Metabolic Abnormalities in Impaired Glucose Tolerance

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Impaired glucose tolerance (IGT) is a state in which there is postprandial hyperglycemia (>7.8 mmol/L, or 140 mg/dL) with minimal elevations of fasting plasma glucose (>5.5 <7.8 mmol/L, >100 <140 mg/dL). This condition generally precedes the development of diabetes mellitus (DM) by several years. However, in IGT many of the metabolic abnormalities of DM are already present and provide insight into the pathogenesis of DM. Impaired early insulin release is the most consistent defect almost universally observed. Insulin resistance, attributable mainly to obesity, decreased physical fitness, or glucose toxicity, is also often present. The main reason that postprandial hyperglycemia occurs in IGT is impaired suppression of endogenous (hepatic and renal) glucose release; this can be largely explained by impaired early insulin release and impaired suppression of glucagon release. Postprandial glucose disposal is normal or increased, the result of hyperglycemia and delayed hyperinsulinemia. Postabsorptive (fasting) rates of glucose release and disposal and circulating levels of free fatty acids, glycerol, ketone bodies, lactate, and alanine are generally normal.

ACCORDING TO THE World Health Organization,[1] impaired glucose tolerance (IGT) is defined as a condition in which individuals have a fasting plasma glucose level less than 7.8 mmol/L (140 mg/dL) and a value 2 hours after a standard oral glucose challenge that exceeds 7.8 mmol/L (140 mg/dL) but is less than 11.1 mmol/L (200 mg/dL). This condition is generally considered a transition state through which pass most, if not all, who are destined to develop diabetes mellitus (DM).

PREVALENCE AND CLINICAL RELEVANCE

The prevalence of IGT varies widely among populations and increases as a function of age. In the United States, for example, the prevalence increases from approximately 8% in those aged 20 to 44 years to greater than 40% in those over 65 years of age.[2] Rates of annual conversion from IGT to DM range from 1.5% to 15% per year.[2,3] Assuming an average annual conversion rate of 7% per year,[2] someone with IGT would have a 75% chance to develop DM over 20 years. This high probability of developing DM obviously places many individuals at risk to develop the microvascular complications of DM if adequate glycemic control is not maintained.[4,5] Moreover, and perhaps more importantly considering their age, people with IGT are more prone to develop macrovascular disease.[6]

RISK FACTORS

Many of the risk factors that predispose people to develop overt diabetes and premature atherosclerosis[7] are already present in people with IGT. These include (1) a family history of diabetes; (2) obesity, especially central obesity and increased intraabdominal fat, (3) decreased physical activity, (4) lipid abnormalities such as high triglycerides and low high-density lipoprotein cholesterol, and (5) a history of gestational diabetes in women. Moreover, many of the metabolic abnormalities characteristic of DM (impaired insulin secretion and insulin resistance) are also already present in IGT.[8,9]

METABOLIC ABNORMALITIES

This review will mainly focus on parameters of carbohydrate metabolism. The 2-hour plasma glucose after an oral glucose challenge is a major predictor for the subsequent development of DM.[7] Therefore, we shall concentrate on the metabolic abnormalities responsible for postprandial hyperglycemia. We shall deal first with the dynamics of glucose release and removal from the circulation and then with alterations in insulin secretion and tissue responses to insulin that might explain these abnormalities.

Postprandial Glucose Dynamics

Theoretically, plasma glucose could increase abnormally after glucose ingestion in individuals with IGT, due to (1) excessively rapid gastrointestinal absorption, (2) decreased splanchnic glucose sequestration (mainly hepatic glycogen repletion), (3) decreased suppression of endogenous glucose release, or (4) reduced nonhepatic glucose uptake by tissues (brain, muscle, and kidney).

Surprisingly, only two studies[10,11] have directly addressed the issues, but both arrived at similar conclusions: (1) Gastrointestinal absorption of ingested glucose is normal in IGT (Fig 1); (2) nevertheless, overall glucose appearance in the systemic circulation is increased, and (3) this is due to impaired suppression of endogenous (hepatic plus renal)[12] glucose release. Absolute overall rates of glucose utilization are normal or increased, as is forearm (muscle) glucose uptake (Fig 2). One can thus conclude that the major abnormality responsible for postprandial hyperglycemia in IGT is the failure to appropriately suppress endogenous glucose release. Similar conclusions have been reached regarding people with DM.[13]

