Drug Induced Diabetes

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ABSTRACT

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Due to the ingestion of a drug, the development of a hyperglycemic state that meets the definition of diabetes is known as drug-induced diabetes. The fasting glucose criterion for diabetes was revised by the American Diabetes Association (ADA) in the year 1997 by lowering the cutoff fasting glucose value from 140mg/dl to 126mg/dl. ADA and World Health Organization (WHO) recognized drug induced diabetes as a separate etiological category. The offending drugs that induce diabetes are grouped based on the mechanism by which they induce diabetes. The rise for developing drug induced diabetes includes an unsuspected and underlying abnormality in carbohydrate metabolism or family history. This review article is mainly focused on the drug classes that cause diabetes like thiazides, β-antagonists, steroids, statins, antipsychotic agents, protease inhibitors and immunosuppressive agents. In case of patients with pre diabetes, diabetes and insulin resistance syndrome, a drug that has the tendency to affect the blood glucose levels must be avoided.

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Introduction

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Decreased insulin secretion, increased glucose production and decreased glucose utilization are the various factors contributing to hyperglycemia. Type 1 diabetes and Type 2 diabetes are the two broad categories in which both are preceded by a phase of abnormal glucose homeostasis. Type 1 diabetes was characterized by complete or near total insulin deficiency where as impaired insulin secretions increased glucose production and insulin resistance are the characteristics of type 2 diabetes mellitus. The incidence of type2 diabetes mellitus was increased day by day. Obesity, sedentary lifestyle and western style diet are some of the features which attribute to cause diabetes.

Both the types vary in clinical presentation, etiology, onset, progression of disease and were associated with macro & micro vascular complications. Among the adults over 18 years of age, the global prevalence of diabetes has increased from 4.7% in 1980 to 8.5% in 2014. In middle and low income countries, the prevalence of diabetes has been increasing more rapidly. According to WHO, diabetes will be the 7th leading cause of death by the year 2030 [1,2].

Drug Induced Diabetes

Due to the ingestion of a drug, the development of a hyperglycemic state that meets the definition of diabetes is known as drug-induced diabetes [3,4]. The fasting glucose criterion for diabetes was revised by the American Diabetes Association (ADA) in the year 1997 by lowering the cutoff fasting glucose value from 140mg/dl to 126mg/dl. ADA and World Health Organization (WHO) recognized drug induced diabetes as a separate etiological category. The developed diabetes may be reversible if the drug is dechallenged or sometimes it may be irreversible also [5].

Drugs that involved in Drug Induced Diabetes

The offending drugs that induce diabetes are grouped based on the mechanism by which they induce diabetes. By interfering with insulin production and secretion, drugs that cause diabetes includes diphenylhydantion, pentamidine, pyriminil, tacrolimus, didanosine, opiates, β-receptor antagonists and L-asparaginase. By reducing the effectiveness (sensitivity) of insulin, drugs that can cause diabetes includes protease inhibitors, growth hormone, β-receptor agonists, oral contraceptives, glucocorticoids and megestrol acetate. Drugs that act on both insulin sensitivity and insulin secretion includes diazoxide,
thiazide diuretics, cyclosporine and atypical antipsychotics. By increasing nutrient flux treatments that induce diabetes includes total parental nutrition and nicotinic acid. The rise for developing drug induced diabetes includes an unsuspected and underlying abnormality in carbohydrate metabolism or family history [6].

### Thiazides

In the past, thiazide diuretics have been used in higher doses than necessary in the treatment of hypertension. At present, lower doses are being used and they possess a slight risk of inducing diabetes. The involvement of β-blockers in drug induced diabetes is very low. But there is evidence that β-blockers when combined with thiazides may be more likely to induce diabetes when compared to the utilization of either drug alone. In patients with a family history of non-insulin dependent diabetes the above combination must be avoided [7]. In patients with hypertension treated with thiazides, an increased incidence of glucose intolerance was observed in various uncontrolled trials. About 22% of patients who were treated with thiazides for a period of 6 years had diabetes which was observed in two investigations [8,9]. The risk of getting diabetes was not only increased by the treatment alone with thiazides but also with the usage of more than one antihypertensive agent. Hypertension itself increases the risk for developing diabetes by two fold or more was found to be the strongest evidence arised from a randomized intervention trial. Over a 12 week treatment period, thiazide therapy increased plasma insulin and decreased index of insulin sensitivity in a randomized double blind study. In hypertensive patients, thiazide diuretics are epidemiologically linked to an increased incidence of diabetes but the above statement was not supported by the randomized controlled trials [10].

