# Contributions of β-Cell Dysfunction and Insulin Resistance to the Pathogenesis of Impaired Glucose Tolerance and Impaired Fasting Glucose

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Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate states in glucose metabolism that exist between normal glucose tolerance and overt diabetes. Epidemiological studies demonstrate that the two categories describe distinct populations with only partial overlap, suggesting that different metabolic abnormalities characterize IGT and IFG. Insulin resistance and impaired β-cell function, the primary defects observed in type 2 diabetes, both can be detected in subjects with IGT and IFG. However, clinical studies suggest that the site of insulin resistance varies between the two disorders. While subjects with IGT have marked muscle insulin resistance with only mild hepatic insulin resistance, subjects with IFG have severe hepatic insulin resistance with normal or near-normal muscle insulin sensitivity. Both IFG and IGT are characterized by a reduction in early-phase insulin secretion, while subjects with IGT also have impaired late-phase insulin secretion. The distinct metabolic features present in subjects with IFG and IGT may require different therapeutic interventions to prevent their progression to type 2 diabetes.

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Glucose is the principal fuel used by humans and is the sole source of energy for the brain. Not surprisingly, glucose homeostasis is tightly controlled, and the fasting plasma glucose concentration is maintained within a very narrow range (70–90 mg/dl) (1). In type 2 diabetes, both insulin secretion and action are impaired (2–4), and chronic hyperglycemia is a characteristic feature of this common metabolic disorder. Unlike type 1 diabetes, where the disease onset is relatively acute, the course of type 2 diabetes is slow and the metabolic abnormalities that lead to hyperglycemia are established long before overt diabetes (as defined by World Health Organization/American Diabetes Association criteria [5,6]) develops (7–9). This state, where abnormalities in glucose metabolism are present but elevation in glucose is below the cutoff point for establishing the diagnosis of type 2 diabetes, is referred to as pre-diabetes (10). Defining cut points for pre-diabetes and diabetes has generated much debate among the medical community (11,12), and these cut off points have been subject to revision over time (5,6,13,14). Pre-diabetes includes subjects with high fasting plasma glucose (FPG) concentration and normal response to a glucose load (IFG), subjects with abnormal postprandial glucose excursion but normal FPG concentration (IGT), and combination of IGT plus IFG (14).

In 1979, an international workgroup defined type 2 diabetes as an FPG ≥140 mg/dl (7.8 mmol/l) or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) following 75-g oral glucose load (14). It also created a new category, IGT, defined as a 2-h plasma glucose of 140–199 mg/dl (7.8–11.0 mmol/l) with normal FPG. IGT was meant to replace the terms "borderline" and "chemical" diabetes. In 1997, the American Diabetes Association revised its diagnostic criteria for diabetes (6), lowering the FPG cut point to ≥126 mg/dl (7 mmol/l), and created a new category, IFG, which identified subjects with a high FPG (≥110 mg/dl [6.1 mmol/l]), which was below the threshold for diabetes (≥126 mg/dl [7.0 mmol/l]). IFG was meant to be "analogous" to IGT and identify subjects with an intermediate stage between normal glucose tolerance (NGT) and overt diabetes. The cut point for IFG recently was revised to include subjects with FPG between 100 and 125 mg/dl (5.6–6.9 mmol/l) (14). This lower FPG of 100 mg/dl (5.6 mmol/l) was chosen to establish a cut point that identified similar percentages of the general population with IGT and IFG, although these need not be the same individuals.

In the current review, we examine metabolic abnormalities that characterize IFG and/or IGT to provide insight into development of therapeutic strategies to slow/halt progression of IFG and/or IGT to type 2 diabetes.

## EPIDEMIOLOGY OF IFG AND IGT

— Epidemiological studies comparing the prevalence of IFG and IGT consistently have demonstrated that they define two distinct populations with only partial overlap (15–26). This observation was consistent in all ethnic groups studied. Only a small percentage of IGT subjects (20–25%) had FPG >110 mg/dl (6.1 mmol/l), and over half of IFG subjects had 2-h plasma glucose <140 mg/dl (7.8 mmol/l). Since most of these studies were done before 2003, an FPG of 110 mg/dl (6.1 mmol/l) was used as cut point for IFG. The prevalence of both IFG and IGT varies considerably based on ethnicity, ranging from a low of 6.3% in Chinese

