Review Paper

Drug-Induced Metabolic Syndrome

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The metabolic syndrome is a cluster of risk factors associated with an increased risk for cardiovascular disease and type 2 diabetes. Based on data from 1988 to 1994, it is estimated that 24% of adults in the United States meet the criteria for diagnosis of the metabolic syndrome. The use of certain medications may increase the risk of the metabolic syndrome by either promoting weight gain or altering lipid or glucose metabolism. Health providers should recognize and understand the risk associated with certain medications and appropriately monitor for changes related to the metabolic syndrome. Careful attention to drug choices should be paid in patients who are overweight or have other risk factors for diabetes or cardiovascular disease. (J Clin Hypertens. 2006;8:114–119) ©2006 Le Jacq Ltd.

The metabolic syndrome is a cluster of risk factors associated with an increased risk for cardiovascular (CV) disease and type 2 diabetes. Although the diagnostic criteria vary among consensus groups, it is agreed that core features of the syndrome include visceral adiposity and abnormal insulin metabolism.[1,2] The Adult Treatment Program (ATP III) of the National Cholesterol Education Program (NCEP)[1] has recently placed major emphasis on the diagnostic criteria and management of the metabolic syndrome to increase awareness of this condition. According to ATP III, a patient has the metabolic syndrome when three or more of the following conditions coexist: hypertension, visceral adiposity defined by a waist circumference >102 cm (38 inches) in men and >88 cm (34 inches) in women, a triglyceride level >150 mg/dL, high-density lipoprotein cholesterol (HDL-C) of <40 mg/dL for men and <50 mg/dL for women, or a fasting glucose of ≥110 mg/dL, indicating insulin resistance.[1]

Based on data from 1988 to 1994, it is estimated that 24% of US adults meet the diagnostic criteria for the metabolic syndrome.[1] The influence of overweight and obesity on development of the metabolic syndrome is well recognized. The prevalence of obesity and overweight continue to rise and constitute a major epidemic worldwide.[3,4] According to 1999–2000 National Health and Nutrition Examination Survey (NHANES)[4] data, an estimated 64% of adults in the United States are either overweight or obese. The epidemic of overweight and obesity among children is even more alarming, with a prevalence rate in children and adolescents of 15%.[5] Unless these trends are reversed, the increasing prevalence of overweight and obesity in children will lead to further increases in adult obesity and the metabolic syndrome.

The use of certain medications may increase the risk of the development of the metabolic syndrome by either promoting weight gain or altering lipid or glucose metabolism. The purpose of this review is to highlight commonly used medications that may increase the risk of the metabolic syndrome. The Table identifies these medications and others that are not as commonly used and beyond the scope of this review.

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ANTIHYPERTENSIVES

Numerous reports have associated adverse metabolic effects such as glucose intolerance and lipid abnormalities with the use of diuretics and β blockers. These agents are among the most prescribed agents used for the treatment of hypertension and CV disease, and thus it is important to consider their potential effects on the metabolic syndrome and to weigh the potential risk against the benefits shown in long-term clinical trials.

Thiazide Diuretics

A meta-analysis of clinical trials conducted from 1966 to 1993 found that thiazides increase total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, particularly at high doses.[6] In another analysis, cholesterol levels returned to normal after 1 year of treatment with diuretics.[7] Thiazides are also reported to contribute to insulin resistance and worsening glycemic control in diabetes, although the mechanisms are unclear. Proposed mechanisms include the effect of hypokalemia on insulin secretion, alterations in hepatic gluconeogenesis, and a direct toxic effect on the pancreas.[8] Furthermore, an increase in free fatty acids associated with the use of thiazide diuretics could alter tissue insulin resistance.[9]

