Review Article

A review of current knowledge: Role of diabetes, cancer and cytochrome P450

Kamrudeen Samani1,*, Uday Raj Sharma1, Abhishek Raj Joshi1, Surendra V1, Manjunath P. M1

1Dept. of Pharmacology, Acharya & BM Reddy College of Pharmacy, Soladevanahalli, Bengaluru, Karnataka, India

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A B S T R A C T

Diabetes mellitus (DM) is a condition which is associated with metabolic diseases and considered as life-threatening illnesses worldwide, characterized by sustained hyperglycemia. DM is linked with diabetes mellitus (especially type 2 diabetes mellitus) and carcinogenesis and biologically it is comprise with Hyperinsulinemia, hyperglycemia and fat-induced chronic inflammation in both diabetes mellitus and cancer. Organs such as pancreas, hepatic breast, endometrium, prostate and kidney are highly involved in the disorder, several medications are available on the market which decrease the risk and some of them raise the risk including metformin, a medication of choice for type 2 DM and its anti-neoplastic and tumor suppressant activities. Research has indicated that metformin shows great positive impact in various organs like breast, pancreas, liver, colon, ovaries and prostate tumors, Cytochromes P450s (CYPs) is the enzyme that catalyzes and aids in drug metabolism with its endogenous CYP substrates like eicosanoids, estradiol, arachidonic acids, cholesterol, vitamin D, and neurotransmitters. We review the role of CYPs in cancer of the renal and breast, and address their importance for atherosclerosis and type 2 diabetes mellitus.

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1. Introduction

Diabetes mellitus is prevalent diseases in the world. It is a category of diseases that are characterized by a sustained hyperglycemia caused by inappropriate function or reduced insulin secretion. Persistent hyperglycemia causes different organs (kidneys, heart, lungs, blood vessels or nerves) to be weakened and dysfunction. Furthermore, DM and carcinogenesis are closely related.1-4 The risk of carcinogenesis in type 1 diabetes mellitus (T1DM) is less evident than in type 2 diabetes mellitus (T2DM), although the risk was also documented.5 T1DM is one of the causes that raise the risk of stomach, cervix, endometrium, squamous skin cancers and acute lymphatic leukaemia.5,6 It is also recognized that tumors are the world’s second-largest cause of death. Since cancer incidence in diabetics is widely observed, it is possible factors connecting these 2 diseases. Maynard and Pearson first identified the link between DM and carcinogenesis in 1910 because the prevalence of T2DM is substantially higher than T1DM, and the cancer association studies are mainly focused on T2DM. A consensus study on potential factors connecting diabetes and cancer was published in 2010 by the American Diabetes Association (ADA) and the American Cancer Society (ACS).7 The risk factors were classified into three group’s 1.non-modifiable risk factors, 2. Modifiable risk factors, and 3. Biological links between diabetes and cancer. (Table 1)

1.1. The relation between Diabetes Mellitus and Cancers

Recently literature research studies found the correlation between tumors located in various organs and DM. The results of studies on the influence of DM on tumorigenesis in different organs remain inconsistent. Nevertheless, the majority of authors implied that DM promotes tumor growth. Such relationship was observed in pancreatic, liver,
Various anti-diabetic medications have been associated with an increased risk of oncogenesis.

### Factors linking DM and cancer

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Non-modifiable risk factors</th>
<th>Biological links between DM and cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight (BMI &gt; 25 &lt; 30)</td>
<td>Physical activity Alcohol consumption</td>
<td>Hyperinsulinemia Insulin resistance</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>Smoking Age (55–60 years or older) Sex</td>
<td>Hyperglycemia Fat-induced chronic inflammation</td>
</tr>
<tr>
<td>Physical activity Alcohol consumption</td>
<td>(men-higher risk) Ethnicity/race (African Americans more susceptible than Caucasians)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
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</tbody>
</table>

The cytochrome P450 (CYP) is a large superfamily of integral membrane conserved proteins present in animals, plants, and microorganisms. The CYP iso enzyme superfamily comprises 57 CYP genes and 58 pseudo genes arranged into 18 families and 43 subfamilies in man. They are heme-containing proteins that catalyze the oxidative metabolism of many structurally diverse drugs and chemicals. The reduced cytochrome P450 iso enzymes when bound to CO has a Soret peak at 450 nm. This peak is not usual for a hem containing protein molecule. Hence, they are called P450. The cytochrome P450 superfamily is located primarily in liver, small intestine and kidney.

