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# Isolated Impaired Fasting Glucose and Peripheral Insulin Sensitivity: Not a Simple Relationship

Sun H. Kim, M.D., M.S. and Gerald M. Reaven, M.D.

Department of Medicine, Stanford University School of Medicine, Stanford, CA

**Running title:** IFG and Insulin Sensitivity

**Corresponding Author:**
Sun H. Kim, M.D.
Stanford University Medical Center
300 Pasteur Drive, Room S025
Stanford, CA 94305-5103
sunhkim@stanford.edu

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## ABSTRACT

*Objective:* In a recent consensus statement, the American Diabetes Association (ADA) concluded that individuals with impaired fasting glucose (IFG) have "normal muscle insulin sensitivity." To subject this conclusion to further validation, we evaluated the relationship between glucose tolerance categories and peripheral insulin sensitivity in a large nondiabetic population.

*Research Design and Methods:* Insulin sensitivity was directly quantified by determining the steady-state plasma glucose (SSPG) concentration during the insulin suppression test in 446 nondiabetic individuals, divided into four groups: normal glucose tolerance (NGT, n= 318), isolated IFG (n=63), isolated impaired glucose tolerance (IGT, n=33), and combined IFG and IGT (IFG/IGT) (n=32).

*Results:* Insulin sensitivity was significantly different in all three groups with prediabetes (IFG, IGT, IFG/IGT) as compared with NGT ($p<0.05$). Using tertiles of SSPG concentration in the NGT group as operational definitions of insulin resistance (highest tertile) and insulin sensitivity (lowest tertile), there was considerable heterogeneity within the prediabetic groups. Thus, 57% of IFG individuals were insulin resistant, and 13% were insulin sensitive. The IFG/IGT group was most homogeneous with 94% classified as insulin resistant and only 3% as insulin sensitive.

*Conclusions:* Peripheral insulin sensitivity varies considerably in nondiabetic individuals with IFG individuals showing the most heterogeneity within the prediabetes group. We believe that this heterogeneity in insulin sensitivity, and the relatively few patients in whom insulin sensitivity has been measured directly in the past, explain the discrepancy between our findings and the recent consensus statement by the ADA.

Measurements of plasma glucose concentration before and two hours (2-hr) after a 75 gram oral glucose challenge provide the information needed to divide individuals into three major diagnostic groups: normal glucose tolerance (NGT), prediabetes, and diabetes (1). These data can also be used to further subdivide individuals with prediabetes into those with isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), or a combination of IFG and IGT (IFG/IGT) (1). The pathophysiological differences between the three categories with prediabetes has been the focus of several reports (2-12), with general agreement that peripheral insulin resistance is the prominent finding in individuals with either isolated IGT or combined IFG/IGT. The findings are less consistent in individuals with isolated IFG, who have been described as having both normal (2-4) and abnormal (5-12) peripheral insulin sensitivities. The reasons for the discrepant findings in persons with IFG are not clear, and may relate to the use of different methods to quantify insulin sensitivity, ranging from sophisticated techniques (i.e., the euglycemic, hyperinsulinemic clamp) to simple formulas (such as the homeostasis model assessment of insulin resistance, HOMA-IR). In addition, it may also be possible that there is sufficient heterogeneity of insulin sensitivity values within each prediabetic group to confound conclusions based on studies of relatively few participants.

The present study was initiated to explore these issues, with particular focus on individuals with IFG. To accomplish this task, we compared differences in peripheral insulin sensitivity as specifically quantified by the insulin suppression test (IST) or estimated by HOMA-IR in the four glucose tolerance groups: NGT, isolated IFG, isolated IGT, and combined IFG/IGT. We also evaluated the percentage of individuals in the lowest, middle and highest tertiles of insulin resistance to determine the degree of heterogeneity of this physiological variable in the various glucose tolerance groups.

## MATERIALS AND METHODS

Study subjects included all individuals who had previously participated in our research studies (1990 to 1998) approved by the Institutional Review Board at Stanford University. All study participants provided informed consent. Individuals considered for inclusion were nondiabetic (13) and in good general health with no history of coronary artery, kidney, or liver disease. All had completed the following assessments: height and weight; systolic (SBP) and diastolic (DBP) blood pressures; oral glucose tolerance test (OGTT); lipid assessment; and IST, a quantitative evaluation of insulin resistance described below. Initially, 490 individuals were identified; 44 were removed for missing data. Out of the 446 remaining individuals, 318 had NGT, 63 had isolated IFG, 33 had isolated IGT, and 32 had combined IFG/IGT.