It should be pointed out that although the absolute rate of glucose disposal by nonhepatic tissues is not reduced in IGT, these "normal" rates are achieved during higher plasma glucose and insulin levels, and consequently, glucose disposal is less than normally efficient. Thus, abnormalities in glucose release and glucose disposal are both present in people with IGT. However, because the defect in glucose release is absolute and the latter defect is just relative, primacy in causing postprandial

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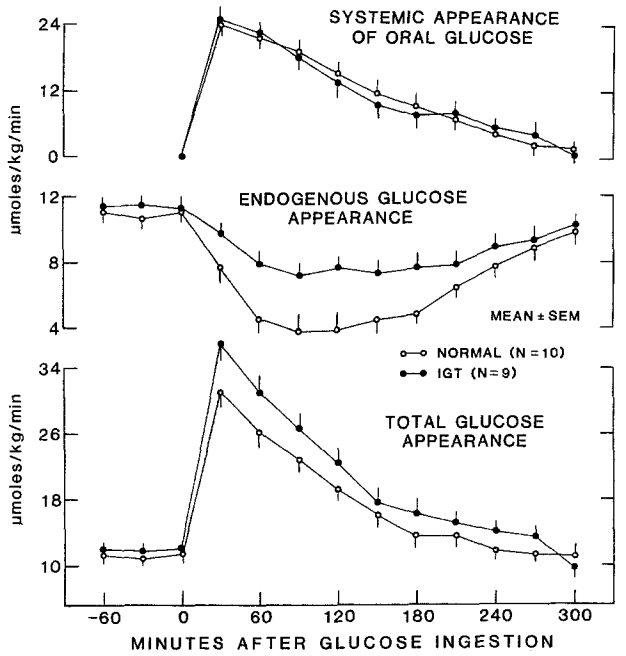

Fig 1. Systemic appearance of oral glucose, endogenous glucose appearance, and total glucose appearance in normal and IGT subjects.

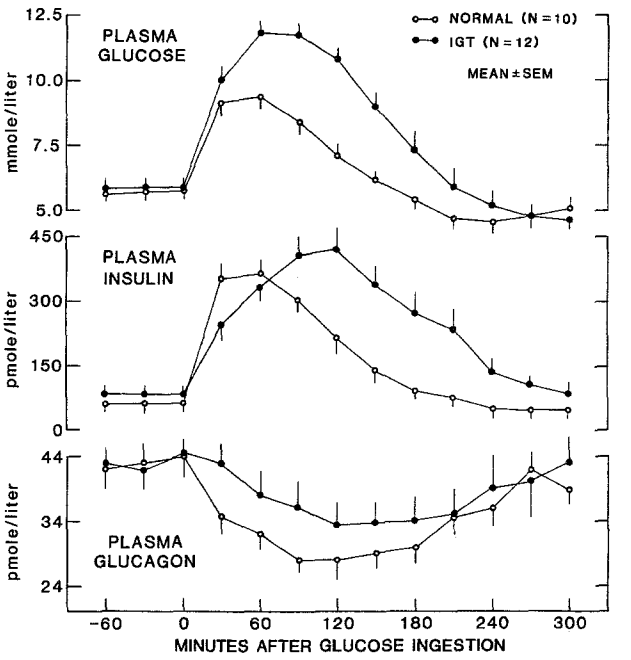

Fig 3. Plasma glucose, insulin, and glucagon in normal and IGT subjects.

hyperglycemia must be given to the defect in glucose release. A point of controversy at the present time concerns to what extent these abnormalities are due to impaired insulin secretion or insulin resistance and to what extent these abnormalities, if present, are genetic or environmental.

Postprandial Insulin and Glucagon Dynamics

Insulin and glucagon secretion are generally regarded to be responsible for the moment-to-moment regulation of glucose homeostasis. In IGI, early release of insulin is decreased and suppression of glucagon secretion is diminished after glucose ingestion, whereas late plasma insulin levels are increased (Fig 3). Since insulin and glucagon have reciprocal effects on hepatic glucose release, the impaired early insulin release and impaired early suppression of glucagon release should lead to delayed suppression of endogenous glucose release. Indeed, plasma insulin to glucagon molar ratios are negatively correlated with postprandial glucose appearance, and this, in turn, is positively correlated with postprandial hyperglycemia (Fig 4).

That early insulin release is a major determinant for glucose tolerance has been demonstrated in experiments in which the early insulin response during an oral glucose tolerance test was delayed by infusion of somatostatin.[14] This resulted in not only glucose intolerance but also late hyperinsulinemia. Thus, late hyperinsulinemia, often invoked as an indicator of insulin resistance,[15] may actually merely be a consequence of impaired early insulin release that leads to greater hyperglycemia and thus a greater stimulus for insulin secretion. Nevertheless, it is likely that this late hyperinsulinemia compensates, in part, for the delayed early insulin release, so overall rates of glucose disposal by peripheral tissues are generally normal in IGT.