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**Abbreviations:** AIR, acute insulin response; CGI, combined glucose intolerance; FPG, fasting plasma glucose; FPI, fasting plasma insulin; GIP, glucose-dependent insulinotrophic peptide; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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**Table 1—*Prevalence of IFG and IGT among different populations***

| Population | Reference | Prevalence (%) of isolated IGT | Prevalence (%) of isolated IFG | % of IGT with IFG | % of IFG with IGT |
|---|---|---|---|---|---|
| European | 21 | 8.8 | 6.9 | 26.0 | 31.0 |
| Australian | 18 | 8 | 5.7 | 24.5 | 31.3 |
| Mauritius | 19 | 13.8 | 4.2 | 19.4 | 44.4 |
| Pima Indian | 17 | 10.7 | 1.9 | 18.9 | 56.8 |
| Swedish | 20 | 20.3 | 9.7 | 27.2 | 43.9 |
| Chinese | 23 | 6.3 | 0.9 | 14.7 | 53 |
| American | 22 | 11 | 4.4 | 26.3 | 46.9 |
| Korean | 16 | 20.1 | 2.7 | 13.4 | 53 |

(23) to a high of 20.3% in a Swedish population (20). The prevalence of IFG also varies among ethnic groups, but its prevalence consistently is lower than that of IGT in all populations (Table 1).

IGT and IFG also differ in their age and sex distribution (27–30). The prevalence of both categories increases with age, but under the age of 55, IGT is more frequent in women, while prevalence of IFG is more than twofold higher in men than women (27–30). The differences between IFG and IGT with respect to prevalence, age, and sex preference, as well as the lack of consistent overlap between both categories, suggest that even though IFG and IGT represent intermediate stages of glucose intolerance, they are likely to be distinct conditions with different pathophysiological etiologies.

## NORMAL GLUCOSE HOMEOSTASIS

— In the postabsorptive state the majority (~65–70%) of glucose uptake (~2 mg · kg$^{-1}$ · min$^{-1}$) occurs in insulin-insensitive tissues (brain, erythrocytes, and splanchnic tissues) (31) and glucose uptake is precisely matched by the rate of endogenous glucose production, primarily by the liver (31) and to a smaller extent by the kidney (32). Thus, hepatic glucose production is the main contributor to the FPG concentration (33) and is regulated primarily by the plasma insulin and glucagon concentrations (34).

Following glucose ingestion, the increase in plasma glucose stimulates insulin secretion. The combination of hyperglycemia plus hyperinsulinemia combines to suppress hepatic glucose production and stimulate glucose uptake by splanchnic and peripheral (primarily muscle) tissues to dispose of the ingested glucose and restore normoglycemia (35,36). The route of glucose entry into the body plays an important role in the maintenance of NGT and tissue distribution of administered glucose (37). Hepatic glucose uptake is much greater with oral compared with intravenous glucose (34). Thus, while only 10–15% of infused glucose is taken up by the liver, this increases to 30–40% when glucose is administered orally.

## METABOLIC CHARACTERIZATION OF IFG AND IGT: METHODOLOGICAL CONSIDERATIONS

— A variety of methods have been utilized to evaluate the contributions of impaired insulin sensitivity and decreased insulin secretion to the genesis of IFG and IGT. We briefly will discuss these methods, since interpretation of published results is highly dependent on methodology used.

### Measurement of insulin sensitivity

The glucose clamp technique (38) in its two variations, hyperinsulinemic-euglycemic clamp and hyperglycemic clamp, is considered the gold standard for measuring insulin sensitivity and insulin secretion, respectively. During the hyperinsulinemic-euglycemic clamp, glucose is given intravenously and skeletal muscle is the major site (80–90%) of glucose disposal (39). Furthermore, the plasma insulin concentration (~80–100 μU/ml) during insulin clamp causes near-complete suppression of endogenous glucose production. Therefore, insulin sensitivity measured with hyperinsulinemic-euglycemic clamp mainly reflects peripheral tissues, primarily muscle. The insulin sensitivity index ($S_i$) measured with the fast-sampling intravenous glucose tolerance test or intravenous glucose tolerance test (IVGTT) (40) reflects both hepatic and muscle insulin sensitivity and correlates well with glucose disposal rate measured with insulin clamp (41).

Measurement of plasma glucose and insulin concentrations under fasting conditions and during oral glucose tolerance test (OGTT) has been used to derive indexes of insulin sensitivity (42–44), and they correlate reasonably with insulin sensitivity measured with the hyperinsulinemic-euglycemic clamp. Homeostasis model assessment of insulin resistance (HOMA-IR) (43) and the quantitative insulin sensitivity check index (QUICKI) (44) indexes (derived from FPG and fasting plasma insulin [FPI] concentrations) have been used most widely in epidemiological studies. Since the FPG primarily is determined by hepatic glucose output (33) and FPI is the main regulator of hepatic glucose production (34), the product of FPG × FPI is an index of hepatic insulin resistance. Since hepatic insulin resistance has ~70% correlation with peripheral (muscle) insulin resistance (45), HOMA-IR correlates reasonably well with insulin resistance measured by hyperinsulinemic-euglycemic clamp (46). However, in cases where liver and muscle insulin resistance are discordant, discrepancy between HOMA-IR and glucose disposal during insulin clamp is observed (47,48).