In several cohort studies, there were no increases in incident diabetes in subjects treated with thiazides compared with β blockers and other antihypertensive agents.[10,11] In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[12] post hoc analysis, the incidence of new diabetes was highest for subjects randomized to a diuretic-based regimen. But despite the increase in new-onset diabetes with the diuretic-based regimen in ALLHAT, the chlorthalidone-, amolodipine-, and lisinopril-based regimens provided similar protection from coronary heart disease and nonfatal myocardial infarction.[12] A retrospective analysis of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study[13] demonstrated an increase in the risk of the metabolic syndrome in patients treated with diuretic/β blocker regimen compared with the angiotensin-converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) regimen. In another large trial of hypertensive, nondiabetic patients followed for 6 years, the pretreatment baseline glucose and randomization to diuretic treatment were independent, although not clinically significant, predictors for new-onset diabetes (there were only 64 CV events among the three groups of patients compared).[14] It is important to note that these studies did not have the incidence of diabetes as a prespecified end point.[15] Despite the potential adverse effects, numerous long-term clinical trials have demonstrated a reduction in morbidity and mortality with diuretic-base therapy. For example, in the Systolic Hypertension in the Elderly Program (SHEP),[16] participants on the thiazide-based regimen had an increase in the risk of new-onset diabetes compared with placebo, but noted a decrease in CV events.

Thiazide diuretics are recommended for consideration as initial therapy in the treatment of primary hypertension, as multiple clinical trials have proven benefit in the reduction of morbidity and mortality.[17] Ongoing clinical trials will prospectively evaluate the incidence of diabetes related to particular drug classes. Until these results are available, health care providers should be aware of potential insulin resistance and diabetes among patients utilizing thiazides.

Table. Medications That May Increase the Risk of the Metabolic Syndrome

Antihypertensive agents
β Blockers
Diuretics
Endocrinologic agents
Corticosteroids
Danazol
Growth hormone
Oral contraceptives
Thiazolidinediones
Neurologic/psychiatric agents
Antipsychotics
Antidepressants
Antiepileptics
Miscellaneous agents
Immunosuppressants
Niacin
Protease inhibitors
Retinoids

Beta Blockers

Beta blockers are also among the agents recommended as initial therapy in the treatment of primary hypertension.[17] Nonselective and β_1-selective β blockers have little effect on total cholesterol and LDL-C levels but lead to a reduction in HDL-C and increased triglycerides. In contrast, plasma lipid levels are relatively stable with labetalol (combined α and β blockers) and β blockers with intrinsic sympathomimetic activity.[6] Carvedilol, a combined nonselective β and α_1 blocker, actually has a favorable effect on lipids and is associated

with an 8% increase in HDL-C and a 20% reduction in triglycerides.[18]

The use of β blockers may enhance the risk of developing insulin resistance and type 2 diabetes. The Atherosclerosis Risk in Communities Study (ARIC)[10] demonstrated that among hypertensive patients, β-blocker therapy was associated with a 28% increased risk of developing type 2 diabetes compared with no antihypertensive therapy. This relationship was not observed with thiazides, CCBs, or ACE inhibitors. It is unclear whether the addition of β-blocker therapy for patients with existing diabetes and hypertension has an adverse effect on glucose metabolism or whether combination therapy consisting of a β blocker and another antihypertensive agent (such as an ACE inhibitor) given to patients without diabetes results in a similar increased risk.[19]

Weight gain associated with the use of β blockers may contribute to other adverse metabolic effects.[20] Mechanisms promoting deleterious effects include reduction in enzyme activities related to lipid metabolism, alterations in insulin clearance and secretion, and reduced peripheral blood flow.[21] The potential adverse effects must be weighed against the proven benefits of β blockers in reducing the risk of CV events.[10] In spite of the potential for metabolic abnormalities induced by β blockers, clinical trials have demonstrated morbidity and mortality benefits in the treatment of hypertension, myocardial infarction, and heart failure.[17]

NIACIN

The use of niacin in patients with diabetes remains controversial. Earlier research demonstrated that niacin may precipitate hyperglycemia in people at risk for diabetes and worsen glycemic control in patients with type 2 diabetes. While lipid profiles improved in patients with type 2 diabetes treated with niacin, mean plasma glucose concentrations increased by 16% and glycosylated hemoglobin levels increased by 21%.[22] More recently, the Arterial Disease Multiple Intervention Trial (ADMIT)[23] demonstrated that niacin can safely be given to type 2 diabetes patients, but only with careful monitoring of blood glucose levels. The mechanisms for hyperglycemia are unknown but may be related to hepatic parenchymal damage, induction of insulin resistance, or decreased ability to respond to hyperglycemic stimuli.[9]

THIAZOLIDINEDIONE (TZD) AGENTS

The TZD agents are widely used for the treatment of diabetes, but are also known to affect fat and cholesterol metabolism. Pioglitazone and rosiglitazone increase insulin sensitization and reduce circulating free fatty acids. In clinical trials, however, the effects on cholesterol and lipoproteins were dissimilar.[24] No large-scale, direct comparison trials have been conducted to evaluate these differences. Retrospective analyses have demonstrated an increase in LDL-C and total cholesterol concentrations with rosiglitazone, and a lesser improvement in HDL-C concentration than with pioglitazone. Furthermore, pioglitazone had a better reduction in triglycerides and no significant effects in either LDL-C or total cholesterol concentrations. Both of these TZD agents may cause similar weight gain.[24] The metabolic effects of TZDs are not fully understood, and more clinical trials are warranted to assess these effects in relation to the metabolic syndrome.