All metabolic testing was performed in the General Clinical Research Center after fasting for 12 hours. During the OGTT, plasma glucose and insulin concentrations were measured before (fasting) and 2-hr after oral ingestion of 75 grams of glucose (14). Using these results, individuals were classified as having NGT (fasting glucose <5.6 mmol/L, 2-hr glucose <7.8 mmol/L); IFG (fasting glucose 5.6-7.0 mmol/L, 2-hr glucose <7.8 mmol/L); IGT (fasting glucose <5.6 mmol/L; 2-hr glucose between 7.8-11.1 mmol/L); and IFG/IGT (fasting glucose 5.6-7.0 mmol/L, 2-hr glucose 7.8-11.1 mmol/L)(1). Lipid measurements were performed by the core laboratory at Stanford University Medical Center by standardized methods approved by the Centers for Disease Control. It included total cholesterol, triglyceride and high-density lipoprotein (HDL-C) and low-density

lipoprotein (LDL-C) cholesterol concentrations.

Insulin resistance was directly measured with the modified version (15) of the IST, initially introduced and validated by our research group (16,17). The values for insulin sensitivity obtained with this approach are highly correlated ($r > 0.9$) with the euglycemic clamp technique (17). Briefly, after an overnight fast, an intravenous catheter was placed in each of the subject's arms. One arm was used for the administration of a 180-minute infusion of octreotide ($0.27 mcg/m^2/min$), insulin ($32 mU/m^2/min$) and glucose ($267 mg/m^2/min$); the other arm was used for collecting blood samples. Blood was drawn at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual. Insulin resistance was also calculated using the formula for HOMA-IR [fasting glucose (mmol/L) X fasting insulin (mU/L)/22.5] (18).

Since there is no objective method to classify individuals as being insulin resistant or sensitive, we used an operational definition based on results of previously published prospective studies demonstrating a statistically significant increase in clinical syndromes in individuals in the highest tertile of SSPG concentration and lack of these outcomes in those in the lowest tertile (19,20). Thus, we quantified the percentage in the lowest, middle, and highest tertile of SSPG among each of the four glucose tolerance groups, using the SSPG values in the NGT group.

Statistical analyses were performed using SPSS (version 12 for Windows; SPSS, Chicago, IL). Triglyceride and insulin concentrations were log transformed to obtain a more normal distribution for statistical tests; geometric means (21) are presented in the results section. Statistical differences between groups were assessed by one-way ANOVA followed by Bonferroni posthoc pairwise comparisons when significant ($p<0.05$). P-values were not otherwise adjusted for multiple comparisons made throughout the study. Indices for insulin resistance (SSPG and HOMA-IR) were adjusted for age, gender, and BMI. Chi-square test was used for categorical variables.

## RESULTS

Table 1 compares the demographic and metabolic characteristics of the four glucose tolerance groups. The NGT group was younger, less heavy, and had lower blood pressures than the three prediabetic groups. However, there were no significant differences in these variables within the IFG, IGT, or combined IFG/IGT groups.

Concerning lipid metabolism, triglyceride concentrations were significantly lower and HDL-C concentrations higher in the NGT group as compared with the three prediabetic groups. Total cholesterol and LDL-C concentrations were also lower in individuals with NGT as compared with IFG. However, there were no differences in any lipid and lipoprotein concentrations within the three prediabetic groups.

Individuals with NGT had lower fasting and 2-hr plasma glucose concentrations and lower insulin concentrations than the three prediabetic groups. Within the prediabetic groups, fasting and 2-hr glucose concentrations differed based on their classification: IFG and IFG/IGT groups had higher fasting glucose compared with the IGT group, and the IFG group had lower 2-hr glucose concentrations compared with the other two groups. Finally, fasting plasma insulin concentrations were significantly higher in the IFG/IGT groups than in those with either IFG or IGT alone, and 2-hr insulin

concentrations were lower in the IFG group compared with the IGT and IFG/IGT groups.

SSPG concentrations increased progressively from NGT to IFG/IGT group (Table 2). The NGT group had significantly lower SSPG concentration than the three prediabetic groups. In addition, the IFG group had lower SSPG concentrations than either the IGT or IFG/IGT groups. Adjusting for age, gender, and BMI tended to lower the SSPG concentrations in the prediabetic groups and accentuated the difference between IFG and IGT groups. Of note, steady-state plasma insulin concentrations (geometric means in pmol/L and 95% CI) were not significantly different between the four groups (p=0.1 by ANOVA): NGT, 347 (336,358); IFG, 368 (334,405); IGT, 393 (323,480); and IFG/IGT, 421 (344,517).

