-income countries (4.0%). Approximately 50% people suffering from diabetes are unaware of it<sup>(14)</sup>.

In 2017, the prevalence of diabetes in people aged 18–99 was measured at 8.4% and expected to increase to 9.9% in 2045. It was reported that there were 451 million people with diabetes nationwide in 2017 (age 18-99 years) and this statistics would rise to 693 million by 2045<sup>(15)</sup>.

### **Molecular Association of Two Chronic Diseases: Cancer and Diabetes Mellitus**

Cancer is world's major causes of death, with 9.6 million mortalities reported in 2018 as cancer is the second major cause of death, while the seventh cause is diabetes (WHO). Diabetes is a life-long disease marked by high sugar level in the blood.

Type II Diabetes can enhance risk of a varied range of tumors, for instance pancreas, liver, ovarian, prostate, lung, breast, acute myeloid leukemia and colorectal cancer. People with diabetes have about 30% higher relative menace of cancer than non-diabetic people. Persistent hyperglycemia could cause permanent damage, dysfunction, and failure of several parts of the human body, such as eyes, heart, nerves, kidneys and blood vessels<sup>(16)</sup>. 18% people with cancer have pre-existing diabetes. Control of diabetes and cancer

patients may be difficult. The level of glycemic control in patients can be affected by cancer treatments, such as chemotherapy <sup>(17)</sup>.

Hyperinsulinemia was suggested as fundamental connection between diabetes and cancer. Insulin enhances cell proliferation via a small path comprising of insulin receptor or insulin-like growth factor (IGF)-I receptor's direct activation and main pathway inhibits Insulin Growth Factor binding proteins (especially IGFBP-1 and IGFBP-2), that leads to augmented insulin growth factor-I as demonstrated in figure1 <sup>(18)</sup>.

### **Lung Cancer and Diabetes Mellitus**

Two increasingly common illnesses are diabetes mellitus (DM) and lung cancer <sup>(19)</sup>. Lung cancer is Pakistan's third most frequently diagnosed and leading cause of cancer death, with an estimated 6,800 (4.6%) new occurrences and 6,013 (5.9%) deaths in 2012 <sup>(20)</sup>. Low amount of HDL cholesterol is correlated with a rise in the incidence of lung cancer, and enhanced to 6.5 times in people if HDL value is less than 20 mg /dl <sup>(21)</sup>.

Lung cancer patients with and without diabetes mellitus had a 1, 2 and 3 year survival of 43% vs. 28%, 19% vs. 11%, and 3% vs. 1%, respectively. The fact that patients with diabetes mellitus showed a reduced frequency of metastatic illnesses may explain the advantage of survival in patients with diabetes mellitus, as most patients with lung cancer die from metastasis and not from the primary tumor <sup>(22)</sup>.

Patients with lung adenocarcinomas have benefited greatly from the advancement of targeted molecular therapies. By comparison, in the control of lung squamous cell carcinoma (lung SCC), these therapies had little value. New treatment options are therefore required for lung SCC based on current genomic and proteomic approaches. In clinical samples of lung squamous cell carcinoma (SCC), over expression of TPD52 was observed, and TPD52 knockdown significantly suppressed cancer cell migration and invasion in lung SCC cell lines <sup>(23)</sup>.

### **Pancreatic Cancer and Diabetes Mellitus**

A systematic review showed that probability of pancreatic cancer for people having diabetes is 82% greater compared to non-diabetics <sup>(24)</sup>. KLK3, a 33kDa glycoprotein secreted by prostatic epithelial cells, was first characterized in 1971 by Hara et al. in forensic studies as a marker for human semen <sup>(25)</sup>. Prostate-specific antigen also known as KLK3 is the most widely recognized member in urological oncology among the proposed KLK cancer biomarkers <sup>(26)</sup>.

In both Asian and Western countries, pancreatic cancer (PC) is the fourth common cause of cancer death. Just 10%-20% of patients were suitable for curative surgery at the time of diagnosis. Due to anti-neoplastic function, metformin, a commonly used antidiabetic drug, has recently received attention. Metformin is a large-scale oral biguanide used as a single or DM combination therapy <sup>(27)</sup>.

### **Breast Cancer and Diabetes Mellitus**

Up to 16% of breast cancer patients have diabetes, and breast cancer is also associated with two major risk factors for type 2 diabetes i.e. old age and obesity. Three mechanisms linking diabetes and breast cancer have been hypothesized: insulin pathway activation, insulin-like growth-factor pathway activation, and endogenous sex hormone regulation. Comparative surveys of cohorts and case-control studies indicate that type 2 diabetes may be correlated with chance of 10–20% breast cancer <sup>(28)</sup>.

