Drug-induced diabetes is defined as the new development of a hyperglycemic state that meets the definition of diabetes and that is due to the ingestion of a drug. In 1997 the American Diabetes Association revised the fasting glucose criterion for diabetes, lowering the cutoff fasting glucose value from 140 mg/dL to 126 mg/dL. This increases the likelihood that medications causing nondiabetic hyperglycemic states will be classified as causing drug-induced diabetes. These offending drugs are grouped according to the mechanism by which they induce diabetes. The first group interferes with insulin production or secretion (e.g., Beta-Blockers), the second group blocks insulin action (e.g., Steroids), the third group interferes with both insulin secretion and action (e.g., Thiazides), and the final group increases blood glucose using mechanisms independent of insulin’s actions (e.g., Nicotinic acid).

Antagonists to b-adrenergic receptor are commonly used medications known to impair insulin secretion. Several studies have linked chronic use of b-blockers with an increased risk for the development of diabetes. The risk for diabetes reported in most studies of b-receptors antagonists exceeds the known twofold increase in the risk for diabetes found in hypertensive population. However, more and larger randomized trials will be needed to assess the true attributable risk of diabetes from b-blockade. Glucocorticoids such as hydrocortisone, dexamethasone, prednisone, and methylprednisolone may induce diabetes. The presence of an asymptomatic underlying genetic risk or metabolic disorder (i.e., glucose intolerance) increases the risk for acute steroid induced diabetes 10-fold. However, the use of corticosteroids as replacement therapy has not been shown to change the risk of the development of diabetes. In summary, thiazide diuretics are epidemiologically linked to an increased incidence of diabetes in hypertensive patients, but these data have not been supported by randomized controlled trials. Potassium depletion due to thiazide diuretics exacerbates the problem. It is likely that new diabetes induced by thiazides is uncommon. Nicotinic acid therapy is associated with increase level of blood glucose in both diabetic and non diabetic patients, and uncontrolled hyperglycemia is a frequent reason to discontinue therapy. The use of long-acting nicotinic acid derivatives may avoid this hyperglycemic adverse effect. In cases in which the drug that induced diabetes must be continued, insulin therapy is the most efficacious approach. And, if possible, a drug which is supposed to have adverse effect on blood glucose level should be avoided in a patient of diabetes, pre-diabetes or insulin resistance.

INTRODUCTION

Incidence of diabetes, as we all know, is increasing at an alarming rate. In such a situation we should leave no stone unturned so far the prevention and treatment of this killer disease is concerned. A large number of pharmacologic agents perturb carbohydrate metabolism. Many of these drugs aggravate the hyperglycemic state of diabetes and cause adjustment in diabetic therapeutic regimens. Fewer agents have been reported to cause new diabetes in previously nondiabetic individuals. Drug-induced diabetes is defined as the new development of a hyperglycemic state that meets the definition of diabetes and that is due to the ingestion of a drug (1,2). In 1997 the American Diabetes Association revised the fasting glucose criterion for diabetes, lowering the cutoff fasting glucose value from 140 mg/dL (7.8 mM) to 126 mg/dL (7.0 mM). This increases the likelihood that medications causing nondiabetic hyperglycemic states will be classified as causing drug-induced diabetes (3). Drug induced diabetes is also recognized by both ADA and WHO as a separate etiological category.

DRUGS THAT INDUCE DIABETES

The offending drugs are grouped according to the mechanism by which they induce diabetes.

Drugs that cause diabetes by interfering with insulin-production and secretion –

| β-receptor antagonists | Tacrolimus |
| Pyriminil (Vacor) | Didansoine |
| Pentamidine | L-asparaginase |
| Diphenylhydantoin | Opitates |
| Drugs that cause diabetes by reducing the effectiveness (sensitivity) of insulin – |
| Glucocorticoids | b-receptor agonists |
| Megasterol acetate | Growth hormone |
| Oral contraceptives | Protease inhibitors |
Drugs that act on both insulin secretion and insulin sensitivity –
- Thiazide diuretics: Diazoxide
- Cyclosporine: Atypical antipsychotic
- Treatments that induce diabetes by increasing nutrient flux –
- Nicotinic acid: Total parenteral nutrition

