Use of Noninsulin Anti Diabetics for Prevention and Treatment of Cancer- Narrative Review Article

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Abstract

Background: Epidemiological evidence shows that cancer and diabetes are major causes of death in the world. Type2 diabetes increases the risk of cancer-specific mortality. This review relates diabetic therapies, diabetes and cancer.
Method: All published papers in this field were searched, looking into such databases as Science Direct, ISI Web of Knowledge, PubMed and Scopus.
Results: In cancer patients, metformin improves patient outcome and reduces cancer risk. Sulfonylureas may increase risk of cancer, but decreased risk of cancer is associated with thiazolidinediones in type2 diabetic subjects. Metformin lowers circulating insulin and it may be important for treatment of hyperinsulinemia-associated cancers, such as colon and breast cancer.
Conclusion: However, laboratory investigations and large-scale population based studies are required for further investigation of association of cancer-preventive, anti-cancer and cancer-mortality of noninsulin antidiabetics.

Keywords: Diabetes, Mortality, Metformin hyperinsulinemia, Malignant, Hyperinsulinemia, Thiazolidinediones

Introduction

Epidemiological evidence shows that cancer and diabetes are major causes of death in the world and number of diabetic patients is increasing rapidly (1). A number of studies identified that individuals with diabetes have increased risk of developing several types cancers (2), notably cancers of the pancreas, endometrium, breast, rectum, liver and colon (3, 4)
Hyperinsulinemia, insulin resistance and impaired glucose tolerance might be associated with increased carcinogenesis (5) as up to 80% of pancreatic cancer patients have identified with Diabetes mellitus type 2 or impaired glucose tolerance (6, 7). Influence of anti-diabetic medications on cancer has recently gained attention. Using metformin, an insulin sensitizer, may decrease cancer development, progression, and mortality due to cancer (8,

9). On the other hand, treatment with insulin secret gouges and insulin (sulfonylureas) are related to increased chances of development and mortality related to cancer (10).

Method

In May 2014, all published papers in this field were searched, looking into such databases as Science Direct, ISI Web of Knowledge, PubMed and Scopus. Key words used included antidiabetics and cancer, diabetes and cancer risk and mechanism of antidiabetics drugs in cancer prevention or treatment. All epidemiological and laboratory studies that investigated the effects of antidiabetics on cancer (treatment, prevention and risk) were studied.

Relationship between diabetesandcancer

Type2diabetes and malignant tumors have become common diseases worldwide. It is shown by epidemiologic studies thattype2diabetesincreases the risk and tumor specific mortality of somecancers. Endogenous and exogenous hyperinsulinemia have mitogenic effect and may increase the risk of cancerin diabetes (11).

Disturbances of carbohydrate metabolism are commonly observed in cancer patients. Complications of malignant diseases and some medications used in their treatment, such as steroids or parenteral nutrition, may increase blood glucose levels, may affect carbohydrate metabolism, whereas diabetes may hamper oncotherapy (12). A mechanism associated with increased risk of cancer in diabetics is probably by activation of protein kinase Ras/Raf/ (mitogen-activated) pathway along with reduced expression of the growth factor (epidermal) receptor (13). Cancer-assiciated dysfunction of organ is observed in pancreatic cancer and it may increase insulin dysregulation leading to hyperglycemia and in turn diabetes (14).

Biguanides

Metformin, a biguanide prescribed as first-line antidiabetic in individuals with type 2 diabetes. History of metformin dates back to the use of Galega officinalis as botanic medicine for treatment of polyurea in medieval Europe (15, 16). Its glucose-lowering effect is result of decreased glucose production from liver and increased glucose utilization (17). Due to safety, recently metformin has been used for other conditions, for example in treatment and prevention of cancer (18)

Mechanism of metformin action

It acts by targeting enzyme AMPK (AMP activated protein kinase) which is involved in inducing muscles to take up glucose from blood (19). Metformin inhibit proliferation of cancer cell through reducing protein synthesis (20).