Hyperinsulinemia in T2DM triggers expression and enhanced ER binding ability. ER activation can also improve the mitogenicity of insulin by encouraging IRS-1 function and activating PI3 K and Ras / MAPK signals. Inflammatory mediators, TNF $\alpha$  and IL-6, which are associated with insulin resistance in T2DM, increased the production of estrogen in both normal and breast cancer cells, and breast cancer cells could be anticipated to develop and proliferate. Insulin resistance management is a major factor in regulating blood glucose and cancer prevention in female patients having diabetes. Clinicians should recommend

changes in lifestyle such as diets for weight loss and exercise in women with T2DM to overcome insulin resistance. Type 2 diabetes mellitus (T2DM), a quickly growing chronic disease globally, is well established as a significant risk factor for different cancer types. Mammographic breast cancer screening has been shown to reduce breast cancer mortality<sup>(29)</sup>.

While many factors affect the development of T2DM and cancer including sex, age, gender, obesity, diet, rates of physical activity, and exposure to the environment, many epidemiological and experimental trials are gradually contributing to information about the interrelation between DM and cancer<sup>(30)</sup>. Evidence recommend that metformin may reduce the risk of breast cancer by decreasing insulin concentrations and reducing cell proliferation<sup>(31)</sup>. Many laboratory studies indicate that metformin use in breast cancer cells is related to suppression of cell growth, likely facilitated by 5'-adenosine monophosphate-activated protein kinase (AMPK) activation. Observational studies also demonstrate that use of metformin has a 20-30 percent lesser incidence of breast cancer<sup>(32)</sup>.

### **Acute Myeloid Leukemia (AML) and Diabetes Mellitus**

Acute myeloid leukemia is a malignant development of the myeloid lineage within the bone marrow hematopoietic progenitor cells. An estimated 21,380 individuals were identified with acute myeloid cancer (AML) in 2017 by the American Cancer Society (ACS) and was common blood cancer among adolescents. Nearly half of these patients die from the disease<sup>(33)</sup>.

AML is the most common type of leukemia which occurs when many immature blood cells are formed in bone marrow, with the largest reported incidence rates in the United States, Australia, and Western Europe. Of 779 cases of acute leukemia analyzed, 77% were myeloid (myeloblastic, promyelocytic, or monocytic) subtypes and 16% were lymphoblastic subtypes<sup>(34)</sup>. The absence of a protein called MTF2 helps to alter gene expression in acute myeloid leukemia (AML) cells to develop chemotherapy resistance. The researchers found that MTF2-deficient AML cells overexpress a gene called MDM2 that promotes cancer. It blocks the protein p53 and disrupts the cycle of cell leading to cell death when cells are damaged by chemotherapy<sup>(35)</sup>.

Risk factors for AML comprise cigarette smoking (up to 25% increased risk of AML), chemicals like benzene, formaldehyde, previous chemotherapy (e.g., alkylating agents, topoisomerase II inhibitors), radiation (depending on the type and region of exposure), and other abnormalities related to blood (e.g., myelodysplastic syndromes, which have a poor prognosis), congenital syndromes (e.g., Down syndrome, trisomy 8), family history, and male gender<sup>(36)</sup>. There are various treatment strategies for AML which include induction, consolidation, maintenance, and relapsed/refractory disease regimens. In particular, cytarabine plus anthracycline (e.g. idarubicin or daunorubicin) are the present standard for induction therapy<sup>(37)</sup>.

### **Colorectal Cancer and Diabetes Mellitus**

CRC is also called colon cancer or large bowel cancer, involves cancer development in colon, rectum and appendix. It is the fourth most prevalent neoplasm in the world and the second major cause of cancer-related fatalities in the United States with approximately 65,000 fatalities per year. Pakistan is a densely populated nation with an estimated 190 million inhabitants in South Asia. Men have a greater incidence than females in Pakistan. It varies from 48.3 to 72.5 per 100,000 per year for males, while it ranges from 32.3 to 56 per 100,000 per year for females. CRC screening can decrease mortality and also decline incidence by stopping cancer by detecting and removing pre-cancer polyps<sup>(38)</sup>.

Individuals with diabetes have an enhanced relative risk of developing colorectal cancer by nearly 30% compared to non-diabetic people. A biologically possible relation of diabetes and risk of colorectal cancer was observed. There is important role of hyperinsulinemia in colorectal carcinogenesis or insulin resistance factors and was suggested as fundamental connection between diabetes and colon cancer. Insulin enhances cell proliferation via a small path comprising of insulin receptor or insulin-like growth factor (IGF)-I

receptor's direct activation and main pathway inhibits Insulin Growth Factor binding proteins (especially IGFBP-1 and IGFBP-2), that leads to augmented insulin growth factor-I<sup>(39)</sup>.

There is a need to establish awareness and attitudes about CRC and present screening methods. Colorectal cancer (CRC) is ranked as 3rd cancer around the globe, with approximately 1.24 million new cases identified in 2008. Clear evidence depicts that diabetes mellitus is an autonomous risk factor for CRC growth. Recent observational studies have shown that use of metformin as an anti-hyperglycemic agent is correlated with a reduced occurrence of CRC and a decrease in deaths related to CRC, indicating that metformin may potentially be used in prevention and treatment of CRC<sup>(40)</sup>.