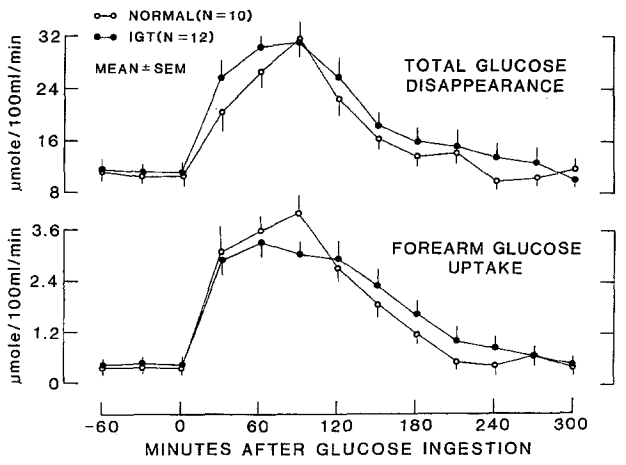

Fig 2. Total glucose disappearance and forearm glucose uptake in normal and IGT subjects.

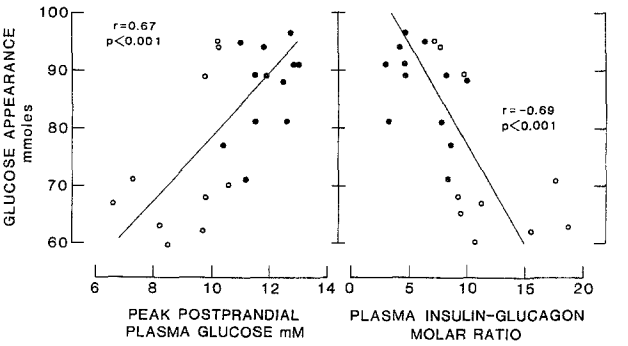

Fig 4. Peak postprandial plasma glucose and plasma insulin to glucagon molar ratio in normal and IGT subjects.

Insulin Resistance in IGT

The first report of delayed early insulin release in IGT can be attributed to the classic studies of Yalow and Berson[16] more than 35 years ago. This has been the most consistent defect found in people with IGT[17,18] and is predictive of the subsequent development of DM.[8,9,19,20] However, insulin resistance is often also present.[8,21,22] The latter most likely is the result of obesity and toxic effects of hyperglycemia[23] rather than a genetic defect, since studies in which subjects have been carefully matched for acquired factors such as obesity have not found insulin resistance in IGT.[17,24-27]

Other Metabolic Defects in IGT

Since fasting plasma glucose levels are only minimally elevated in people with IGT, one would not expect to observe abnormalities in glucose metabolism in the postabsorptive state, and this has been generally found in terms of rates of glucose production and utilization.[10,11,22,28-31] On the other hand, if one includes subjects with values approaching diabetic levels (7.8 mmol/L, or 140 mg/dL), it would not be surprising to find increased glucose production in such individuals, as some investigators have.[32,33]

In general, postabsorptive circulating levels of free fatty acids, ketone bodies, and other metabolic intermediates such as glycerol, lactate, and alanine are normal in IGT.[28,30,32,34,35] Studies using the hyperinsulinemic glucose clamp have found variable results: some have shown no resistance of the ability to suppress glucose production and stimulate glucose disposal,[17,24-27] whereas others have shown reduced glucose disposal.[15,21,29-31,34,35] When measured, impaired nonoxidative glucose disposal was found to account for the overall reduction in glucose disposal.[30,34,35] Rates of lipid oxidation have been reported to be normal[34,35] or less suppressed.[30]

SUMMARY AND CONCLUSIONS

At the present time, it appears established that the major cause of postprandial hyperglycemia in IGT is impaired suppression of endogenous glucose release. This can be largely explained by impaired early insulin release and impaired suppression of glucagon release, but in some individuals, especially those who are obese, it may also involve insulin resistance. However, at this point in time, insulin resistance other than that due to obesity, physical inactivity, and glucose toxicity probably plays a minor role. This is not to say that insulin resistance is unimportant in the pathogenesis of IGT, but that it is an acquired rather than a genetic defect, unlike the impairment in insulin secretion.[36]

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