Metformin inhibits gluconeogenesis in liver and stimulates uptake of glucose in muscles(21). At cellular level, metformin is involved in regulation of protein kinase activated by AMP (AMPK), activated by elevated level of AMP(intracellular)

(22, 23). AMPK (24) is involved in regulating transcription of genes that regulate gluconeogenesis in liver and genes encoding transport of glucose in muscles. As a result, metformin increases sensitivity of insulin and decreases blood glucose (fasting) and level of insulin in diabetic individuals. In a series of in vitro studies evidence for the direct action of metformin on growth of cancer cell has been established. Indeed, metformin exhibits a consistent and strong antiproliferative action on several cancer cell lines with differences in sensitivity of different cancer cell lines (25).

Metformin activates AMPK indirectly by disrupting mitochondrial respiratory chain complex I, leading to decreased ATP synthesis and increase cellular ratio of AMP: ATP (26) this results in stimulation of activity of AMPK. AMP activates AMPK allosterically, facilitating catalytic subunit's phosphorylation by liver kinase B1 (LKB1 which is upstream kinase also called STK11), which is protein product of tumor suppressor gene which is mutated in Peutz-Jeghers cancer predisposition syndrome(27). Dephosphorylation of AMPK Thr172 by protein phosphatases is also prevented by binding of AMP to AMPK. After activation, AMPK cause phosphorylation of many targets as a result a number of catabolic processes are activated for example glycolysis and fatty acid β-oxidation that generates ATP and suppresssing many processes, depending on ATP supply by cell, for example synthesis of protein and fatty acid, gluconeogenesis and cholesterol synthesis(28).

Mechanism of action in cancer

Many epidemiological studies show diabetes as a risk factor for cancer. Metformin has been associated with reduced risk of cancer as well as mortalities as compared to other glucose loweringagents. However, intarindividual variability of pharmacokinetic parameters in patient response of Metformin is evident (29). Possible anticancer mechanism of noninsulin antidiabetics and their influence is shown in Table 1:

Metformin targets initiating cancer cells. For example, in mice metformin inhibits growth of breast cancer cells in culture and reduces tumor

forming ability (30). According to a study link between AMPK and LKB1 was investigated by deleting LKB1 in livers of mouse (31). This prevented activation of liver-specific AMPK and mice became refractory to glucose lowering action of metformin, demonstrating the primary mechanism of metformin action through active-ting AMPK, p53 a metabolic regulator, depends on AMPK to induce autophagy (32). Activation of AMPK improves survival of stromal cells that are stressed bioenergetically (33).

For energy production cancer cells depend on glycolysis so, adapt a hypoxic environment. For many years, this high rate of glycolysis has been considered as by-product of process of cancer, but evidences suggest that it is required for progression of malignancy (34).

Metformin effects cancer cell metabolism

The mechanism that was demonstratedby Warburg in 1927, called "Warburg effect" describes the observation that the cancer formation takes place due to inefficient cellular respiration. This indicates that even in the presence of oxygen the cancer cells prefer fermentation. Another possible pathophysiological mechanisms related to malignancies is decrease in immune status it has been incriminated as deficient immune system would not be capable to recognize malignant cells (35).

Oxygen consumption is inhibited by metformin in colon cancer cells, and it is consistent with inhibition of oxidative phosphorylation. Metformin is associated with an increased glycolysis in prostate cancer cells (36). All these observations show that metformin inhibits anabolic pathways, decreases cellular metabolism, and induces a stress similar to the metabolic stress. As a result, depending on cell type cellular response varies from autophag, apoptosis, and cell cycle arrest.

Increased IGF-I concentrations

According to hypothesis-increased concentrations of IGF-I increases cancer risk, it increases chances of survival of the cells gathering genetic damages (37) and increases proliferation of cells during the process of stepwise carcinogenesis. There is another possibility (relating insulin levels to poor outcome) that insulin can stimulate neoplastic behavior of the transformed cells. Insulin-like growth factors and insulin affect chances and risk of cancer (38). MCF-7 cells (breast cancer cell line) are responsive to insulin-like growth factors insulin. Metformin functions as growth inhibitor not as insulin sensitizer for MCF-7 breast cancer cells. Hyperinsulinaemia may also be associated with an accelerated tumor growth through its effect on IGF-1 cancer cell overexpressing insulin and IGF-1 (39). It inhibits mTORC1-pathway by direct and indirect mechanism.