Following glucose ingestion, the suppression of hepatic glucose production is much less complete than during the euglycemic insulin clamp (49), and ~30–40% of ingested glucose is taken up by splanchnic area (37). Consequently, plasma glucose concentration during OGTT is affected both by hepatic insulin resistance and insulin resistance in peripheral (muscle) tissues, which dispose of ~60–70% of ingested glucose. Thus, indexes of whole-body insulin sensitivity derived from plasma glucose and insulin concentrations during OGTT, e.g., Matsuda index, reflect both muscle and liver insulin sensitivity. Such indexes correlate well (*R* value ~0.70) with insulin sensitivity measured with euglycemic insulin clamp (42).

### Measurement of insulin secretion

Insulin secretion is markedly influenced by the route of glucose administration. When glucose is administered via gastrointestinal tract, a much greater stimulation of insulin secretion is observed compared with similar hyperglycemia created with intravenous glucose. The difference in insulin secretion between intravenous versus oral glucose administration is referred to as the incretin effect (50) and is mediated by glucagon like peptide-1

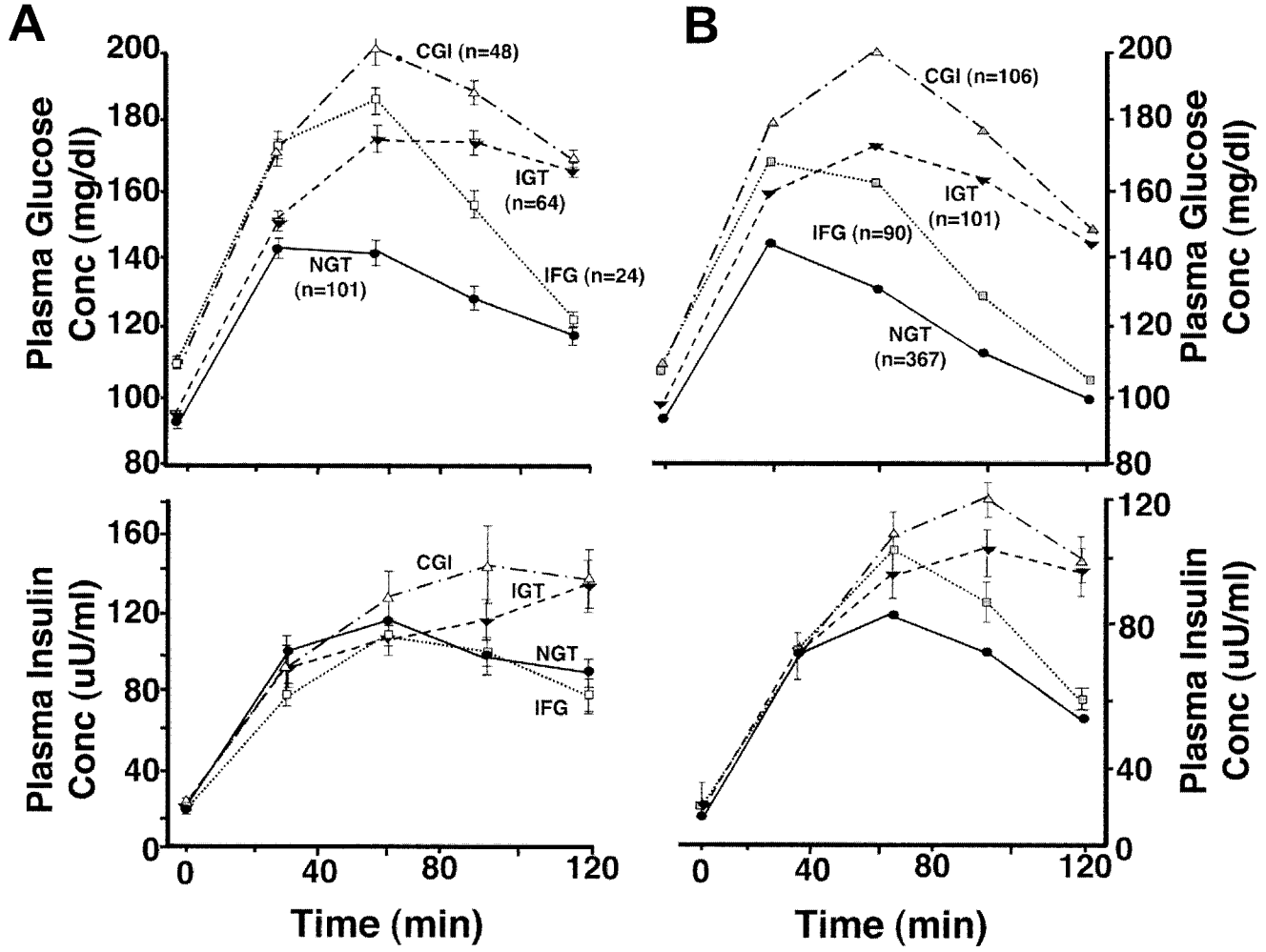


**Figure 1**—*Plasma glucose and insulin concentration during OGTTs performed in subjects with NGT, IGT, IFG, and CGI. Data represent results from Abdul-Ghani et al. (48)* (A) *and Hanefeld et al. (68)* (B).