### **Prevention and Management of Diabetes & Cancer**

Major clinical trials have shown that healthy diet and changes in lifestyle in high-risk individuals are beneficial in cure of T2D. Diabetes management approaches are essential to decrease the incidence of problems of diabetes mellitus, including lifestyle changes, social support and medication adherence<sup>(41)</sup>. By altering risk factors such as obesity and insulin resistance, primary diabetes preclusion is feasible. In the health care agenda, priority should be provided to national programs encouraging healthy lifestyle among the population, beginning from a young age<sup>(42)</sup>. Selective estrogen receptor modulators (SERMS) can lessen breast cancer risk and aspirin has ability to prevent colorectal cancer (NCI).

Research suggests that most instances of type 2 diabetes could be avoided through good nutrition and regular physical activity, up to 80% according to some research. A healthy diet involves lowering calories when you are overweight, substituting saturated fats (such as cream, cheese, butter) with unsaturated fats (such as avocado, nuts, olive and vegetable oils), eating nutritional fibers (such as fruit, vegetables, whole grains), and avoiding use of tobacco and alcohol<sup>(43)</sup>.

### **Combinational Therapy of Diabetes & Cancer**

Metformin is the most commonly used type II diabetes treatment drug. It's inexpensive, popular, and well accepted. Increasing preclinical, medical, and epidemiological research indicates that metformin can be a beneficial cancer therapy drug as well. Patients with metformin-treated diabetes have a reduced risk and mortality rate of breast, pancreatic, hepatocellular, and colorectal cancer. Metformin can affect tumor cells through direct and indirect mechanisms, including the activation of 5'-AMP-activated protein kinase (AMPK), the primary cellular energy stress sensor.

Metformin may also have direct effects on tumor cells, including TSC2 (Tuberous Sclerosis Complex 2 also known as Tuberin, is a protein that in humans is encoded by the TSC2 gene) stabilization facilitated by AMPK and consequent mTORC1 (mammalian target of rapamycin complex 1) is a protein complex that functions as a nutrient/energy/redox sensor and controls protein synthesis inhibition. A decrease in circulating insulin levels may also result in the down regulation of INSR signaling pathways in cancers expressing INSR (insulin receptor) and attenuation of the proliferative and anti-apoptotic signals. Supporting such a possibility, non-diabetic breast cancer patients given metformin for 6 months displayed an average 22% reduction in insulin levels. Moreover, a 2-week administration of metformin in between diagnosis and surgery led to a reduction in circulating insulin levels, a decrease in INSR expression and down regulation of AKT(also called protein kinase B is a serine/threonine- specific protein kinase that plays an important role in multiple processes like glucose metabolism, apoptosis, cell proliferation, transcription and migration of cell) and MAPK (mitogen-activated protein kinase is a type of protein kinase specific to the amino acids serine and threonine) signaling pathways in their tumors<sup>(44)</sup>.

### **Conclusion:**

Epidemiological evidence recommends that the incidence of cancer is related to diabetes and to certain risk factors and treatments for diabetes. There was also a positive association between diabetes and vulva and vaginal cancer. Subsequent in vitro studies showed that metformin (antidiabetic agent reduces cancer

mortality in patients with diabetes) inhibits the proliferation of cancer cells and kills cancer stem cells selectively. Metformin therapy relatively minimize levels of both circulating glucose and insulin in patients with insulin resistance and hyperinsulinemia. Diagnosis and treatment have made some progress in recent years, but CRC is still a major public health problem in the world. In order to reduce CRC mortality, early diagnosis, effective treatment and analysis prognosis were therefore of great importance. A better understanding of the relevant factors affecting cancer prognosis is urgently needed to guide the decision-making process for therapeutic strategies for cancer patients and improve their prognosis. Eventually DM-specific strategies for different cancer s are explored.

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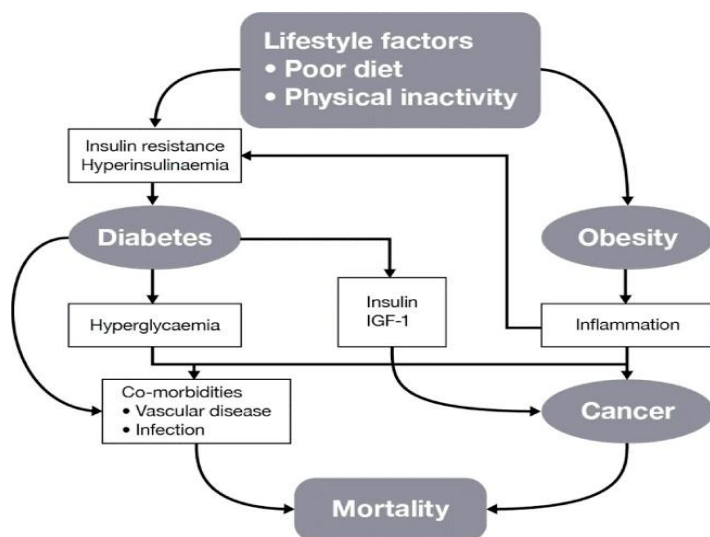


Figure 1: Interrelationship between pathological mechanisms and modifiable and non-modifiable risk factors involved in diabetes, obesity and cancer.