GLUCOSE REGULATION

Diabetes and Insulin Resistance in the Neuropsychiatric Population

Samuel Dagogo-Jack, MD

Incidence of diabetes in the general population has increased dramatically in recent years. In only 9 states is the current prevalence of diabetes below 6%. Persons with mental illness are at higher risk for diabetes because of a variety of factors; incidence of diabetes in schizophrenic persons is estimated at about 10%. Insulin resistance can precede the development of diabetes by several years. Mental health professionals as well as primary care physicians should screen patients with mental illness for signs of insulin resistance and diabetes before starting therapy with antipsychotic medications. Patients receiving antipsychotic medications should also have their blood glucose levels monitored regularly so that any metabolic disturbances that may arise can be evaluated and treated promptly

Key words: Antipsychotic agents • Diabetes mellitus • Insulin resistance

Diabetes is epidemic not only in the United States but around the world. In 1990, when the CDC first began tracking diabetes incidence, there were just 4 states in which the prevalence of diabetes was 6% or higher (Figure 1A).[1] By 2000, in only 9 states was the prevalence below 6% (Figure 1B).[2] This shift has occurred in just 1 decade.

The population of persons with diabetes continues to expand, and with 40% of cases of diabetes undiagnosed, these estimated prevalence rates are vastly understated.

Projections are that, if the national trends of poor dietary habits, weight gain, and abhorrence of exercise continue unabated, the incidence of diabetes will approach the current prevalence rate of diabetes in the schizophrenic population, which is estimated at about 10%.[3]

Dr Dagogo-Jack is professor of medicine and associate director of the General Clinical Research Center at the University of Tennessee College of Medicine in Memphis.

PATHOPHYSIOLOGY

Although the incidence of type 1 diabetes is also increasing, 90% to 99% of the diabetes burden in the United States is attributable to type 2 diabetes.[1] Unlike type 1 diabetes, the cause or causes of type 2 diabetes are not as clearly understood, and there appear to be multiple contributing factors. Onset of type 2 disease is gradual. Several years before type 2 diabetes is diagnosed, tissues have altered behavior in response to insulin.

Type 2 diabetes used to be called adult-onset or maturity-onset diabetes because it seemed that a person needed to grow old enough or attain a certain body proportion to manifest this condition. Everyone who became diabetic by age 45 presumably was healthy at age 18, but something changed in their bodies, which we have termed "insulin resistance." Persons with type 2 diabetes can have adequate, sometimes even elevated, amounts of insulin in their blood, yet blood glucose levels remain high because the insulin is not working as it

should. With the development of insulin resistance, the pancreas is called upon to increase its production of insulin. If this is successful, glucose is forced through whatever is impeding its transport, and blood glucose levels are normalized.

The development of insulin resistance is necessary but not sufficient for type 2 diabetes to develop. There must also be inadequate compensation by the pancreas when blood glucose levels rise.

Recent research has shown that the liver also plays a role in the development of insulin resistance syndrome.[4] The liver makes a finite amount of glucose to feed the brain during sleep. In persons with type 2 diabetes, the liver makes proportionately more insulin and less glucose. Thus, a person may be having problems getting glucose from the bloodstream because he or she is insulin resistant and not making enough insulin. Yet, at the same time, this person's liver is producing glucose at a higher rate than normal, which is paradoxic.

Insulin resistance can precede the diagnosis of diabetes by several years. Abnormal function of pancreatic β cells also occurs early during the transition from normal metabolism to diabetes.[5] The earliest defect seen in the pancreas is the loss of first-phase insulin secretion. This first phase normally prevents the excessive rise of blood glucose levels after eating and

