Whatever the definition of prediabetes may be, at present or in the future, its pathophysiology is a direct extension of the physiology of glucose control. In fact, all evidence indicates that progression to diabetes occurs along a continuum, not necessarily linear with time, of glucose concentration and mechanisms; plasma glucose thresholds, on the other hand, are practical clinical constructs, generally used for diagnosis and treatment. Therefore, it is appropriate, and equivalent, to describe the pathophysiology of prediabetes both in terms of continuous changes in glucose parameters and as shifts in glucose tolerance category.

The glucose system is highly homeostatic, swinging in plasma glucose concentrations rarely exceeding 3 mmol/L (54 mg/dL) in normal people. At any given time, the plasma glucose concentration represents a balance between entry of glucose into and exit from the circulation via cellular metabolism or excretion; excessive release or defective removal (or combinations of the two) results in increasing glucose levels. Entry and exit of glucose are subject to multiple regulatory mechanisms, with insulin and glucagon principally controlling entry and insulin governing exit. The pathophysiology of prediabetes can therefore be reduced to the following questions: Is glucose release abnormal? If so, is it because of changes in β-cell or α-cell function or hepatic sensitivity to these hormones? Is glucose disposal abnormal? If so, is it caused by β-cell dysfunction or changes in peripheral tissue sensitivity to insulin? Are there relationships between glucose release and removal?

A preliminary consideration is the unique organization of the insulin/glucagon system. For many protein and nonprotein hormones, action is modulated by at least 1, often 2, hierarchical hormonal feedback pathway (eg, corticotropin-releasing hormone and adrenocorticotropic hormone for cortisol, gonadotropin-releasing hormone and gonadotropins for sex steroids). In these cases, sensitivity is provided by the circulating hormone concentrations acting on specific hormone receptors.

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located on target tissues as well as on the master gland of the feedback loop (eg, the pituitary). In the case of insulin and glucagon, there is no major pituitary or hypothalamic relay; target tissues control secretion directly. Thus, the circulating concentrations of substrates (mostly glucose, but also amino acids, free fatty acids [FFAs], and ketone bodies), which result from insulin action on intermediary metabolism in different tissues, feed signals back to the β-cell and the α-cell. Sensitivity gating is provided by insulin and glucagon receptors on target tissues. An additional level of regulation is paracrine in nature, ie, insulin receptors on the β-cell and the α-cell.

**GLUCOSE RELEASE**

Under normal circumstances of a short (10–14 hours) overnight fast, most glucose is produced by the liver, with the kidney making a marginal contribution. Within the liver, glucose is both synthesized, in approximately equal parts from glycogenolysis and gluconeogenesis, and taken up, such that what is eventually released into the bloodstream is the net sum of these simultaneous processes. With the use of labeled glucose, the amount of glucose released in the fasting state (endogenous glucose production, EGP) can be measured with acceptable accuracy. In nondiabetic healthy men and women with normal glucose tolerance (NGT) and in individuals with either impaired fasting glucose (IFG, fasting glucose between 110–126 mg/dL [6.11–7.00 mmol/L]) and a 2-hour glucose level less than 200 mg/dL (<11.1 mmol/L on a standard oral glucose tolerance test [OGTT]) or impaired glucose tolerance (IGT, fasting glucose <126 mg/dL [<7.0 mmol/L]) and a 2-hour glucose level of 140 to 199 mg/dL (7.8–11.1 mmol/L), EGP is directly and linearly related to both fat-free mass and fasting plasma glucose (FPG) concentration (Fig. 1). The mean values of the individuals with IFG/IGT fall to

![Graph](image)