β-ANTAGONISTS
Antagonists to b-adrenergic receptor are commonly used medications known to impair insulin secretion, especially agents that are not selective for the b₂-receptor subtype. b-receptor blockade inhibits insulin secretion by pancreatic islets in response to glucagon, glucose, or arginine. Several studies have linked chronic use of b-blockers with an increased risk for the development of diabetes. In two studies of men treated for hypertension (4, 5) there was a relative risk of 6 to 6.1 compared with non-hypertensive controls. Most recently, a review of the use of antihypertensives in the Atherosclerosis Risk in Communities (ARIC) study in 3,804 subjects indicated that there was a relative risk of 2.43 for the development of diabetes in those with hypertension over a 6-year period, and a multivariate analysis indicated the risk for diabetes was 28% greater in those using a b-blocker than those using other medications (6). The risk for diabetes reported in most studies of b-receptors antagonists exceeds the known twofold increase in the risk for diabetes found in hypertensive population (7). But, Propranolol therapy induced small increases in fasting glucose levels in 687 men treated in a Veterans Administration study for 48 months from 99.6 to 106 mg/dL (8). However, more and larger randomized trials will be needed to assess the true attributable risk of diabetes from b-blockade. Similarly the LIFE study (9) comparing Losartan with Atenolol in hypertensives showed a lower incidence of new onset diabetes in persons using Losartan. However, again it is not clear whether this was due to a protective effect of Losartan or a detrimental effect of Atenolol. Regarding Cardiodefective beta-blockers it can be said that the potentially adverse results are all reported with atenolol; newer and more beta-1 selective agents may be more metabolically neutral; moreover, presence of comorbidity like symptomatic coronary artery disease mandates the use of beta-blockers (10).

STEROIDS
Glucocorticoids such as hydrocortisone, dexamethasone, prednisone, and methylprednisolone may induce diabetes. These drugs are used in a wide variety of disorders and in wide range of doses. The actual incidence of diabetes induced by these agents is unknown because of these variations and because the most powerful influences on the risk for steroid-induced diabetes are likely to be the underlying metabolic and nonmetabolic disorders of the patient (11). This is underscored in data presented in a study from 1954, in which Fajans and Conn (12) proposed a new combined cortisone glucose tolerance test to identify those at risk for diabetes. In the report, 50 to 62.5 mg of oral cortisone (12-15 mg of prednisone) was administered 8.5 and 2 hours before a glucose challenge. Of 37 individuals with normal glucose tolerance, 1 developed a diabetic degree of glucose intolerance after the cortisone, an incidence of 2.7%. However, when 75 individuals with normal glucose tolerance but also a family history of diabetes were tested, 24% had a diabetic response to the glucose load. Thus, the presence of an asymptomatic underlying genetic risk or metabolic disorder (i.e., glucose intolerance) increase the risk for acute steroid induced diabetes 10-fold. However, the use of corticosteroids as replacement therapy has not been shown to change the risk of the development of diabetes. In patients with hypopituitarism taking standard (30 mg/day of hydrocortisone) replacement corticosteroids, 96% had normal glucose tolerance to a 75-g oral glucose load (13).

Megestrol acetate is a progestin steroid used to stimulate appetite and weight gain in cachexia related to cancer and AIDS. There are two case reports of new-onset diabetes in patients with AIDS who were taking 80 mg of megestrol four times a day. In one report, diabetes resolved when megestrol was discontinued but recurred upon rechallenge. The mechanism has not been studied but is probably a combination of steroid-induced decreased sensitivity to insulin and increased caloric intake (14, 15).

Oral contraceptives are steroid combinations that are known to increase average glucose concentrations in patients with and without diabetes by decreasing insulin sensitivity. However, in large epidemiologic studies, there is little evidence to link the use of modern low-dose estrogen or triphasic oral contraceptives and diabetes. In the Nurses Health Study of 121,700 women over more than 15 years, current oral contraceptive use did not increase the relative risk (RR) for diabetes (RR = 0.86), and past use conferred a small increase (RR = 1.12) that was not related to dose or duration of exposure (16).