ORAL CONTRACEPTIVES (OCS)

Estrogen and androgenic progestin have a dose-dependent effect on glucose tolerance. Progestin has the greatest impact on carbohydrate metabolism. High-dose OCs often result in abnormal glucose tolerance tests.[25] The use of low-dose combination OCs, however, results in minimal change in glucose tolerance or insulin resistance.[26]

The hormonal components of OCs exert major effects on plasma lipoprotein metabolism. In general, estrogen increases serum triglycerides and HDL-C but lowers the levels of LDL-C. The androgenic progestins in OCs usually increase serum LDL-C and decrease HDL-C.[25]

Combination OCs used in the United States tend to raise levels of plasma triglycerides and LDL-C. The changes in HDL-C reflect the combined effects of the estrogen dose and progestin component. The lipoprotein changes are dose dependent, but may be significant in lower-dose preparations as well. Women taking OCs should be advised to have evaluations of lipid profiles.[25] This is of particular significance for women who have other risk factors for the development of the metabolic syndrome.

PROTEASE INHIBITORS

Protease inhibitors are widely used in the antiretroviral treatment of acquired immunodeficiency syndrome. A common adverse effect of these agents is acquired lipodystrophy, a syndrome similar to the very rare inherited forms. The cause of protease inhibitor-induced lipodystrophy is unknown. Possible mechanisms include impaired differentiation on apoptosis of adipocytes. There is evidence that messenger RNA of key transcription factors regulating adipogenesis is involved in

the development of acquired lipodystrophy.[27,28] Recent studies also point to changes in the signaling pathway regulating the peroxisome proliferator-activated receptor-γ.[29]

Patients with lipodystrophy develop criteria for the metabolic syndrome and are at increased risk for CV disease and type 2 diabetes. Lipodystrophy is characterized by subcutaneous fat wasting in the face, arms, and legs, with central adiposity. Patients may develop excess fat in the neck and upper back. Dyslipidemia and insulin resistance are also typically associated with the syndrome. Lipodystrophy is associated with all of the protease inhibitors following long-term use. They may increase total cholesterol 40% and triglyceride levels may increase by 200–300 mg/dL.[30]

PSYCHIATRIC/NEUROLOGIC MEDICATIONS

Antipsychotics

Antipsychotic medications are widely used to treat a variety of psychiatric disorders including schizophrenia, depression, bipolar, and developmental disorders. Since the introduction of the atypical or "second generation" antipsychotics, the older "first generation" medications are used less frequently because of potential adverse effects, which include affective and cognitive impairment and extrapyramidal effects. Weight gain and associated morbidities, however, are common and significant with atypical antipsychotic drug use. The prevalence of obesity and diabetes in patients with psychiatric illness is 1.5–2.0-fold greater than in the general population.[31] Average weight gain varies from 0.5 kg to 5 kg, depending on the specific antipsychotic treatment. Clozapine and olanzapine are associated with the greatest weight gain, followed by risperidone and quetiapine. Ziprasidone and aripiprazole are associated with the least amount of weight gain. The mechanisms by which antipsychotic medications induce weight gain and metabolic alterations are unknown. Antipsychotic pharmacology is complex. Activity at serotonin, norepinephrine, dopamine, and histamine-H_1 receptors are all implicated in regulation of body weight.[32] Changes in appetite and satiety leading to increased caloric intake and altered glucose metabolism are proposed associations. Increased leptin secretion may be related to increased adiposity, although it is unclear whether this is related to medication use or a consequence of increased adipose tissue.[32] Drugs with the highest affinity for histamine H_1 (e.g., clozapine, olanzapine) are associated with more weight gain than with those agents that have a lower histamine-H_1 affinity (e.g., ziprasidone, aripiprazole).[33,34] This dose-dependent effect occurs despite body weight changes and may be related to drug effects on pancreatic insulin secretion.