(GLP-1) and glucose-dependent insulinotrophic peptide (GIP) (51). Reduced glucose-stimulated GLP-1 secretion consistently has been observed in type 2 diabetes (52), and this will have a major impact on measurement of insulin secretion during OGTT, while having no effect on measurement of insulin secretion in response to intravenous glucose. In contrast to GLP-1, GIP levels are elevated in type 2 diabetes and resistance to GIP is a characteristic feature of the diabetic state (53). GLP-1 and GIP secretion in individuals with IGT and IFG has been less well characterized (54,55).

Insulin secretion in response to intravenous glucose also differs from oral glucose in its temporal pattern. Following glucose ingestion there is a gradual rise in plasma glucose concentration (reflecting the slow rate of glucose absorption), and this is accompanied by gradual increase in plasma insulin. The abrupt rise in plasma glucose following intravenous glucose causes a rapid and transient increase in plasma insulin concentration (first-phase insulin secretion), which lasts for ~10 min. This is followed by a slower, sustained rise in plasma insulin (second-phase insulin secretion), which persists as long as plasma glucose remains elevated (38).

In clinical studies, insulin secretion is evaluated by measuring plasma insulin or C-peptide response to oral or intravenous glucose. The amount of insulin secreted must be related to the increment in plasma glucose concentration, which provides the stimulus to β-cells (56). In NGT subjects, the amount of insulin secreted in response to glucose is correlated inversely with peripheral insulin sensitivity (2,3,57,58). Reduced insulin sensitivity, through as-yet-unidentified mechanism(s), enhances plasma insulin response to any given glucose stimulus. Therefore, if one wishes to compare β-cell function between subjects with different insulin sensitivity, an insulin secretion/insulin resistance index (disposition index) should be used (59,60).

The hyperglycemic clamp is considered the gold standard for measuring first- and second-phase insulin secretion. Although first-phase insulin secretion is an "artifact" only observed with acute intravenous glucose administration (there is no identifiable first-phase insulin secretion following glucose ingestion), many studies have demonstrated that loss of first-phase insulin secretion is a strong predictor of type 2 diabetes (62–64). The IVGTT also has been widely used to assess insulin secretion. The acute (0–10 min) insulin response (AIR) correlates with first-phase insulin response during the hyperglycemic clamp (65). A disadvantage of IVGTT is that the plasma glucose concentration declines rapidly following

glucose injection, and second-phase insulin secretory response cannot be measured. Use of the IVGTT also precludes assessment of the incretin affect.

Indexes of insulin secretion derived from OGTT provide an estimate of insulin secretion during the more physiological route of glucose administration. The insulinogenic index (increment in plasma insulin ÷ increment in plasma glucose) during the first 30 min of the OGTT has been utilized widely in epidemiological studies as a surrogate measure of first-phase insulin secretion, although it has not been extensively validated. One early study demonstrated a modest correlation ($r = 0.61$, $P < 0.001$) between $\Delta I_{0-30}/\Delta G_{0-30}$ and acute insulin response during IVGTT (66), but a weaker correlation ($r = 0.47$, $P = 0.0005$) was observed in a more recent study (47). $\Delta$I (area under the curve)$_{0-120}$/$\Delta$G(area under the curve)$_{0-120}$ also has been used as an index of insulin secretion during the OGTT (60). Ideally, these indexes should be related to severity of insulin resistance, e.g., $\Delta I_{0-30}/\Delta G_{0-30}$ ÷ IR (insulin resistance). This requires an independent measure of insulin sensitivity.

## ORAL GLUCOSE TOLERANCE IN SUBJECTS WITH IGT OR IFG

— Approximately 20–25% subjects with IGT also have IFG and ~30–45% of IFG subjects have IGT (rev. in 15). To understand the metabolic abnormalities that are present in subjects with IGT or IFG, we will limit our discussion to studies that have assessed subjects with isolated IGT (2-h plasma glucose 140–199 mg/dl [7.8–11.0 mmol/l] and normal FPG <100 mg/dl [5.6 mmol/l]) or isolated IFG (FPG 100–125 mg/dl [5.6–6.9 mmol/l] and 2-h plasma glucose <140 mg/dl [7.8 mmol/l]).