Role in gluconeogenesis and its link to chemoprevention

Metformin inhibits hepatic glucose output by inhibiting gluconeogenesis, leading to decrease in insulin levels (20).

Insulin-dependent effects

The mechanism that supports the association between use of metformin and reduced risk of cancer is found to be same to the mechanism involved in antidiabetic effect. Activation of AMPK Indirectly (via LKB1-dependent mechanism) (40) pathway in skeletal muscles and hepatocytes via metformin leads to lowering of plasma glucose and reducing level of insulin through down regulation of gluconeogenesis regulating genes and stimulating uptake of glucose by muscles (41), both are known to contribute to tumorigenesis. Consequently, metformin shows its action indirectly and reduces negative effects of insulin on progression and growth of tumor and directly inhibits multiplication of cells and colony formation and stimulates partial arrest of cell cycle in cancer cell lines (42).

AMPK-dependent effects

Publication by Shaw et al revealed that AMPK is activated by a gene that is encoding tumor suppressor protein kinase LKB1 (43). LKB1, functions as a tumor suppressor protein and this explains why exercise is beneficial in primary and secondary prevention of certain types of cancers. AMPK is also involved in regulation of genes. Its

activation can suppress expression of lipogenesis-associated genes that are glucose-activated (44).

Breast cancer

Three mechanisms are suggested to define link of diabetes to pathological process of breast cancer, first: activation pathway associated with signaling of insulin, second: activation of pathway of IGFs, third: regulation of sex hormones in body (45, 46). Type 2 diabetics administered pre-operative breast cancer chemotherapy and metformin was presumed to have higher chances of complete remission as compared to the patients not receiving metformin (47). Long-Term use of metformin reduces risk of breast cancer (48). Metformin and doxorubicin culture combination destroys both non-stem cancer cells and cancer stem cells, and decreases tumor mass. That is why combination of chemotherapeutic drugs and metformin improves condition of patients with breast cancer (49).

Metformin reduces breast cancer incidence, reduced colony formation, prognosis (50), and partial arrest of cell cycle at G1 phase leading to improved survival of patients with type 2 diabetes and breast cancer. Metformin's anti-breast cancer activity is due to ability to activate AMP-dependent protein kinase (AMPK) that it is a key regulator of the energy balance in the cells and in whole organism (51).

High level of serum testosterone increases risk of Breast Cancer, particularly in ER-positive Breast Cancer type (52, 53). Reduction of level of testosterone is noticed with Metformin (54). Metformin has shown activity against both estrogen receptor negative (ER) and estrogen receptor positive, when erbB2 breast cancer cell lines were studied. In case of overexpressing erbB2 breast cancer cell lines, Metformin might function in a different way, positively on women who are estrogen-deficient (55) and at elevated concentrations erbB2 expression is decreased, and at low concentrations, it is involved in inhibition of activity of erbB2 tyrosine kinase These evidences show that metformin might be therapeutically useful against ER negative, ER positive, erbB2 normal and overexpressing cells in breast cancer. Two to three fold elevated risk of PR- and ER-positive breast cancer

was observed in women whose estradiol and testosterone levels were in higher quartiles as compared to women in lower quartile (46).

After menopause androgen is mainly derived from adrenal gland. Main circulating androgen is DHEA (Dehydroepiandrosterone) (56). In adipose tissues DHEAS and its metabolite androstenediol, are converted to delta4 androgens (57). This conversion is major source of circulating testosterone and androstenedione. Ovary produces approximately 25% to 45% of testosterone, 15% of DHEA and androstenedione (58).

Peutz-Jeghers syndrome is associated with Loss of LKB1 function, in which multiple gastrointestinal polyps are formed and significant increased risk (approaching 80%) of different epithelial cancers, for example breast cancer (59).