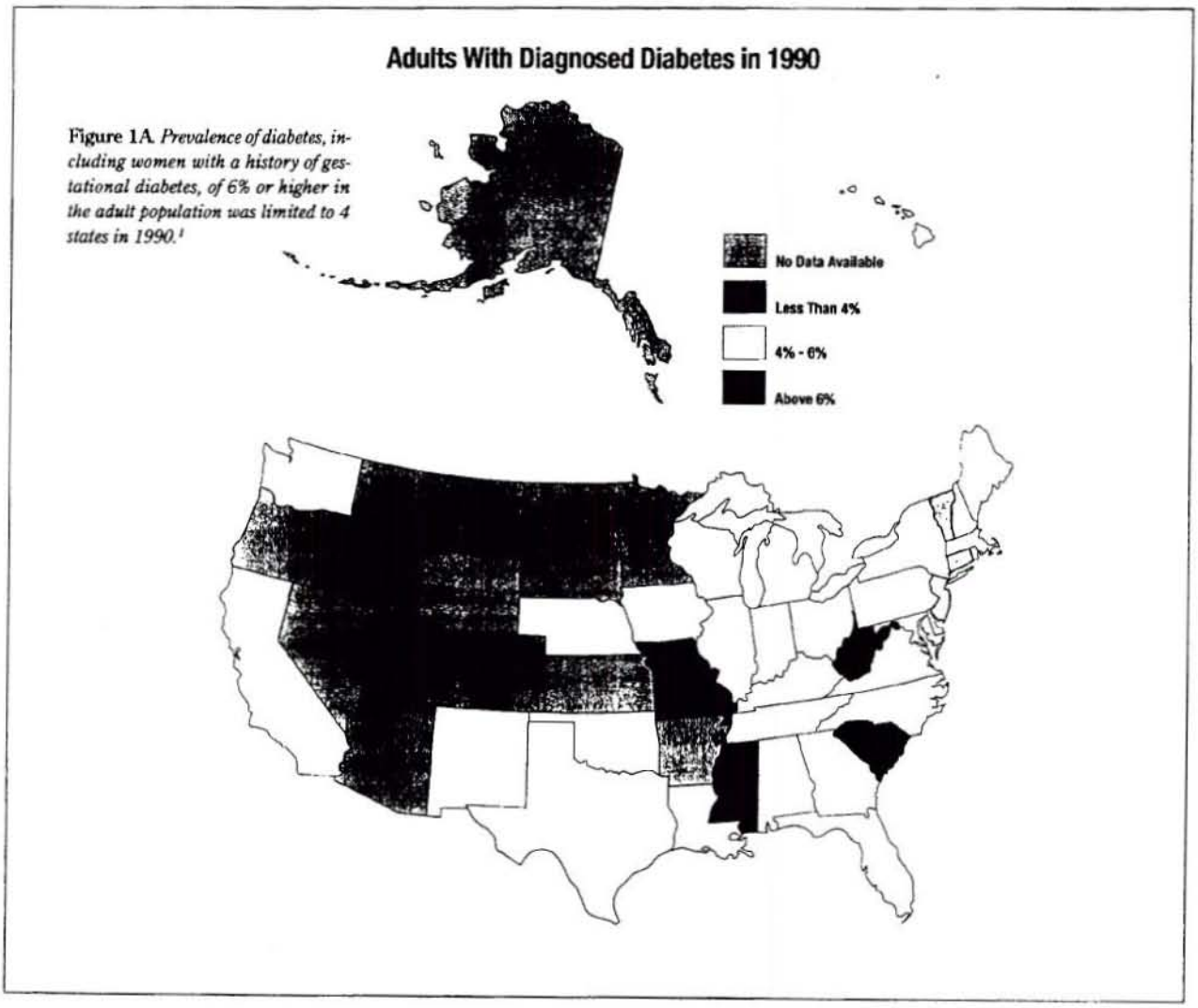

Figure 1A. *Prevalence of diabetes, including women with a history of gestational diabetes, of 6% or higher in the adult population was limited to 4 states in 1990.*[1]