### β-antagonists

Insulin secretion can be impaired by the β-adrenergic receptor antagonists especially the agents which are not selective for the β1 receptor subtype. Insulin secretion by pancreatic islets in response to glucagon, glucose or arginine can be inhibited by β-receptor blockade. Various research reports revealed that chronic use of β-blockers resulted in drug induced diabetes. In majority of the studies, the risk for diabetes reported by the β-receptor antagonists exceeds the two fold increase in the risk of having diabetes observed in hypertension patients. In a veterans administration study, treatment with propranolol induced a slight increase in fasting glucose level. In a comparative study between the antihypertensives Losartan and Atenol, the incidence of diabetes was found to be low with Losartan [11-13].

### Steroids

Glucocorticoids (prednisone, methylprednisolone, hydrocortisone and dexamethasone) may induce diabetes. The underlying metabolic and non metabolic disorders of the patient are the most powerful influences on the risk for steroid induced diabetes [14]. A 10 fold increase in the risk for acute steroid induced diabetes can be seen due to the presence of an asymptomatic underlying genetic risk or metabolic disorder [15]. In order to stimulate appetite and weight gain in cachexia related to cancer and AIDS, a progestin steroid- megastrol acetate is used. Two case reports revealed that megastrol (80mg) four times a day resulted in new onset of diabetes in patients with Acquired Immuno Deficiency Syndrome (AIDS). When megastrol was dechallenged the patient was relieved from diabetes but recurred upon rechallenge. The exact underlying mechanism has not been studied but probably it may be due to increased caloric intake and steroid induced decreased sensitivity to insulin [16,17]. In patients with and without diabetes, oral contraceptives are known to increase the average glucose concentration levels by decreasing the insulin sensitivity. However, very few evidences were observed to link the use of modern low dose estrogen or triphasic oral contraceptives and diabetes in large epidemiologic investigations [18].

### Statins

According to a metaanalysis, statins have shown an excess risk of 9% of progression to diabetes in patients who were under statin therapy. A recent comparative study revealed that high dose versus moderate dose statin therapy exposed that increased risk of developing diabetes was associated with statin use [19].

### Antipsychotic agents

In order to overcome from the extrapyramidal side effects associated with the use of conventional antipsychotics, atypical antipsychotics were introduced into the market. These drugs are most efficacious in the aspects of their pharmacological
effect but they are almost 50% more likely to cause diabetes. The most common drugs that include are clozapine, olanzapine and risperidone. The exact mechanisms behind the antipsychotic induced metabolic changes were unknown. Research is ongoing to rule out the underlying mechanisms [20].

Protease inhibitors

In highly active antiretroviral therapy (HAART) protease inhibitors like ritonavir plays a crucial role. According to a multicentred AIDS cohort study, about 14% of patients who were under the highly active antiretroviral therapy developed diabetes [21].

Immunosuppressive agents

Immunosuppressive agents like tacrolimus and ciclosporin resulted with a high prevalence of post transplantation diabetes found in 13.4% of the individuals with solid organ transplantation [22].

Others

Nicotinic acid is mainly used in the treatment of dyslipidemias. Uncontrolled hyperglycemia can be seen very frequently with nicotinic acid. Enhanced hepatic glucose output due to increased gluconeogenesis is the underlying mechanism for nicotinic acid induced hyperglycemia [23-25]. Transient hyperglycemia can be caused by various drugs like aspirin, theophylline, nalidixic acid and isoniazid in overdoses. But drugs such as alloxen, streptozotocin and the rodenticide vacor have the ability to induce permanent diabetes [7].

Conclusion

It is very difficult to control the diabetes, if the patient continues to take the medication. If the patient discontinues the drug that caused diabetes then it is quiet easy to manage the glucose levels. Insulin therapy is the most efficacious approach in cases where the drug that has to be continued for the benefit of the patient even though it induced diabetes. Sulfonylureas would not be expected to be effective treatment as they are primarily act by enhancing endogenous insulin secretion. In case of patients with pre diabetes, diabetes and insulin resistance syndrome, a drug that has the tendency to affect the blood glucose levels must be avoided.

References