Hyperlipidemia has been recognized as a CV risk in patients treated for psychiatric illness. In addition to weight gain and alterations of glucose metabolism, there is increasing evidence that atypical antipsychotics, particularly clozapine and olanzapine, induce hyperlipidemia. While much of the literature on CV risk and antipsychotic use is related to body weight and glucose metabolism, recent guidelines for the management of patients treated with these medications also include monitoring recommendations for hyperlipidemia.[35]

Antidepressants

Patients with a diagnosis of depression may either gain weight or lose weight as a result of their condition. Some antidepressants have been linked to weight gain. Tricyclic antidepressants, particularly amitriptyline, and monoamine oxidase inhibitors, are associated with the greatest weight gain. These agents are no longer widely used. Of the selective serotonin reuptake inhibitors, paroxetine is most likely to cause weight gain. Data are limited on other selective serotonin reuptake inhibitors and their effect on weight. The atypical antidepressants bupropion and nefazodone are considered to have a neutral effect on body weight. Bupropion has actually been associated with long-term weight reduction.[36]

Antiepileptic Medications

Antiepileptic medications are used in a variety of therapeutic areas including treatment of seizure disorders, bipolar disorders, migraines, and diabetic neuropathy. Many of these medications are associated with weight gain, although attention to this potential adverse effect has not been consistent in clinical trials.[36]

Valproate is associated with significant long-term weight gain. In patients treated with valproate, there is evidence that a low resting metabolic rate, rather than excessive food intake, contributes to increased body weight.[37] Weight gain has also been reported in patients treated with high doses of gabapentin. Compared with valproate treatment, lamotrigine-treated patients are less likely to have significant weight increase. Topiramate has therapeutic potential in many nonseizure disorders and is being investigated in the treatment of obesity. Weight reduction with the use of topiramate has been observed in clinical trials of epilepsy, bipolar disorder, diabetic neuropathy, and binge eating.[36]

IMMUNOSUPPRESSIVE MEDICATIONS

Cyclosporine and tacrolimus are immunosuppressive agents used to prevent post-transplant organ rejection. Cyclosporine may cause hyperglycemia through toxic effects on β cells or by the development of insulin resistance. Its effect on carbohydrate metabolism appears to be dose dependent.[9]

Hyperglycemia, glucose intolerance, and type 2 diabetes occur more often with tacrolimus than with cyclosporine. The multicenter FK506 Kidney Transplant Study[38] reported that compared with cyclosporine-treated individuals, there was a relatively high incidence of insulin-dependent diabetes mellitus in tacrolimus-treated patients (20% vs. 4%). The mechanism underlying the development of diabetes with tacrolimus is unclear.

Glucocorticoids are well recognized for their diabetogenic potential, risk of elevated blood pressure with long-term use, and effect on lipid changes. Altered glucose control with glucocorticoid steroid use is related to several mechanisms. These include increased hepatic gluconeogenesis, the direct suppression of insulin secretion from pancreatic cells, and increasing body weight and, thus, insulin resistance with impaired glucose uptake.[39] The hyperosmolar nonketotic syndrome has been reported in patients with early subclinical diabetes or glucose intolerance on glucocorticoid steroid treatment.[39]

TREATMENT OF DRUG-INDUCED METABOLIC SYNDROME

Health providers and the public are increasingly aware of overweight and obesity as a health risk. The metabolic syndrome as a multiplex of risk factors for CV disease deserves more attention by health providers and further education of the public as to its significance.

A weight-reduction diet should be prescribed for all overweight and obese patients who are classified as having the metabolic syndrome. More aggressive approaches may be necessary for obese individuals with multiple metabolic syndrome risk factors. There is some evidence that the metabolic syndrome is more than the sum of its parts and that there may be synergistic relationships among some of its components, particularly dyslipidemia, hypertension, and hyperglycemia. Therefore, appropriate treatment of all of these disturbances is imperative in reducing CV risk in overweight or obese patients with the metabolic syndrome.

The choice of medications for a variety of conditions may affect one or more components of the metabolic syndrome. The association of medication use and development of the metabolic syndrome is increasingly being recognized with many common medications. Careful attention to drug choices should be given in all patients who are overweight or obese or who have other risk factors for diabetes or CV disease.

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