CYPs catalyze different oxidation and some reduction reactions. Examples of the substrates of CYPs include exogenous (xenobiotics) and endogenous compounds such as cholesterol, testosterone, progesterone, prostaglandin H2, corticosterone, retinoic acid vitamin D3 and arachidonic acid.

Breast, kidney, bladder, endometrial, colorectal and head and neck cancers. Inverse association between these 2 diseases was observed only in prostate cancer. Here we discuss the current knowledge of the relationship "Diabetes Mellitus and site-specific cancer" which attempts to pose the risk of oncogenesis in different organs (Table 2).

### 1.2. Correlation between Anti-diabetic Therapies and increase Risk of Oncogenesis

It is suggested that anti-diabetic therapies interfere with cellular growth, proliferation and metabolism, and subsequently influence on potential oncogenesis. The Hyperinsulinemia and hyperglycemia are risk factors for carcinogenesis, thus lowering insulin and glucose levels seems to be an important matter in prevention of carcinogenesis.

Antidiabetic medications are likely to have different effects on cancer risk due to the various doses of insulin induce. While sulfonylureas and exogenous insulin enhance insulin level, metformin and thiazolidinediones (TZD) are able to reduce its concentration. Moreover, metformin and TZD may reduce insulin resistance. A retrospective cohort study in the UK suggested that monotherapy with metformin is involved in the lowest risk of carcinogenesis.

Sulfonylureas presented increased risk of developing cancer in comparison with nonusers. Another study suggested that anti-diabetic therapy does not modify the risk of cancer in patients with T2DM. Here we suggest the recent studies about the mechanisms of action of various anti-diabetic medications and their potential influence on oncogenesis. (Table 3).

### 1.3. Incretin-Based Drugs (GLP-1 agonists, DDP-4-i)

#### 1.3.1. Alpha-glucosidase inhibitors

Glucagon-peptide 1 agonists (GLP-1 agonists, including exenatide and Liraglutide) act as an Incretin hormone that leads to increased insulin secretion and decreased glucagon secretion. Such medicines also slow gastrointestinal motility. Dipeptidyl peptidase-four, inhibitors (DDP-four which include Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin) increase GLP-1 levels by inhibiting the DDP-4 (also known as CD26) enzyme that degrades GLP-1. The GLP-1 agonist therapy has been known to induce carcinogenesis in rodent C-cells but similar effects of GLP-1 agonists on human thyroid C-cells have not been elucidated possibly due to different doses of GPL-1 Rs in rodent and human cells (high in rodents and low in human cells).

GLP-1R activation in rodent C-cells causes both Diabetes Mellitus and cancer, which is the leading cause of death worldwide. Since studies show that T2DM promotes carcinogenesis, it is important to reduce modifiable risk factors for Diabetes Mellitus, particularly in patients with age, sex, ethnicity, genetic susceptibility which is non modifiable risk factor. Obesity is an important modifiable factor for T2DM as well as for cancer. Reducing weight decreases insulin resistance, Hyperinsulinemia and adiposity-related chronic inflammation (all of the aforementioned states are tumor-promoting mechanisms and increase risk of T2DM). Multiple studies established that Diabetes Mellitus increases the risk of occurrence of cancers in various organs and decreases the potential risk of prostate cancer incidence. Furthermore, the fact suggest that diabetics presently increased risk of different cancers incidence, the overall survival, they should develop cancer, is worse than in no diabetics (Table 4 & 5).
### Table 2: Risk of oncogenesis in patients with DM

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk of oncogenesis in patients with DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>↑↑</td>
</tr>
<tr>
<td>Liver</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Breast</td>
<td>↑↑</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑</td>
</tr>
<tr>
<td>Endometrial</td>
<td>↑↑</td>
</tr>
<tr>
<td>Colon/colorectal</td>
<td>↑↑</td>
</tr>
<tr>
<td>Bladder</td>
<td>↑</td>
</tr>
<tr>
<td>HNC</td>
<td>Larynx↑/no significance association/↓ Oral cavity ↑ Oropharynx ↑ Nasopharynx ↑ HNSCC ↓</td>
</tr>
<tr>
<td>Prostate</td>
<td>↓↓↓/↑</td>
</tr>
</tbody>
</table>