**Fig. 1.** Relationship between EGP and fat-free mass (top) and FPG concentration (bottom). The blue lines are best fits, and the dotted red lines are their 95% confidence intervals. Mean and standard deviation for the group with NGT (n = 355) and for the group with IFG/IGT (n = 38) are plotted. (Unpublished data from the RISC Study, Ferrannini E, Balkau B, Coppuck SW, RISC Investigators, et al. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab 2007;92:2885–92.)
the right of those with NGT but on the same regression line. These relationships have important implications. First, EGP appears to be geared to the mass of metabolically active tissues: the larger the mass, the higher EGP. What drives this association is not known. It is possible that, as fat-free mass increases in parallel with fat mass (e.g., during phases of weight gain, glucose consumption increases proportionately and minimally), chronic reductions in blood glucose levels signal the liver to rev up glucose release by autoregulation; other metabolic factors, for example, circulating FFAs, may be at work (see later). Second, as individuals with IFG/IGT frequently have higher body mass index (BMI, calculated as the weight in kilograms divided by the height in meters squared) than those with NGT (28.4 vs 25.8 kg/m², \( P < .001 \), for the subjects in Fig. 1) and hence larger fat-free mass as part of their phenotype (see last section), their EGP tends to be higher, especially in individuals with IFG. As a consequence, expressing EGP in units (\( \mu \)mol/min) normalized for fat-free mass eliminates differences between groups (15.7 vs 16.2 \( \mu \)mol.min\(^{-1}\).kg\(_{ffm}^{-1} \), \( P = .67 \)). Third, if the adaptive changes in EGP were perfect, FPG would be identical in individuals with IFG/IGT and in those with NGT. As this is not the case—fasting glycemia is significantly, if slightly, higher in individuals with IFG/IGT than in those with NGT (97 vs 90 mg/dL [5.4 vs 5.0 mmol/L], \( P < .0001 \))—the EGP response is maladaptive. The reason for this response is insulin resistance. In fact, fasting plasma insulin concentrations are significantly higher in individuals with IFG/IGT than in those with NGT (9 vs 6 \( \mu \)U/mL [55 vs 36 pmol/L], \( P < .0001 \)), indicating that the ability of the hormone to restrain EGP is impaired. By using the product of EGP (normalized per kilogram of fat-free mass) and fasting insulin, an empiric index that has been termed insulin resistance index and used in several studies, one now finds a relatively strong general relationship between glucose output and fasting glycemia (independent of body mass), along which the group with IFG/IGT is clearly separated from that with NGT (895 vs 574 \( \mu \)mol.min\(^{-1}\).kg\(_{ffm}^{-1} \) pM, \( P < .001 \)) (Fig. 2). Once overt diabetes ensues, EGP further increases even in absolute terms, especially in poorly controlled patients.

During absorption of a glucose load or a mixed meal, EGP is substantially suppressed in individuals with NGT, significantly less so in patients with diabetes. The situation in prediabetes is intermediate in that EGP is suppressed to normal absolute levels but at higher prevailing plasma insulin concentrations; calculation of a hepatic insulin resistance index under these circumstances indicates an impairment in the ability of a stimulated insulin response to adequately block postprandial glucose output.

In patients with diabetes, circulating glucagon levels are insufficiently inhibited by the hyperglycemia and hyperinsulinemia that follow glucose or meal ingestion; in fact, they may increase paradoxically. Furthermore, recent studies have shown
that elevated fasting glucagon levels are independently associated with insulin resistance in nondiabetic individuals.\textsuperscript{13} This finding can be interpreted as evidence that the α-cell, which is richly equipped with insulin receptors, is less responsive to the inhibitory influence of the hormone in states of generalized insulin resistance such as prediabetes.\textsuperscript{14} The hepatic sensitivity to glucagon, on the other hand, has been reported to be preserved in patients with type 2 diabetes and presumably is similarly intact in prediabetes, although the relative contribution of glycogenolysis and gluconeogenesis to EGP may be shifted in favor of the latter as a source of circulating glucose.\textsuperscript{15}

With regard to glucose uptake, the liver takes up circulating glucose (as does the gut), but its contribution to overall glucose disposal, as assessed by the hepatic vein catheterization technique\textsuperscript{4} and, more recently, by positron emission tomography with \(^{18}\text{F-}	ext{fluorodeoxyglucose (FDG-PET)},\textsuperscript{16}\) is limited in humans. Although sensitive to insulin,\textsuperscript{17} the liver mainly responds to hyperglycemia by a mass action effect.\textsuperscript{4,18} Studies using \(^{18}\text{FDG-PET}\) have shown that insulin-mediated glucose uptake by the liver is impaired in patients with type 2 diabetes, in proportion to the severity of hyperglycemia\textsuperscript{19}; presumably, a lesser extent of impairment is present in prediabetes, although this has not been directly determined in these patients. In contrast to glucose, the liver extracts 2 to 3 times more circulating FFA (especially shorter-chain FFA\textsuperscript{20}) than resting muscle (as measured by PET [positron emission tomography] and \(^{18}\text{F-6-thia-heptadecanoic acid},\textsuperscript{21}\) ). Although liver FFA uptake is slightly reduced in patients with IGT,\textsuperscript{22} hepatic oxidation of this substrate is increased in obese patients.\textsuperscript{23} Because prediabetic individuals are often overweight or obese, enhanced liver fat oxidation is likely another metabolic feature of prediabetes. FFAs do not contribute net carbon to de novo glucose synthesis, but their oxidation stimulates the activity of key gluconeogenic enzymes (pyruvate carboxylase, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase) as well as provides the energy for the process.\textsuperscript{24} Furthermore, FFA inhibit liver glycolysis,\textsuperscript{25} thereby completing an intra-hepatic substrate competition cycle analogous to the one described by Randle\textsuperscript{26} in isolated skeletal muscle. The prediction that an augmented availability of FFA results in a reduction in liver glucose uptake has in fact been verified in PET studies using an exogenous lipid infusion to increase FFA delivery to the liver.\textsuperscript{27}