During an OGTT, plasma glucose concentration in NGT subjects reaches a peak 30–60 min following glucose ingestion (Fig. 1) (42,48,67–69). Thereafter, it declines toward the fasting glucose level, reaching values <140 mg/dl (7.8 mmol/l) after 2 h. In NGT subjects, the peak plasma glucose concentration rarely rises >150–160 mg/dl (8.3–8.9 mmol/l). Subjects with isolated IGT, when compared with subjects with NGT, have comparable FPG concentrations (48,69, 70–78). However, following glucose ingestion, the plasma glucose rises rapidly at 30 min, continues to rise after 60 min, and remains >140 mg/dl (7.8 mmol/l) at 120 min (42,48,67–69,79). On mean, the plasma glucose concentration at 120 min is not different from that at 60 min. Thus, subjects with IGT manifest two abnormalities during OGTT: rapid and continuous rise in plasma glucose concentration and lack of decline in plasma glucose at 2 h. Subjects with IFG have higher FPG than individuals with NGT or IGT (48,67,70–78). Following glucose ingestion, plasma glucose concentration at 30 and 60 min increases to levels greater than in NGT and IGT. However, unlike subjects with IGT, the plasma glucose concentration in IFG progressively declines, reaching levels <140 mg/dl (7.8 mmol/l) at 120 min (48,68,69,79,80). Thus, subjects with isolated IFG have an elevated FPG, an exaggerated early rise in plasma glucose concentration following glucose ingestion, and plasma glucose similar to NGT at 120 min.

## INSULIN RESISTANCE IN IGT AND IFG

— Insulin sensitivity (measured with hyperinsulinemic-euglycemic clamp or IVGTT) in subjects with isolated IGT consistently has been shown to be decreased compared with NGT (48,70–73). In three studies using hyperinsulinemic-euglycemic clamp (48,70,71), a mean decrease in insulin-stimulated glucose disposal of 30% was observed in IGT versus NGT. The impairment in insulin-stimulated glucose disposal was observed in all ethnic groups studied: 27% reduction in Pima Indians (70), 32% in Hispanics (48), and 21% in Japanese (71). In two (48,71) of the three studies, a 21% increase in insulin-stimulated glucose disposal was observed in IFG versus NGT. In the third study (70), insulin-stimulated glucose disposal was reduced in IFG versus NGT subjects. However, IFG subjects were significantly (25%) more obese than NGT or IGT subjects. When insulin-stimulated glucose disposal was adjusted for BMI (70), insulin sensitivity was similar in IFG and NGT subjects, while IGT subjects still manifested reduced insulin sensitivity compared with NGT.

Van Haeften et al. (74) and Pimenta et al. (81) also observed a 28% decrease in glucose infusion rate during hyperglycemic clamp studies performed in subjects with isolated IGT compared with NGT. Consistent with these observations, Festa et al. (72) and Osei et al. (73) reported 42% reduction in $S_i$ measured with IVGTT in IGT subjects. Since insulin-stimulated glucose disposal during insulin clamp primarily measures muscle insulin sensitivity, these studies collectively indicate that subjects with isolated IGT are characterized by muscle insulin resistance. The magnitude of decline (~30–35%) in muscle insulin sensitivity in IGT is comparable to that in normoglycemic first-degree relatives of diabetic subjects (7,82–84). These results suggest that muscle insulin resistance in type 2 diabetes is, at least in part, inherited and precedes development of overt diabetes. An inherited component of muscle insulin resistance has been demonstrated in type 2 diabetic individuals in populations as diverse as Pima Indians (85) and Swedes (86).

In contrast to IGT, subjects with isolated IFG generally have been reported to have normal or even enhanced insulin-stimulated muscle glucose disposal (48,71). The only exception to this is the study by Festa et al. (72), who reported a modest decline in $S_i$ in IFG subjects. However, this could be explained by failure to completely suppress hepatic glucose production during IVGTT. Since subjects with isolated IFG have been shown to have hepatic insulin resistance (see below), impaired suppression of hepatic glucose production would result in slower decline in plasma glucose during IVGTT. Thus, although $S_i$ is decreased, it could reflect hepatic, not muscle, insulin resistance.

During epidemiological studies, insulin sensitivity usually has been assessed with surrogate measures, most commonly HOMA-IR. In all populations, subjects with isolated IFG or isolated IGT had a significantly elevated HOMA-IR (~40 and ~30%, respectively) compared with NGT (48,68,69,72,75–78,86,87) (Table 2). In contrast to the suggestion by Festa et al. (72), we do not believe that this "discrepancy" between HOMA-IR and insulin clamp–derived measurements of insulin resistance in IFG subjects reflects methodological inconsistencies. Rather, this apparent discrepancy most likely reflects the different underlying physiological processes quantitated with the two techniques. HOMA-IR primarily reflects hepatic insulin resistance, while insulin clamp mainly reflects muscle insulin resistance. Our interpretation of the published results is that IFG individuals primarily are characterized by hepatic insulin resistance with normal muscle insulin sensitivity, while IGT subjects mainly have muscle insulin resistance with mild