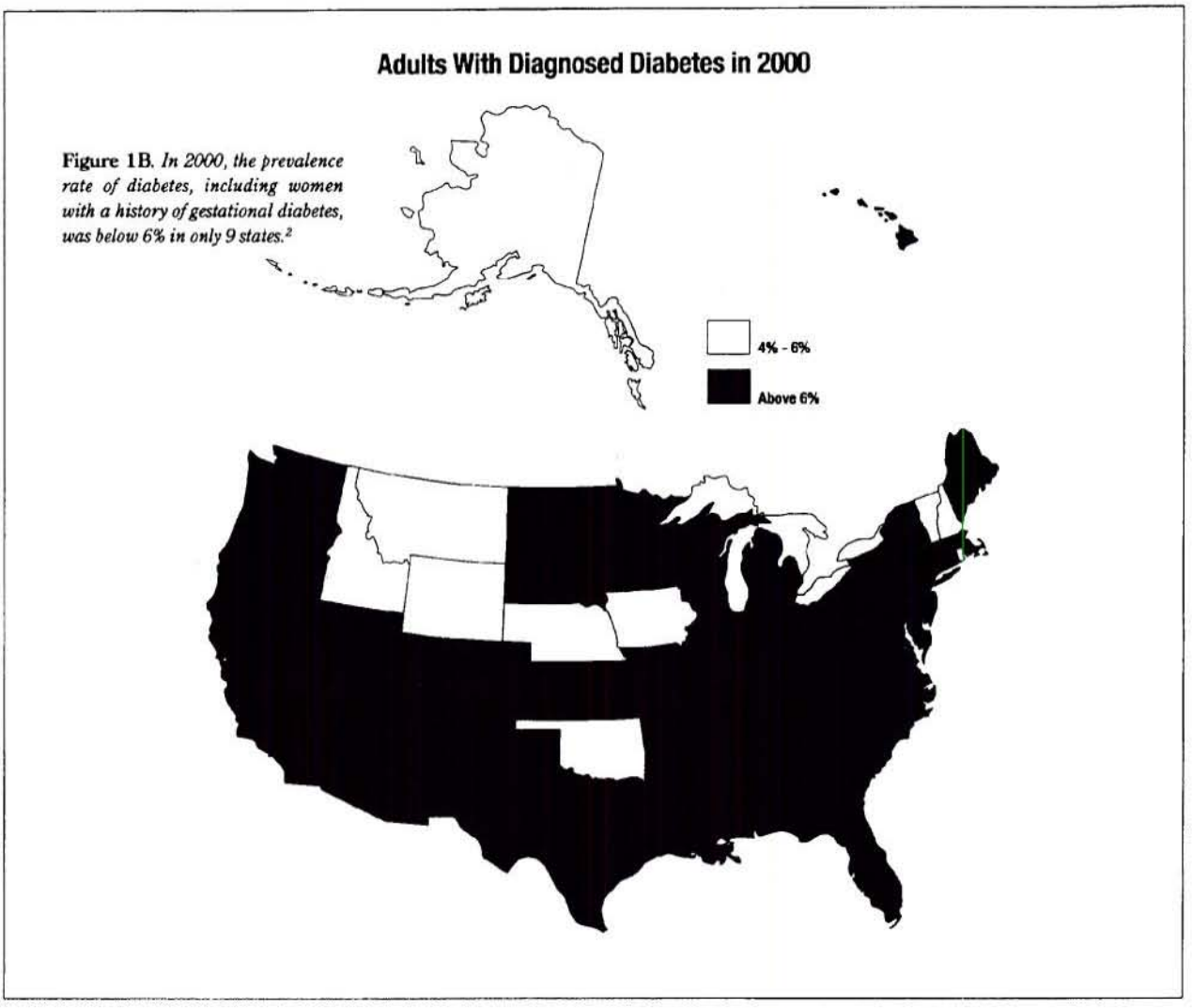

Figure 1B. *In 2000, the prevalence rate of diabetes, including women with a history of gestational diabetes, was below 6% in only 9 states.*[2]

is the first defense against postprandial hyperglycemia.

Preformed insulin granules stored within the islet cells of the pancreas are released with the stimulation of eating or drinking. A study by Pfeifer and associates[6] demonstrates how this process occurs in persons who do not have diabetes. In healthy volunteers, 20 g of glucose was infused as an intravenous bolus. From another venous line, blood was drawn at frequent intervals to track insulin secretion. At baseline, these test subjects had insulin levels around 10 µU/mL. Within 3 to 8 minutes of glucose administration, the insulin secretion increased 10-fold to more than 100 µU/mL. In contrast, patients with type 2 diabetes are unable to produce first-phase insulin secretion in response to the same stimulus.

Such acute insulin secretory failure, a sine qua non of type 2 diabetes, can be demonstrated years before type 2 diabetes is evident. Development of type 2 diabetes is not an overnight phenomenon. Persons progress to it from documented stages of lesser impairment, an important consideration when diabetes and insulin resistance are discussed in the psychiatric population.

Researchers have observed for several decades that there is a 2- to 4-fold increased prevalence of type 2 diabetes in psychiatric patients compared with the general population.[7-10] These studies evaluated patients with

depression,[11] bipolar disorder,[10-12] Alzheimer disease,[13-15] and schizophrenia.[8,9,16-18] Among the earliest reports was that of Braceland and colleagues[16] in 1945, noting increased incidence of diabetes in persons with mental health conditions and severe mental illness compared with persons who are mentally healthy.

RISK FACTORS

What risk factors in the general population might be operating disproportionately in the psychiatric population to trigger this increased prevalence of diabetes?

