DRUG INDUCED DIABETES

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ABSTRACT

Several Epidemiological studies have suggested that rate of development of diabetes mellitus consequent to taking diverse types of medication is increasing now a days. Several medications have been found to be associated with causation of diabetes. Various pharmacological medications which are commonly used in clinical practice are found to affect glucose homeostasis and interfere with the balance between various hormones like insulin, glucagon, catecholamines, growth hormone, and cortisol. Mechanism for the diabetes caused due to medications is associated with a reduction in insulin production, some with reduction in insulin sensitivity, and some appear to be associated with reduction in insulin production along with the insulin sensitivity. It is very difficult to establish a precise cause and effect relationship between a medication and development of diabetes. Various clinical studies of medications typically concentrate on evaluation of effectiveness and are not powered to evaluate side effects. Several covariant such as the weight gain associated with medication such as steroids or antipsychotics also make it difficult to find that whether the development of diabetes was a primary or secondary effect of the medication. Mechanisms for the causations of diabetes have been linked with range from decreased insulin secretion to decreased insulin action to direct neural effects. Stopping or switching medication is considered as the first step in treating the drug induced diabetes. While the information to support many of the consensus recommendations for treatment drug -induced diabetes is lacking. To establish the optimal therapy for Drug induced diabetes, it is quite essential to understand the potential mechanism which interrupts the metabolism of carbohydrates.

Keywords: *Diabetes, insulin sensitivity, glucose homeostasis, medication-induced diabetes, optimal therapy.*

INTRODUCTION

Diabetes is defined as a metabolic disorder which is characterized by hyperglycemia (1,2) and it causes alteration in the metabolism of proteins, fats and carbohydrates (3). Incidences of diabetes are increasing now a day at an alarming rate (1).

Several Epidemiological studies have suggested that rate of development of diabetes mellitus consequent to taking diverse types of medication is increasing. There are wide variety of frequently prescribed medications which are known to affect the glucose homeostasis (4) and lead to causation of the glucose intolerance and participate in the causing the diabetes in non-diabetic patients (1, 5) and worsening the glucose control in the patients with established diabetes. These drugs exert their effects on glucose homeostasis by affecting the insulin secretion and/or causing insulin resistance (6). Thus drug induced diabetes is defined as the hyperglycemic state caused due to ingestion of drugs and meets the definition criteria of diabetes and an explanation has been provided by individual differences regarding the causation of diabetes due to medication by the pharmacogenomics (7, 8).

The drugs which induces diabetes are groups according to the mechanism by which they cause diabetes like inhibition of insulin secretion, causing insulin resistance, interferes with insulin secretion and/or insulin action (7).

Classification of the drugs causing diabetes
Drugs that interferes with insulin production and secretion B blockers Pentamidine Tacrolimus Phenytoin Pyriminil
Drugs that reduces effectiveness of insulin(insulin sensitivity) Glucocorticoids Growth hormones Protease inhibitors Oral contraceptives
Drugs that act on both insulin secretion and insulin sensitivity Thiazide diuretics Cyclosporine Atypical antipsychotics

GLUCOCORTICOIDS

Glucocorticoids are used in treatment of wide variety of disorders and in wide range of doses. Glucocorticoids regulate several physiological systems in the body (9). Short term acute therapy is used in chronic obstructive pulmonary disease, acute gout, chemotherapy protocols, for fetal lung maturation in pregnant women, bacterial meningitis etc (10). Chronic

glucocorticoids treatment plays a vital role in modulating immune system (11). Despite their role as anti-inflammatory and immunosuppressant, glucocorticoids are associated with the several side effects (12) including hypertension, osteoporosis, diabetes and many more (11). Diabetes mellitus is one of the most common side effects of the glucocorticoids treatment (13, 14).

Glucocorticoids cause disturbance in the glucose metabolism through the impairment of the glucose metabolism through the impairment of the multiple pathways as beta cell dysfunction, decrease in the insulin secretion (9, 15). Depending upon the glucocorticoids effects either acute or chronic, extent of the bet cell dysfunction and tissue insensitivity to the insulin varies (16).