**Table 2—*Insulin secretion and insulin sensitivity in IFG and IGT***

| | | | | | IFG* | | | IGT* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Reference | Population | Index of insulin secretion | Index of insulin resistance | FPI | Insulin secretion | Insulin resistance | FPI | Insulin secretion | Insulin resistance |
| Wasada | 71 | Japanese | II | M | 1.05 | 0.41 | 1.21 | 1.33 | 0.72 | 0.79 |
| Osei | 73 | African American | AIR | $S_i$ | — | — | — | 1.23 | 0.64 | 0.51 |
| Weyer | 70 | Pima Indians | AIR | M | 1.74 | 0.67 | NS | 1.4 | 0.92 | 0.73 |
| Pimenta | 81 | Brazilians | 1st & 2nd | GIR | — | — | — | 0.9 | 0.38 (1st) 0.49 (2nd) | 0.6 |
| van Haeften | 74 | Caucasian | 1st & 2nd | GIR | — | — | — | — | 0.80 (1st) 0.80 (2nd) | 0.84 |
| Festa | 72 | Mixed | AIR | $S_i$ | 1.37 | 0.64 | 0.81 | 1.25 | 0.82 | 0.65 |
| Abdul-Ghani | 48 | Hispanic | II | M | 1.33 | 0.77 | 1.21 | 1.17 | 0.37 | 0.58 |
| Snehalatha | 77 | Indian | II | HOMA-IR | 1.13 | 1.03 | 0.75 | 1.26 | 0.93 | 0.8 |
| Carnevale Schianca | 87 | Caucasian | HOMA-B | HOMA-IR | 1.19 | 0.42 | 0.63 | 1.61 | 1.47 | 0.58 |
| Piche | 75 | Caucasian | II | HOMA-IR | 3.04 | 1.03 | 0.26 | 2.08 | 0.57 | 0.45 |
| Hanefeld | 68 | Caucasian | II | HOMA-IR | 1.34 | 0.78 | — | 1.35 | 0.63 | — |
| Davies | 76 | Caucasian | None | HOMA-IR | 1.32 | 0.7 | 0.7 | 1.3 | 0.65 | 0.77 |
| Abdul-Ghani | 69 | Arabs | II | HOMA-IR Matsuda | 1.57 | 0.51 | 1.95 0.69 | 0.94 | 0.22 | 0.97 0.88 |
| Tripathy | 86 | Swedes | II | HOMA-IR | 1.11 | 0.92 | 0.65 | — | 0.6 | 0.89 |
| Novoa | 78 | Spanish | HOMA-B | HOMA-IR | 1.24 | 1 | 0.65 | 1.46 | 1.5 | 0.69 |

*Ration of IFG to NGT or IGT to NGT. 1st & 2nd, first and second phase of insulin secretion during hyperglycemic clamp; GIR, insulin-mediated glucose disposal during hyperglycemic clamp; HOMA-B, HOMA of β-cell activity; II, insulinogenic index; M, insulin-mediated glucose disposal during insulin clamp.

hepatic insulin resistance. This conclusion is consistent with two studies where hepatic glucose production was measured with tritiated glucose. In isolated IFG, the hepatic insulin resistance index (basal hepatic glucose production × FPI) was markedly increased, while in IGT it was only minimally elevated (48,70). Subjects with isolated IFG also had impaired suppression of hepatic glucose production during insulin clamp (70).

## INSULIN SECRETION IN IGT AND IFG

— Under fasting conditions, subjects with isolated IFG and isolated IGT have higher FPI concentrations than NGT subjects (Table 2). The basal insulin secretion rate (deconvolution of fasting plasma C-peptide concentration) increases linearly with the increase in FPG in both IGT and IFG and is not correlated with the 2-h plasma glucose concentration (88). In all published studies, the plasma insulin concentration at 30 min during OGTT in subjects with isolated IFG and isolated IGT is comparable to or significantly lower than in NGT, despite a significantly higher plasma glucose concentration (68,69,75–78,86,87). Thus, reduced $\Delta I_{0-30}/\Delta G_{0-30}$ is a consistent finding in subjects with IGT and IFG, indicating an impaired early insulin secretory response to ingested glucose (Table 2). Unfortunately, the insulin secretion/insulin resistance index only has been determined in one study (48), and $\Delta I_{0-30}/\Delta G_{0-30} \div$ IR was reduced to a significantly greater extent in isolated IGT (73%) than in isolated IFG (23%). Viewed collectively, these studies demonstrate that subjects with isolated IFG and isolated IGT have a significant reduction in early (0–30 min) insulin response during OGTT. Total insulin response $\Delta I_{0-120}/\Delta G_{0-120}$ during OGTT also is significantly reduced in subjects with isolated IFG and isolated IGT (48,68). The insulin secretion/insulin resistance index ($\Delta I_{0-120}/\Delta G_{0-120} \div$ IR) has been examined in only one study (48), and subjects with IGT had a more severe reduction than subjects with IFG. The insulin secretion/insulin resistance index ($\Delta I_{60-120}/\Delta G_{60-120} \div$ IR) during the 2nd hour of OGTT was similar in subjects with isolated IFG and NGT but reduced by 58% in isolated IGT. This reduction is comparable to the decrease (57%) in insulin secretion/insulin resistance index during the first 30 min of OGTT.