- *Demographics.* The US population is aging, and there is a strong correlation between age and the development of diabetes and glucose intolerance. By the age of 70 in the United States, 1 in 3 persons is at risk for diabetes.
- *Genetic and familial factors.* Persons with a family history of diabetes in a first-degree relative are at higher risk for diabetes than are persons without such a family history.
- *Weight gain and obesity.* (See "Mechanisms affecting glucose regulation.")
- *Physical inactivity.* Patients who are manic might be overactive, but in general, the psychiatric population tends to be socially withdrawn, and these individuals are not spending time at fitness centers working out on exercise machines.
- *Intrinsic stress and the activated hypothalamic-pituitary-adrenal axis.* The end product of this activation is the production of cortisol, an anti-insulin and diabetogenic hormone. Cortisol causes release of free fatty acids that the liver uses to make more glucose. So increased stress can contribute to increased incidence of diabetes. A study conducted by Eaton and colleagues[19] demonstrated that depression can precede the onset of diabetes, and another study by Lustman and associates[20] showed that managing depression can improve glucose control in patients with established diabetes.
- *Medications.* Can diabetes be drug-induced, such as with atypical antipsychotics? Use of typical antipsychotics has been reported to either worsen diabetes[21] or trigger new-onset diabetes.[22] In a 1968 study by Thonnard-Neumann[23] of patients being treated with chlorpromazine versus controls, investigators found a 4-fold increase in the incidence of diabetes.

With the atypical antipsychotics being more widely used, there are reports of metabolic abnormalities reminiscent of the old literature. These agents have been associated with exacerbation of preexisting diabetes, new-onset diabetes, and even ketoacidosis. Virtually all available agents in the class, including clozapine,[24-27] olanzapine,[28-31] risperidone,[26,32,33] and quetiapine,[33,34] have been associated with hyperglycemia. The newer drug, ziprasidone,[35] which has been less widely used, has so far not been implicated in metabolic perturbation. Nonetheless, based on available data, there is no discernible hierarchy of antipsychotic drugs with regard to their propensity for inducing glucose dysregulation.

MECHANISMS AFFECTING GLUCOSE REGULATION

In patients who are receiving antipsychotic medications, a variety of mechanisms can affect glucose regulation. These include weight gain, insulin resistance, serotonergic mechanisms, β-cell function, pancreatitis, prolactin levels, and drug interactions. Weight gain is well known to increase diabetes risk, as seen in the Nurses' Health Study.[36] Weight gain up to a body mass index (BMI) of about 40 kg/m^2 led to a 60-fold increase in the risk of diabetes. Weight gain is certainly an issue, but is it the smoking gun?

Insulin resistance is a precursor to type 2 diabetes. Indeed, type 2 diabetes does not develop without evident insulin resistance and defective β-cell insulin secretory response.

There have been anecdotal reports of pancreatitis in persons receiving atypical antipsychotics, but causality is unproven. In any case, pancreatic exocrine damage is an unlikely mechanism for a major increase in diabetes risk, because the islets of Langerhans are usually spared.

Weight gain in patients receiving antipsychotic medications is seen across all drug classes, more so in some than in others. The relationship of weight changes to use of atypical antipsychotic agents was examined by Allison and coworkers.[37] Patients receiving haloperidol or ziprasidone were found to be at low risk for weight gain, while those receiving clozapine were at the highest risk for weight gain. In 1 study, significant weight gain (up to 8%) was seen in patients being treated with clozapine.[38] In a longitudinal study (160 weeks) comparing weight gain in patients receiving haloperidol or olanzapine, patients receiving olanzapine gained more weight than those receiving haloperidol. Of note, however, is the fact that the weight gain with olanzapine was not continuous and plateaued at 39 weeks.[39]

Weight gain, though, is not synonymous with use of atypical antipsychotics. In fact, up to a quarter of individuals lost weight while receiving olanzapine therapy. In addition, the individual's baseline BMI can play a role