In summary, in the liver of the prediabetic patients, insulin resistance is manifested as a reduced ability of insulin to restrain glucose release, especially from gluconeogenesis, and to stimulate glucose uptake. Enhanced FFA flux, uptake, and oxidation compete with glycolysis and stimulate gluconeogenesis, thereby adding a purely metabolic component to the cellular defects in insulin action.\textsuperscript{28} In recent years, it has become evident that body fat distribution is an additional factor in the control of EGP (and in general, of liver function). Independent of total body fat mass, accumulation of adipose tissue within the visceral/abdominal region and the liver is associated with an accentuation of insulin resistance of gluconeogenesis.\textsuperscript{29} Inflammatory changes in adipose depots and consequent release of inflammatory cytokines are probable mechanisms for this effect.\textsuperscript{30}

**GLUCOSE DISPOSAL**

When assessed by the euglycemic clamp technique (and expressed as the total amount of glucose used normalized by fat-free mass as well as steady-state clamp insulin concentrations [M/I]), insulin sensitivity is found to be progressively impaired from NGT to IFG to IGT to overt type 2 diabetes (Fig. 3). To emphasize the continuous nature of the relationship between insulin sensitivity and glucose tolerance, Fig. 4
shows the regression of M/I on the OGTT 2-hour plasma glucose concentration adjusted for gender, age, and BMI; all else being equal, M/I decreases by approximately 11 units per each mmol/L increase in 2-hour plasma glucose concentrations. Thus, peripheral insulin resistance is a central metabolic feature of prediabetes independent of factors, such as gender, age, and obesity, which themselves affect insulin action. Even within the realm of NGT, individuals with higher glucose increments during a standard dynamic test such as the OGTT are more insulin resistant than those whose glucose excursions are lower. Ethnicity may contribute to insulin resistance independent of glucose tolerance and other determinants. In a study using the insulin clamp technique, Mexican-Americans were shown to be more insulin resistant than non-Hispanic whites, regardless of whether they were with NGT, IGT, or diabetes.31

With regard to the tissues responsible for impaired insulin-mediated glucose uptake, skeletal muscle dominates because it typically represents approximately 40% of body weight.32 However, adipose tissue makes a significant contribution to whole body glucose disposal, as demonstrated by an 18FDG-PET study,33 especially in an overweight phenotype as the prediabetic individual. Moreover, in the adipocyte,
insulin resistance of glucose uptake limits the availability of α-glycerophosphate, which is necessary for FFA reesterification, resulting in excessive FFA net release into the bloodstream. In turn, the augmented delivery of FFA to insulin target tissues causes their preferential uptake over that of circulating glucose, thereby realizing the classical Randle cycle. In fact, studies combining indirect calorimetry with the clamp technique have demonstrated that lipid oxidation rates are increased and glucose oxidation rates are correspondingly decreased in insulin-resistant individuals both in the fasting state and during insulinization (clamp or OGTT), a phenomenon that has been later renamed metabolic inflexibility. In the heart, this chronic shift in substrate use imposes a preferential use of FFAs, which are more oxygen costly than glucose as a fuel, a demand that may be undesirable under ischemic conditions. Another consequence of insulin resistance on glucose oxidation is an increase in the accumulation of lactate in the circulation, a hallmark of ischemia, and reduced glycogen accumulation.

Of note is that peripheral insulin resistance is influenced by fat distribution in the same negative direction as hepatic insulin resistance. It is therefore not surprising that peripheral and hepatic insulin resistances, when expressed in appropriate units, are found to be quantitatively related to one another (Fig. 5), as is also the case between skeletal and myocardial muscles. IFG and IGT differ somewhat in the relative severity of hepatic versus peripheral insulin sensitivity, the hepatic insulin sensitivity being worse in IFG, peripheral insulin sensitivity in IGT. However, this distinction is rather tenuous because IFG is associated with IGT in more than 60% of the cases; isolated IFG is rare in the population and carries little population attributable risk for diabetes.