Studies using the IVGTT (70,72,73) have reported a decrease in AIR in both isolated IFG and IGT compared with NGT. Weyer et al. (70) reported 33% (IFG) and 8% (IGT) reductions, while Festa et al. (72) reported 36% (IFG) and 18% (IGT) reductions, respectively, in AIR compared with NGT. Ahren and Pacini (89) found a 32% decrease in AIR in Caucasian postmenopausal women with IGT. In the three studies in which it was measured (70,72,74), subjects with isolated IGT had lower $S_i$ than subjects with isolated IFG, indicating that the insulin secretion (AIR)/insulin resistance index is reduced similarly in IFG and IGT.

Two studies have measured insulin secretion with hyperglycemic clamp in IGT (75,82). Both studies found significant reductions in first- and second-phase insulin secretion. Van Haeften (74) reported 35 and 30% reductions, while Pimenta (81) reported 62 and 51% reductions compared with NGT. Although they did not calculate the insulin secretion/insulin resistance index, in both studies IGT subjects had significantly lower glucose infusion rates (despite increased plasma insulin responses) than NGT subjects. Therefore, expression of first- and second-phase insulin secretion in relation to insulin resistance would have yielded a more profound reduction in insulin secretion in IGT. No study has measured first- and second-phase insulin secretion with hyperglycemic clamp in IFG subjects

The decrease in early insulin response (0–30 min) during OGTT in IFG and IGT is consistent with reduced AIR during IVGTT in both groups (70,72,73). It also is consistent with reduced first-phase in-

sulin secretion observed in IGT subjects studied with hyperglycemic clamp (74,81). These studies collectively suggest that subjects with IFG or IGT have impaired first-phase insulin secretion, which may explain their high risk for conversion to type 2 diabetes in epidemiological studies (15). The pivotal role of β-cell dysfunction in the conversion of IGT to type 2 diabetes is emphasized by intervention studies, which demonstrated that preservation of β-cell function decreases the conversion rate of IGT to diabetes (90,91).

Although reduced insulin secretion (insulinogenic index during OGTT and first-phase insulin response to intravenous glucose) consistently has been observed in all ethnic groups (Pima Indians, Hispanic, Caucasians, and Japanese), considerable variability in the magnitude of the decrease exists. Weyer et al. (70) reported an 8% reduction in AIR in Pima Indians with IGT, while Festa et al. (72) observed a greater reduction (18%) in AIR in Hispanic IGT subjects. An even greater decrease was reported in Caucasian women with IGT (32%) (89). This variation might simply reflect genetic differences or might be explained, in part, by differences in tissue sensitivity to insulin. In NGT subjects insulin secretion is related inversely to severity of insulin resistance (57,58). Thus, in NGT Pima Indians (a population characterized by severe insulin resistance [92[), the β-cell must function close to its maximal capacity to maintain normal glucose homeostasis. Consequently, a small decline in β-cell function will cause a significant deterioration in glucose tolerance, leading to IGT. In Hispanics (a population characterized by insulin resistance but not as severe as in Pima Indians), a greater decrease in insulin secretion is needed to cause a deterioration in glucose homeostasis, leading to IGT. In Caucasians, who are more sensitive to insulin than Hispanics, a much greater reduction in insulin secretion is required to lead to IGT. Other factors, such as age, total body fat content/distribution, plasma free fatty acid levels, and β-cell fat content may contribute to the differences in magnitude of reduction in AIR.

An interesting but as-yet-unanswered question relates to the etiologic significance of the impairment in insulin secretion, i.e., whether it is a primary or acquired defect. In longitudinal studies, reduced first-phase insulin secretion in NGT is a strong predictor of progression to IGT and subsequently to type 2 diabetes (91,93,94). Studies that have assessed insulin secretion in IGT, using plasma C-peptide deconvolution (61) and graded glucose infusion (95), also have demonstrated impaired β-cell function. These observations suggest that impaired insulin secretion in IGT is primary and precedes the impairment in glucose intolerance. On the other hand, a small persistent rise in plasma glucose concentration has been shown to have a deleterious effect on β-cell function. This "glucotoxic" effect has been demonstrated in vivo in humans and animal and in vitro in cell culture systems (96–99). In partially pancreatectomized NGT rats, a small increment (16 mg/dl) in mean day-long plasma glucose markedly impaired first-phase insulin secretion (98). A similar defect in humans could explain the reduction in early-phase insulin secretion in subjects with isolated IFG or isolated IGT. In animal studies, correction of chronic hyperglycemia with phlorizin in diabetic rats restores first-phase insulin secretion, indicating that in this animal model, impaired first-phase insulin secretion results from chronic hyperglycemia and is reversible upon restoration of normoglycemia (97). Although a similar study in humans will be required to definitively establish the pathogenic role of chronic hyperglycemia in development of impaired insulin secretion, some indirect evidence supports this scenario. Thus, correction of hyperglycemia with insulin in type 2 diabetes improves insulin secretion (100), while acute hyperglycemia in NGT subjects impairs the normal oscillatory β-cell response to glucose (101).