↓-- decreased risk  
↑-- increased risk

### Table 3: Anti-diabetic drugs, their Mechanism of action and risk of oncogenesis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Risk of oncogenesis</th>
</tr>
</thead>
</table>
| Metformin                | **Systemic effects:** ↓serum glucose level  
↓hepatic gluconeogenesis and glycolysis  
↓gastrointestinal absorption of glucose  
↓insulin level  
Inhibited inflammatory response  
**Cell intrinsic effects:**  
↓ATP level  
Activation of LKB1-AMPK pathway  
Inhibition of mTOR signaling  
Activation of p53, p21, cyclin D1  
Inhibition of UPR  
Cell cycle arrest  
Apoptosis induction  
↓ROS production  
↓NADH utilization  
↑CD8 T-cell production  
 Destruction of cancer stem cells | Breast ↓ Pancreas ↓ Liver ↓ Colorectum  
↓/↑ Prostate ↓ Lung ↓ Ovaries ↓ Kidney ↓  
HNC ↓/no significant reduction |
| Sulfonylureas            | Closing potassium channels ↑insulin secretion  
↑fasting and postprandial insulin level  
↑ insulin concentration | Gliclazide ↓ Glibenclamide ↑/↓ Colon ↑  
Liver ↑ Prostate ↓ |
| Exogenous insulin        |                                                                                                        | Prostate ↓ Liver ↑ Pancreas ↑  
Stomach ↑ Kidney ↑ Colon ↑ (glargine)  
Breast↑ (glargine) Endometrium↑  
(glargine) Prostate↑ (glargine) Neutral effect of glargine |
| α-glucosidase inhibitors | Delayed digestion of polysaccharides by inhibiting enzymes sucharase and maltase in proximal small intestine | Stomach ↓ Lungs ↓ Kidney ↑ |
| DDP-4-i                  | Inhibition of DDP-4 ↑level of GLP-1  
↑secretion of insulin ↓secretion of glucagon  
Delayed gastrointestinal motility  
Inhibition of PI3K/AKT pathway | Pancreas ↑ Colon ↓ No tumor-promoting effect |
| GLP-1 agonists           |                                                                                                        | Pancreas ↑/↓ proliferation of prostate, colon and breast cancer cells ↑in rodent C-cells but not in human C-cells |
| TZD                      | Activation of PPAR, Suppression of Bcl-2/Bcl-xL function, Inhibition of androgen activation | Pancreas ↓ Breast ↓ Colorectum ↓ Lungs ↓  
Kidney ↓ Liver ↓ Colon ↓ |

↓-- decreased risk  
↑-- increased risk

### Table 4: Cancers of digestive system and DM.

<table>
<thead>
<tr>
<th></th>
<th>Increased risk in diabetics</th>
<th>Decreased risk in diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer</td>
<td>↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Colon/colorectal</td>
<td>↑</td>
<td>-</td>
</tr>
</tbody>
</table>

↓-- decreased risk  
↑-- increased risk
Table 5: Cancers of genitourinary system and DM.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Increased risk in diabetics</th>
<th>Decreased risk in diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder cancer</td>
<td>↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

1.4. Role of CytochromeP450 in Cancers

1.4.1. Renal cancer

It has been shown that the cytochrome P450 (CYP3A) types are reliably expressed in kidney cancer cells using immunohistochemistry, western blot analysis, and reverse transcriptase PCR. This research indicated that the CYP3A expressed could be involved in the development of renal cancer, and that these types of CYP3A are the source of the multidrug resistance found in this cancer. In addition, they indicated that the presence of CYP3A types in the renal cells would be useful for treating renal cancer. For instance, the agent AQ4N, an alkylaminoanthroquinone is bio activated by CYP3A forms to a highly cytotoxic metabolite in the hypoxic conditions of the tumor cells, but the AQ4N would not be cytotoxic for the normal cells where the conditions are normoxic.\(^{21}\) the cytochrome CYP1B1 was also shown to be present in renal cell carcinoma. It is also expressed in wide variety of cancers and not detected in normal cells.\(^{22}\)

It has been proposed that since CYP1B1 is the metabolizing enzyme for the anticancer drugs (e.g. cyclophosphamide, paclitaxel, doxorubicin, docetaxel, cisplatin, 5-fluorouracil) its inhibition may be a good strategy for cancer therapy.\(^{23}\) Recently, it has been suggested CYP1B1 is significantly unregulated in renal cell carcinoma, and that it promotes this cancer progression.\(^{24}\)