Prostate Cancer

IGF-I plays role in prostate carcinogenesis (60).Level of IGF-I in body is a heritable trait. Men with higher level of circulating IGF-I are at higher risk of developing prostate cancer (61). Prostate cancer risk is affected by inherited variation in IGF1 (62).

Bladder cancer

In US, bladder cancer is found to be ninth most common malignancy in the world (63). Diabetic patients have an increased risk of developing urinary tract infection, and it has been related to the risk of bladder cancer independent of antidiabetic agents used (64).

In circulation, IGF-I bind to IGF binding protein, IGFBP-3 (65) and may play role in development of prostate, breast, colorectal and bladder cancer. Animal studies support role of IGF-I in tumorigenesis of bladder (66).

Thiazolidinediones

Thiazolidinedione decreases risk of lung, breast and colorectal cancers, and a decreased overall cancer risk. Although limited data is available, it is suggested by some studies that increased risk of bladder cancer is associated with pioglitazone and no increase in risk was observed with rosiglitazone (67-71).

Insulin resistance increases risk of cancer and is reduced by drugs like glitazones and metformin (72).

According to a study, use of pioglitazone in Taiwanese patients having type 2 diabetes mellitus does not influence oral cancer risk, it was suggested that use of pioglitazone had no association with the oral cancer (73).

Complex biological effects are associated with thiazolidinedione peroxisome proliferator activated receptor gamma (PPARγ) ligands (74) for example growth inhibitory action, but increase in risk of cancer is not predicted by these results (75). PPARγ related signaling is not involved, in observed urothelial cancer. Crystal formation may lead to chronic bladder irritation in urothelial cancer (76, 77).

Table 1: Possible anticancer mechanism of noninsulin antidiabetics and their influence

Drugs	Possible anticancer mechanism	Influence
Biguanide (Metformin)	o effects cancer cell metabolism o Increased IGF-I concentrations o Role in gluconeogenesis and chemoprevention o Reduces insulin resistance	Reduced risk of cancer
Thiazolidinedione	o Reduces insulin resistance	Moderately reduced risk of cancer
Sulfonamides	o Increase level of circulating insulin	Increased risk of cancer

Sulfonylurea

A recent retrospective study has revealed that sulfonylureas may increase cancer related mortality and cancer risk (78) without exploring differences among individual drugs of sulfonylurea. However, it is still not clear whether increase in cancer-related mortality risk is due to metformin's protective effect or due to unfavorable effect of insulin and sulfonylurea (79).Sulfonylureas stimulate tumorigenesis (80) but the exact mechanisms that relates sulfonylurea to cancer is unknown. According to a hypothesis is sulfonylureas lead to increase in insulin and IGF-1 level and increased activation of insulin receptor, which leads to enhanced risk of cancer.Increase in chances of cancer-associated mortality is studied in diabetic patients given insulin and sulfonylureas in comparison with metformin treated patients. They might be associated with increased risk of thyroid cancer by increasing levels of circulating insulin in body (81).

Conclusion

Insulin is associated with decreases apoptosis and increased proliferation of cells. Diabetes mellitus type 2 patients have a high level of circulating insulin so; have increased chances of developing cancer as compared with nondiabetic people. In cancer patients, metformin improves patient outcome, Sulfonylureas may increase risk of cancer and modest, but decreased risk of cancer is associated with thiazolidinediones in type2diabetic subjects. Metformin may has a double effect it decrease hyperinsulinemia and hyperglycaemia and at cellular level, inhibiting mTORC1-pathway (cancer supporting) through AMPK- independent and dependent mechanism. Metformin remarkably reduced risks of cancer of breast, colorectum, lungs and liver. Above findings suggest that metformin potentially has an anticancer action.

Use of thiazolidinedione is associated with modest, but reduced risk of lung, breast and colorectal cancers, and a decreased overall cancer risk. However, increased risk of bladder cancer was associated with pioglitazone use. Sulphonylureas may increase cancer related mortality and cancer risk. However, it is still not clear whether increase in cancer-related mortality risk is due to metformin's protective effect or due to unfavorable effect of insulin and sulfonylurea.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or fal-

sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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