Glucocorticoids also have effect on glyceroneogenesis (11). In the adipose tissue gluceroneogenesis controls the fatty acid release rate in the blood. Synthesis of triacylglycerol from the fatty acid and glycerol is also regulated by the glyceroneogenesis in the liver (12). These processes in the liver and adipose tissue are regulated by the enzyme phosphoenylpyruvate carboxy Kinase (PEPCK) (17). Glucocrticoids suppresses the gene expression of PEPCK enzyme in the adipose. Thus it inhibits the glyceroneogenesis. While in the liver PEPCK stimulates the production of glycerolas the result the fatty acid concentration is increased through the lipoprotein lipase (18).

Thus as a net result there is increase in the release of the fatty acids in the blood and this increase in the fatty acid release causes insulin resistance through interfering with the glucose utilization especially in the skeletal muscles (12).

Skeletal muscle is responsible for the insulin mediated glucose uptake. Glucocorticoids interfere with the components of the insulin signaling cascade like glycogen synthase kinase-3, glycogen synthase and GLUT-4 translocation. Thus causing impairment in the insulin mediated glucose uptake (19).

Proposed risk factors for the glucocorticoids induced diabetes includes age, family history, BMI and impaired glucose intolerance (20). Apart from all these, obesity, increased appetite and visceral lipogenesis are also found as the major factors involved in the glucocorticoids induced diabetes (21).

ATYPICAL ANTIPSYCHOTICS

The atypical antipsychotics, also known as second generation antipsychotics, have become the preferred treatment for the schizophrenia and schizoaffective disorders. These drugs have several advantages over the other antiosychotics drugs (22). But on the other hand these agents are also associated with many side effects including impaired glucose intolerance, weight gain, disturbance of the lipid metabolism, diabetes and many more (23, 24). It has been found that thses drugs are associated with the increased risk of the hyperglycemia or type 2 diabetes (25, 26).

Olanzepine and clozapine being the most likely to increase the risk of diabetes when used by the schizophrenia patient (27). In the study of koller et al, it was found that diabetes was developed in the patients who were on the olanzapine and resperidone treatment in less than 6 months (28, 29). In many case reports, weight gain was reported prior to the development of the diabetes with the use of antipsychotics. (30). While meyer found increase in the fasting

glucose levels with the use of olanzapine, which was not correlated with the changes in the weight (31). It has also been found the schizophrenia itself contributes to the development of diabetes (32).

Atypical antipsychotics are positively associated with the excessive weight gain (33-35). In addition to the weight gain, atypical antipsychotics also cause several metabolic disturbances like low HDL Levels, high triglycerides (36- 38), increase in the free fatty acid (39). According to the NHANES III, schizophrenic patients who are on atypical antipsychotics treatment, represents 3 or more out of 5 syndromes which include waist girth, hyperglycemia, hypertension, hypertriglyceridemia and low HDL cholesterol. This prevalence is twice to three times greater than the matched controls (40).

There are several reports which showed that patients developed diabetes without prior weight gain after the treatment with the atypical antipsychotics (41). Atypical antipsychotics were found to disturb the insulin mediated glucose transport (42) and increase in the lipogenesis (43). Abnormal glucose metabolism and insulin resistance was reported in the patients on olazapine and clozapine treatment (44-46)

Leptin hormone, synthesized by adipocytes, plays a major role in controlling the body weight (47). Leptin is also correlated with the fat mass and insulin resistance (48).

Hagg et al., found that in the patients who were on clozapine treatment, plasma levels was increased independently of the weight (49).

It is postulated that insulin resistance may be responsible for the antipsychotics induced diabetes. But it may not be the only factor in diabetes development after atypical antipsychotics treatment (50).

Apart from the insulin resistance, atypical antipsychotics also have effect on the several neurotransmitter systems (33). Atypical antipsychotics have antagonistic action on multiple receptors sub types with a range of affinity for dopamine, serotonin. Histamine and adrenergic receptors (22,51).

As dopamine, serotonin, noradrenergic, acetylcholine and histamine have been implicated in the regulation of food intake, insulin resistamce and glucose metabolism and decreased sympathetic nervous system activity is also involved in causing the increase in lipid storage and inhibition of lipolysis (33). It has also been found that incidences of diabetes are more with atypical antipsychotics which block both dopaminergic and dopaminergic receptors compared with neuroleptics which block only dopaminergic receptors (52).