1.4.2. Breast Cancer

It has been documented that CYP2E1 in breast cancer cells contributes to the production of the reactive oxygen species (ROS). Furthermore, CYP2E1 controls autophagy, induces the tension of endoplasmic reticulum, and suppresses the BC cells’ metastatic potential. CYP2E1 expression shows to greatly increase in BC cells as well as tissues adjacent to the tumor. The overexpression of the CYP2E1 enzyme may be beneficial to the cancer patient this advantage comes from the activation property of CYP2E1 pro drugs and that the metabolism of some CYP2E1 substrates contributes to ROS development and oxidative stress. This will ultimately lead to apoptosis inhibition but will accelerate the death of the necrotic cancer cells. In a review the expression profile of CYP450 enzymes in (BC) in Caucasian population was studied. It has been confirmed that the CYP4X1, CYP2S1 and CYP2U1 regulations exist.\(^{25}\)

1.5. Roles of CytochromeP450 in Diabetes

CYP2E1 oxidizes ethanol and stimulates procarcinogens such as N-nitrosodimethylamine, benzene and N-alkylformamides.\(^{26}\) it has been shown that CYP2E1 is over-expressed in alcohol-induced liver damage and non-alcoholic steatosis.\(^{27}\) Diabetes is generally associated with fat mobilization because it will be the first source of energy that will contribute to non-alcoholic production.\(^{28}\)

1.6. Roles of Cytochrome P450 in Atherosclerosis

Arachidonic acid is metabolized to epoxyeicosatrienoic acids (EETs) by CYP450 (CYP 2B, 2C8, 2C9, 2C10, 2J2), or arachidonic acid epoxygenase. The EETs function as a hyperpolarizing factor (EDHF) derived from endothelium that acts as a vasodilator in all vasculatures including the coronary arteries.\(^{29}\) The EDHF metabolite of arachidonic acid by CYP2C has been shown to be the most vital cause of endothelial relaxation in cultivated human endothelial cells and native porcine coronary artery endothelial cells.\(^{30}\) Other relaxing factors include prostacycline (PGI2) and nitric oxide (NO).\(^{31}\) Hence, these CYP450 enzymes prevent or regress atherosclerosis.\(^{32}\)

1.7. Cytochrome P450 Gene Polymorphism

Genetic polymorphisms in CYPs are a major cause of the inter individuals variation in drug metabolism. They lead to the occurrence of variation in response to the drugs ranging from adverse effects to lack of efficacy.\(^{33}\) From the 50 identified CYPs iso enzymes that catalyze the drug metabolism, there are more than 20 genes of CYPs are functionally polymorphic, for instance the CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP1B1, and CYP1A2. Therefore, about 40% of drug metabolism is catalyzed by the polymorphic CYPs.\(^{34}\)

2. Conclusion

The study indicated that both diabetes and cancer are linked to each other with modifiable risk factors, non-modifiable risk factors, and biological linkages between Diabetes Mellitus and cancer, these create the leading cause of death in both developing and developed countries and considered to be life-threatening diseases across the world globe. Persistent hyperglycemia causes different organs (kidneys, heart, lungs, blood vessels or nerves) to be weakened and dysfunction. Additionally, Diabetes Mellitus and carcinogenesis are closely related. The risk of carcinogenesis in type 1 diabetes mellitus (T1DM) is...
less apparent than in type 2 diabetes mellitus (T2DM). The T2DM is associated with an increased incidence and mortality from many cancers such as breast cancer, renal cancer. The use of metformin has been linked with a reduction in cancer incidence and mortality and several ongoing randomized trials examine the impact of metformin on cancer-related outcomes. The cytochrome p450 is the enzyme that enhances the various oxidation and reduction reaction and several other drug. These cytochrome p450 has shown it significant role in several cancer which include breast cancer, renal cancer. Mainly in the breast cancer the CYP2E1 has it great role for producing reactive oxygen species (ROS) and controlling autophagy, induce endoplasmic reticulum tension and suppresses BC cell that provide the better anticancer activity in patient whereas in another associated cancer such as renal cancer CYP3A form play great significant role which was identified by immunohistochemistry, western blot analysis and reverse transcription PCR. Hence provide the better treatment with their associated risk for the disease. The cytochrome p450 has also its role in various other which include diabetes, atherosclerosis, and gene polymorphism.

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4. Source of Funding

None.

5. Conflict of Interest

None.

References


Author biography

Kamrudeen Samani Student
Uday Raj Sharma Associate Professor
Abhishek Raj Joshi Student
Surendra V Associate Professor
Manjunath P. M Associate Professor