**β-CELL FUNCTION**

Plasma glucose concentrations increase minimally even in the presence of profound insulin resistance as long as the β-cell response is adequate; the hyperglycemia that defines prediabetes ensues when some critical aspect of β-cell function becomes defective. The normal β-cell adaptive response to insulin resistance is an upregulation of its set point: at each plasma glucose concentration absolute insulin secretion rates, both in the fasting state and throughout an OGTT, are higher in insulin-resistant individuals than in insulin-sensitive individuals. In prediabetic individuals, the relationship between insulin secretion and insulin sensitivity is a similar curvilinear function as in....

*Fig. 5. Log-log plot of the relationship between the hepatic insulin resistance (IR) index and insulin sensitivity (as the M/I) for the subjects in Fig. 1.*
those with NGT, only shifted upward as a result of their higher plasma glucose levels (Fig. 6). The higher plasma glucose levels, therefore, are not explained by a deficiency in the absolute amount of secreted insulin. The cause of hyperglycemia is the reduced ability of the β-cell to respond to increasing glucose levels in a timely fashion during stimulation, which is clearly shown when plotting insulin secretion rates against concomitant glucose levels: for each increment in glucose concentration during an OGTT insulin secretion is less in prediabetic states than in NGT states (Fig. 7). Analogous to the concept of insulin resistance, the slope of the relationship between insulin secretion and glucose concentration is an expression of β-cell glucose sensitivity. Once again, the mechanism represents a continuum, from NGT to diabetes through prediabetes.

This dynamic aspect of β-cell function is crucial for 2 reasons: (1) it is largely independent of insulin sensitivity and (2) it is tightly linked with glucose tolerance (Fig. 8). In fact, in the RISC study database both insulin resistance and β-cell glucose insensitivity are independently associated with IFG/IGT: in a multiple logistic regression model adjusting for sex, age, and BMI, an M/I value in the lowest quartile of its distribution carries an odds ratio of 3.7 (with a 95% confidence interval of 2.4–5.7), while a value of β-cell glucose sensitivity in the bottom quartile carries an odds ratio of 5.1 (95% confidence interval: 3.5–7.6). Individuals falling into the bottom 25% of both physiologic variables have a 9-fold increase in the likelihood of being prediabetic. The codominant role of insulin resistance and β-cell glucose insensitivity in predicting incident dysglycemia has been confirmed in an observational follow-up study of a cohort enriched with individuals with a family history of diabetes.

It should be noted that empiric indices of β-cell function, such as the acute insulin response to intravenous glucose (AIR) and the insulinogenic index on the OGTT, have also been used to signal defective β-cell function in prediabetes. Although qualitatively related to β-cell glucose sensitivity, these indices are much less sensitive in discriminating IFG/IGT from NGT (see Fig. 8).

**Fig. 6.** Relationship between total insulin output over the 2 hours after glucose ingestion and insulin sensitivity (as the M/I). The lines are the separate power function fit for the NGT group and the IFG/IGT group. The intercept of the 2 lines are significantly different (P<.001). (Data from the RISC Study, Ferrannini E, Balkau B, Coppack SW, et al, RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab 2007;92:2885–92.)
If numerically unrelated, the two main pathophysiologic defects responsible for the loss of glucose tolerance, that is, insulin resistance and β-cell glucose insensitivity, tend to occur together in prediabetes as well as overt diabetes and to covary consensually over time. It has therefore been natural to ask the question, whether there is a structural link or cause-and-effect relationship between them. Knocking out insulin receptors selectively in β-cells impairs glucose sensing of the isolated perfused pancreata from these mice. More recent studies have indicated that insulin potentiates

![Graph](image1)

**Fig. 7.** Insulin secretion rates against concomitant plasma glucose concentrations during a standard OGTT. The color areas encompass mean and standard error of the slope calculated for the 3 groups by mathematical modeling. (Data from Ferrannini E, Mari A. Beta cell function and its relation to insulin action in humans: a critical appraisal. Diabetologia 2004;47:943–56.)