Increased antagonistic affinity of olanzapine and clozapine for the muscarinic and histaminergic receptors may be responsible for the increased weight gain and metabolic impairments associated with these drugs (30).

THIAZIDE DIURETICS

Thiazide diuretics are very effective in treating the patients with the hypertension (53, 54). But despite their effectiveness, major findings about the use of thiazide diuretics involves impaired glucose tolerance, hypokalemia, increased serum cholesterol and increased serum uric acid (7, 55). All of these factors are responsible for the potential of the thiazide diuretics to increase the cardiovascular risk either through arrhythmogenesis or artherosclerotic risk

(56). Since from the introduction of thiazide diuretics as antihypertensive, association of these drugs with glucose impairment is well known (57).

Data from randomized controlled trials and epidemiological studies have shown that thiazide therapy is associated with new diagnosis of diabetes and other metabolic abnormalities (53, 58).

It is also observed that risk of new onset diabetes increases in the patients with central obesity and other components of cardiometabolic syndrome (59). Use of the thiazide diuretics was also supported by ALLHAT as the initial pharmacotherapeutic agent for treating the hypertension. A debate was renewed by ALLHAT about the metabolic adverse effects of thiazide diuretics (60).

The mechanism by which thiazide diuretics cause glucose intolerance is not completely understood, but the preliminary reports of national heart lung and blood institute concluded that most likely cause of the diabetes induced by thiazide diuretics is hypokalemia (59). Low serum levels of potassium has been found to be involved with the β cell insulin secretion and insulin metabolic signaling in skeletal muscle, liver and adipose tissue (55). An inverse relationship between potassium and glucose levels is also well documented (60). An association between the hypokalemia and insulin secretion may partially explain this association with potassium and glucose Additionally thaizide diuretics also activates rennin angiotensin aldosterone syatem which may be in concert with sympathetic activity, increases serum glucose levels (55, 62). Thus inhibition of rennin angiotensin aldosterne sysytem axis may be helpful in mitigating the effects of thiazide diuretics on serum glucose levels (62).

Other factors which are contributing for the pathogenesis of impairment of glucose metabolism induced by thiazide diuretics especially in hypertensive patients with abdominal obesity and other components of cardio metabolic syndrome involves increased systemic and tissue inflammation (63, 64).

It has been suggested that potassium homeostasis maintenance by supplementation or concominent ACE inhibiton may be helpful in preventing the thiazide induced dysglycemia (54).

β BLOCKERS

It has been found that as a result of the β blockers, people with diabetes often have elevated fasting blood glucose levels (65). One study showed that atenolol caused new diabetes in people with abdominal obesity and exacerbated hyperglycemia (66). β-blockers are notion to make a contribution to the causation of hyperglycemia through impairing the discharge of insulin from the pancreatic β-cell (67)

PROTEASE INHIBITORS

Protease inhibitors are important additives of antiretroviral remedy for the remedy of human beings with HIV and AIDS. Protease inhibitor–related hyperglycemia might also additionally arise in handled human beings without or with diabetes and happens in 3–17% yearly in remedy or after full-size and extended use. Protease inhibitor capsules are idea to create a homeostatic pressure reaction that decreases insulin sensitivity, thereby selling insulin resistance–related hyperglycemia. (68) Ritonavir has been proven to immediately inhibit

glucose transporter kind four interests in vivo, accounting for its cappotential to motive hyperglycemia (69).

CONCLUSION

Several medications have been associated with elevated blood glucose and frank diabetes mellitus. Mechanisms range from impaired insulin secretion to impaired insulin action to direct neural effects. Only a few people who take these medications develop diabetes, suggesting that some people are more susceptible to these undesirable effects or they may also have other conditions that put them at risk for carbohydrate metabolism perturbations. Some medications may elevate blood glucose levels, including- β blockers, thiazide diuretics, corticosteroids, antipsychotics, and protease inhibitors. It is first important to consider stopping or switching medications for diabetes caused by medications. Further it is also of prime significance that no matter whether a patient has been diagnosed with diabetes or not, clinicians should be aware t hat drugs can lead to elevated blood glucose levels. There are few data to support many of the consensus recommendations for treatment of medication-induced diabetes, but knowledge of potential mechanisms by which a drug can disrupt carbohydrate metabolism may help determine optimal therapy to overcome this problem.

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