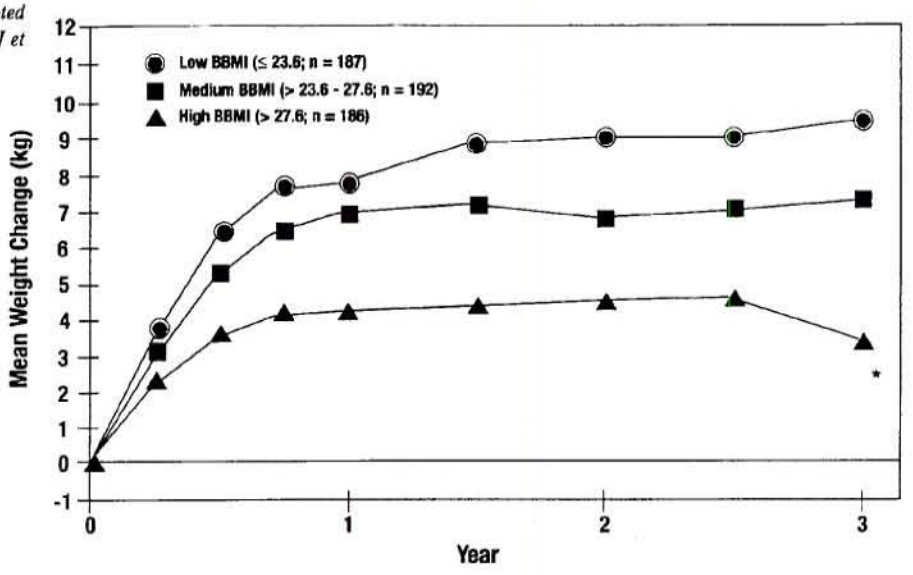

Figure 2. *In patients receiving olanzapine, weight gain is related to the individual's BMI and plateaus across all weight levels. (Adapted with permission from Kinon BJ et al.* J Clin Psychiatry. *2001.[39])*

in the amount and rapidity of weight gain.[39] When comparing persons who are underweight, of moderate weight, or overweight, those who are overweight at baseline appear to gain less weight than those who are underweight. In a study of patients receiving olanzapine,[39] the mean weight change was 3 to 9 kg, but there was a 3-fold difference in the amount of weight gain in persons with a low baseline BMI than in those with a high baseline BMI (Figure 2).

The characteristic plateau point across all weight classes and the noncontinuity of the weight gain effect argue against a fundamental cause-and-effect relationship. A more complex metabolic interaction exists, demonstrated by the leveling of weight gain over time. Furthermore, the available data do not indicate a linear or significant relationship between the amount of weight gain and alterations in blood glucose levels.[39] Of 571 patients receiving olanzapine in the 2.5-year study, nearly one quarter did not gain weight, 1 patient gained 40 to 50 kg, and most patients were in the category of gaining 10 kg or less. There was no statistically significant correlation between the amount of weight gained and change in blood glucose levels.

ATYPICAL VERSUS TYPICAL ANTIPSYCHOTICS

Based on clinical reports from the field of mental health, the advent of the atypical antipsychotic agents has been a major therapeutic advance in terms of efficacy, safety, and tolerability. Notably, adverse effects, such as tardive dyskinesia and other extrapyramidal symptoms, occur at much lower frequency with the atypical agents as compared with the older drugs. Arguably, the burden of side effects of glucose alteration or weight gain seems to be a fair price to pay for the benefits that these agents provide.

According to the 2003 recommendations issued by the American Diabetes Association (ADA),[40] all Americans aged 45 years and older are eligible for diabetes screening. The screening should be done every year or every 3 years, if results of the first year's test are normal and there are no risk factors. Patients with risk factors, such as a family history of diabetes, habitual inactivity, certain ethnic heritage (African American, Asian American, Hispanic, Native Ameri-

can), or diagnosis of hypertension or vascular disease, should be tested at a younger age and more frequently.

What is missing in the new ADA recommendations is the specific listing of the mental health population in the high-risk group. The data support such a listing. In fact, data concerning the risk of diabetes among persons with mental illness have been available for a long time.

Mental health professionals as well as primary care physicians should be encouraged to monitor their patients with mental illness for signs of diabetes and insulin resistance before and during therapy with agents that may cause a metabolic disturbance. Timely education and dietary modification as well as physical activity should reduce the diabetes risk. If diabetes is diagnosed during screening, appropriate therapy can be initiated promptly. If caught early and treated, diabetes does not pose the degree of risk caused by severe mental illness and the possibility of suicide.

For example, in a diabetes prevention program, patients were encouraged to increase their physical activity and modify their diets. Walking was a favorite activity for the majority of subjects; the results, after approximately 3 years of study, showed a 60% reduction in the risk of type 2 diabetes developing. Patients who are physically active can improve their insulin sensitivity independent of weight loss. ●

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