![Graph](image2)

**Fig. 8.** Reciprocal association between β-cell glucose sensitivity and mean plasma glucose level during an OGTT (upper panel). For the NGT and IFG/IGT groups, the lower panel shows (as box plots) values for the acute insulin response (AIR) to intravenous glucose, the insulinogetic index (ratio of insulin-to-glucose increments 30 minutes into the OGTT), and β-cell glucose sensitivity measured in the same group. The group difference is only significant for the measure of β-cell glucose sensitivity. (Data from the RISC Study, Ferrannini E, Balkau B, Coppack SW, et al, RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab 2007;92:2885–92.)
glucose-stimulated insulin secretion in vivo in healthy humans. The precise cellular mechanisms linking insulin signaling to glucose sensing in the β-cell remain to be clarified, as do the in vivo circumstances under which this interaction becomes important.

THE CLINICAL PHENOTYPE

The abnormalities of glucose concentrations and their determinants are part of a constellation of subclinical abnormalities that consistently occur together in prediabetic individuals. As compiled in Fig. 9, in comparison with NGT controls, patients with IFG/IGT have a higher family history of diabetes, are slightly more often men than women, are somewhat older, are definitely heavier, and have a more central distribution of body fat; values of heart rate and systolic and diastolic blood pressures are higher as are serum lipid levels (low-density lipoprotein cholesterol, triglycerides, and FFA), whereas high-density lipoprotein cholesterol concentrations are lower, and hyperinsulinemia is present both in the fasting state and 2 hours after glucose ingestion. Importantly, the strong association between insulin resistance and β-cell glucose insensitivity with prediabetes resists statistical adjustment for the lipid and hemodynamic abnormalities as well as familial diabetes. This finding supports the notion that the genetic imprint conveyed by familial diabetes is phenotypically specified as the pathophysiologic mechanisms of hyperglycemia. In fact, multiple common

![Fig. 9. Mean clinical and metabolic characteristics of NGT and IFG/IGT individuals. The data are arranged as graduated spokes, each representing a variable, along which the blue square plots the mean value of the NGT group and the black dot that of the IFG/IGT group; the profile results from connecting the 2 series of dots and filling it in light blue for the NGT group and in red for the IFG/IGT group. The variables are men %, percentage of male subjects; FHD %, percentage of persons with a positive family history of diabetes; age (in years); BMI (in kg/m²); WHR, waist-to-hip ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol in mmol/L; HDL-C, high-density lipoprotein cholesterol in mmol/L; and TG, triglycerides in mmol/L; FFAs in mmol/L; FPG; 2-h PG, 2-hour plasma glucose on the OGTT in mmol/L; FPI, fasting plasma insulin; 2-h FPI, 2-hour fasting plasma insulin on the OGTT in pmol/L; HIR, hepatic insulin resistance index; M/I, insulin sensitivity from the clamp technique; and β-cell GS, β-cell glucose sensitivity from mathematical modeling of the OGTT. (Data from the RISC Study, Ferrannini E, Balkau B, Coppack SW, et al, RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. J Clin Endocrinol Metab 2007;92:2885–92.)](image-url)
variants of type 2 diabetes genes are associated with defects in β-cell function.\textsuperscript{49,50} The clustering also suggests that insulin resistance/hyperinsulinemia may link diabetes with clinical hypertension and dyslipidemia either mechanistically or by genetic linkage (or both).

Recent work has emphasized that the phenotype in Fig. 9 is closely predictive of nonalcoholic fatty liver disease.\textsuperscript{51} A meta-analysis of available evidence has concluded that prediabetes per se (IFG, IGT, or both combined) is associated with a modest but significant increase in risk for cardiovascular disease.\textsuperscript{52}

**SUMMARY**

Prediabetes encompasses conventional diagnostic categories of IFG and IGT (or, in the future, HbA\textsubscript{1c}\textsuperscript{53}) with thresholds subject to change, but actually is a band of glucose concentrations and a temporal phase over a continuum extending from conventional NGT to overt type 2 diabetes. Insulin resistance, at the level of the liver and peripheral tissues, and defective glucose sensing at the β-cell are the central pathophysiologic determinants that together cause and predict the defining hyperglycemia. Regardless of the cellular origin of the insulin resistance, excessive tissue fat utilization is a consistent metabolic mechanism. Although genetic influences affect β-cell function, becoming overweight is the main acquired challenge to insulin action.\textsuperscript{54} The phenotype of prediabetes includes dyslipidemia and higher arterial blood pressure, thereby representing a common soil of atherogenic risk.

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