It is noteworthy that the decline in insulin secretion in IGT becomes progressively more severe as 2-h plasma glucose increases from 100 to139 mg/dl (5.6–7.7 mmol/l), values considered to be within the range of NGT (60). Similarly, the decline in first-phase insulin secretion begins when FPG increases >90 mg/dl (5 mmol/l), which also is well within the range considered to represent normal FPG concentration (102).

### Combined glucose intolerance

Approximately 15–20% of all subjects with glucose intolerance have combined glucose intolerance (CGI), i.e., both IFG (FPG 110–125 mg/dl) and IGT (140–199 mg/dl) (15–22). Subjects with CGI share the metabolic characteristics of IGT and IFG: marked fasting hyperinsulinemia (48,70), reduced insulin sensitivity during insulin clamp (similar to isolated IGT) (48,70,71), and high HOMA-IR (similar to isolated IFG) (48,68,70,72). Insulin resistance during the clamp reflects muscle insulin resistance, while HOMA-IR indicates hepatic insulin resistance. Subjects with CGI also have a profound reduction in insulin secretion (insulinogenic index) during OGTT (48,68,69,70–72). The combination of severe liver/muscle insulin resistance and markedly impaired insulin secretion in CGI subjects may explain their very high risk (twofold greater than IGT and IFG) for progression to type 2 diabetes in prospective epidemiological studies (15).

## SUMMARY AND CONCLUSIONS

— Although IFG and IGT are intermediate states between NGT and overt type 2 diabetes, they represent distinct states of glucose intolerance, which are characterized by different pathophysiologic mechanisms. Both IGT and IFG are insulin-resistant states, but they differ in site of insulin resistance. Subjects with IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, while individuals with IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance. Subjects with CGI manifest both forms of insulin resistance in severe form. The pattern of impaired insulin secretion also differs between the two groups. Subjects with isolated IFG manifest a decrease in first-phase insulin secretory response to intravenous glucose and early-phase insulin response to oral glucose. However, late-phase plasma insulin response during OGTT is less severely impaired than in IGT. Subjects with IGT have severe defects in both early- and late-phase insulin responses to intravenous and oral glucose.

The metabolic characteristics described above help to explain the plasma glucose profile following glucose ingestion in IGT, IFG, and CGI. Since first-phase insulin secretion plays an important role in priming the liver and inhibiting endogenous glucose production during an OGTT or a meal (33), the defect in early-phase insulin secretion in IFG and IGT would be expected to impair suppression of hepatic glucose production and contribute to the excessive rise in plasma glucose during the first 60 min of OGTT. In subjects with IGT, the combination of deficient second-phase (late phase during OGTT) insulin secretion

plus muscle insulin resistance results in less efficient disposal of glucose during OGTT. As a result, plasma glucose concentration continues to increase after 60 min and remains elevated at 120 min (Fig. 1). Subjects with IFG start with a high FPG (due to hepatic insulin resistance), but the incremental rise in plasma glucose concentration at 30–60 min is only slightly greater than in NGT (Fig. 1), and, by 120 min, plasma glucose concentration has returned to values similar to those in NGT despite the excessive initial rise. This profile is explained by normal muscle insulin sensitivity (measured with insulin clamp) (48,70,71) with an intact late-phase insulin secretory response (measured by plasma C-peptide deconvolution) (M.A.A.-G., R.A.D., unpublished data), which together maintain a near normal incremental plasma glucose response during OGTT. Individuals with CGI start with a high FPG concentration because of hepatic insulin resistance and have the greatest rise in plasma glucose during OGTT because of muscle/hepatic insulin resistance plus impaired insulin secretion.

In summary, a clearer understanding of the pathophysiologic abnormalities which characterize IGT and IFG provides insights about interventions to slow/halt the progression to type 2 diabetes. Subjects with IFG, who manifest predominant liver insulin resistance, are most likely to benefit from agents, e.g., metformin, that reduce hepatic insulin resistance, as was demonstrated in the Diabetes Prevention Program (103), while subjects with IGT, who predominantly have muscle insulin resistance plus severely impaired insulin secretion, are more likely to respond to agents that improve skeletal muscle insulin resistance, such as peroxisome proliferator–activated receptor-γ agonists (91), in combination with an insulin secretagogue, such as GLP-1 analog.

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