THIAZIDES
Thiazide diuretics, a commonly prescribed class of agents for control of hypertension, are often cited as causes of drug induced diabetes. Many small uncontrolled trials show an increased incidence of glucose intolerance in patients with hypertension treated with thiazides; in two studies, up to 22% of patients treated for 6 years had diabetes (17, 18). Gurwitz et al. (19) found that the risk for developing diabetes was not increased by treatment with thiazides alone but was increased with more than one antihypertensive agent. The ARIC study analysis also failed to show an association of the use of thiazide agents and the increased risk for diabetes in patients with hypertension. However, the strongest evidence would be that arising from a randomized intervention trial, since hypertension itself increases the risk for developing diabetes by twofold or more. The European Working Group on Hypertension in the Elderly randomly assigned 348 patients to 25 mg hydrochlorothiazide and 50 mg triamterene or placebo for up to 3 years (20). Although the blood glucose levels before and after challenge with glucose were increased by 13.2 and 30.2 mg/dL, respectively, there were no new cases of diabetes noted in the treated group. Acute administration of thiazide diuretics has been
shown to cause a 27% decrease in endogenous insulin response to a hyperglycemic clamp protocol (21). Gorden (22) had noted glucose intolerance and diminished serum insulin in association with potassium-depleted stae, and Heldren et al. (23) repeated the hyperglycemic clamp studies to show that the majority of the defect could be corrected by careful potassium repletion. In a randomized double-blind study, thiazide therapy increased plasma insulin and decreased index of insulin sensitivity over a 12-week treatment period (24). In summary, thiazide diuretics are epidemiologically linked to an increased incidence of diabetes in hypertensive patients, but these data have not been supported by randomized controlled trials. Potassium depletion due to thiazide diuretics exacerbates the problem. It is likely that new diabetes induced by thiazides is uncommon.

NICOTINIC ACID

Nicotinic Acid is an effective therapy for dyslipidemias. Nicotinic acid therapy is associated with increase level of blood glucose in both diabetic and non diabetic patients, and uncontrolled hyperglycemia is a frequent reason to discontinue therapy. Henkin et al. reviewed 82 patients treated with nicotinic acid, including 17 hearts transplant recipients. In the transplant recipients who had not previously had diabetes, there was a 33% incidence of new diabetes while on nicotinic acid. In the non transplanted patients, the incidence of new-onset diabetes was 15%. The two groups differed in that the transplant patients were taking additional diabetogenic agents, such as steroids and cyclosporine, and the mean dosage of nicotinic acid in the transplant patients (2.5 ± 0.4 g/day) was nearly twice that of the non transplant patients. The mechanism for nicotinic acid-induced hyperglycemia is an increase in hepatic glucose output due to enhanced gluconeogenesis (25). Actually, acute nicotinic acid administration results in a diminished flow of free fatty acids (FFAs) to the liver and diminished gluconeogenesis. However, the effects of nicotinic acid are short lived, and a rebound increase in FFAs, by 50% to 100% over baseline, occurs after cessation of therapy (26). Khan et al. demonstrated a decline in both the responsiveness to insulin and the insulin sensitivity index in 11 patients treated for 2 weeks with nicotinic acid. Serum insulin levels increased, indicating an insulin-resistant state. Because of this mechanism, the use of long-acting nicotinic acid derivatives may avoid this adverse effect (27).

CONCLUSION

Drug-induced diabetes occurs due to a variety of drugs and mechanisms (28). An underlying and often unsuspected abnormality in carbohydrate metabolism in the patient or a family history of diabetes greatly increases the risk for developing drug induced diabetes. In most cases, the drug has induced a perturbation in metabolism that exceeds the patient’s adaptive capacity. This suggests that sulfonylurea, which act primarily by enhancing endogenous insulin secretion, would not be expected to be effective therapy. In cases in which the drug that induced diabetes must be continued, insulin therapy is the most efficacious approach. And, if possible, a drug which is supposed to have adverse effect on blood glucose level should be avoided in a patient of diabetes, pre-diabetes or insulin resistance syndrome (29). Last but not least light to moderate consumption of alcohol (1 to 3 drinks daily) has been associated with enhanced insulin sensitivity compared with that in non-drinkers. But then, an intake of more than 3 drinks of alcohol per day is associated with a 50% increased risk of diabetes (30).

REFERENCES

12. Fajans SS, Conn JW. An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisolone, Diabetes 1954:3,296.
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