HOMA-IR was also lowest in the NGT group and highest in the IFG/IGT group. However, in contrast to SSPG concentrations, the increase in HOMA-IR was not progressive across the four groups. Thus, HOMA-IR values were higher in the IFG group than in the NGT group, and lower than in the IFG/IGT group. On the other hand, values were not lower in the IFG group as compared with the IGT group. Adjusting for age, gender, and BMI attenuated the difference between NGT and IGT groups.

Figure 1 shows the distribution of insulin resistance (SSPG concentration) in the four groups and demonstrates a progressive increase in the median SSPG concentrations from the NGT to the IFG/IGT group. While there is considerable overlap between the groups, the length of the boxes (depicting the interquartile range) was greatest in those with IFG and least in the IFG/IGT group. In addition, for the IFG group, the median was centered between the interquartile range. This was not true of the other three groups, with the extreme example being those with IFG/IGT, demonstrating a much narrower distribution in SSPG values above the median than below.

To quantify the proportion of individuals in each of the four groups based on their insulin action, we divided them into tertiles based on the SSPG concentrations of the NGT group (Table 3): lowest tertile 1 (insulin sensitive), middle tertile 2, and highest tertile 3 (insulin resistant). There was a significant difference in the percentage of individuals in each SSPG tertile among the four glucose tolerance groups ($p<0.001$ by chi-square test). Thus, the percentage of individuals in Tertile 3 (insulin resistant) increased progressively from NGT (33%) to IFG (57%) to IGT (76%) to IFG/IGT (94%); the percentage of individuals in Tertile 1 (insulin sensitive) decreased from NGT (33%) to IFG (13%) to IGT (3%) to IFG/IGT (3%). As indicated in the Methods section, the decision to use tertiles of SSPG concentrations in the NGT group to classify individuals as being insulin resistant or sensitive was based on results of prospective studies showing that these cut points identified individuals who did, or did not, develop clinical syndromes associated with insulin resistance (19,20). However, as seen in Table 3, the relative proportion of insulin resistant individuals in the IFG group remained high even when the upper quartile (53%) or quintile (44%) of SSPG in the NGT group was used as the definition. Finally, limiting the analysis to the non-Hispanic White population did not meaningfully alter the results (not shown).

## DISCUSSION

The results presented emphasize the heterogeneity of peripheral insulin sensitivity in individuals with NGT, as well as those classified as having prediabetes. Although we arbitrarily used the SSPG tertiles in the NGT group to define insulin sensitivity (lowest tertile) and insulin resistance (highest tertile), this definition has been shown in two prospective studies to predict disease outcomes including type 2 diabetes

and cardiovascular disease (19,20). Using this definition, the IFG group was the most heterogeneous of the prediabetes group with 57% who were insulin resistant and 13% who were insulin sensitive. The thrust of these findings remained when individuals with IFG were divided into SSPG quartiles (53% insulin resistant, 6% insulin sensitive) or quintiles (44% insulin resistant, 6% insulin sensitive).

In the most general sense, our findings are similar to several others in that prediabetic individuals tend to be older and heavier, with higher blood pressure and with dyslipidemia (2,3,5-8,10,11)—changes seen in the three prediabetes group in our study. Controversy, however, remains concerning the degree of peripheral insulin resistance in individuals with isolated IFG. Specifically, how do values of insulin sensitivity in individuals with IFG differ from those with NGT, IGT, or IFG/IGT? Prior publications disagree in their conclusions; some report that individuals with IFG are more insulin resistant than those with NGT (5-11), while others have found that IFG individuals are similar to those with NGT (2-4), and more insulin sensitive than those with IGT and IFG/IGT (2,4). It is not possible to review in detail all previous publications addressing this issue, but it seems likely that some of the discordance results from use of surrogate markers, rather than direct measurements of insulin sensitivity. For example, HOMA-IR tends to overemphasize the degree of peripheral insulin resistance in the IFG group. This is due to the HOMA-IR formula which is simply based on fasting glucose and insulin: [fasting glucose (mmol/L) X fasting insulin (mU/L)/22.5]. By definition, the IFG group has higher fasting glucose than the NGT or IGT groups; therefore, they will tend to have higher HOMA-IR than either group. Thus, Table 2 indicates that the IFG group tends to have higher HOMA-IR than the IGT group, although by a specific measure of insulin resistance (SSPG), the IFG group is less insulin resistant. This discrepancy has been seen in other studies where both HOMA-IR and a more specific measure of insulin resistance have been reported (2,3,7).

Limiting consideration to studies utilizing direct measurements of insulin sensitivity does not remove uncertainty as to the degree of peripheral insulin resistance in IFG. Thus, Weyer et al. quantified insulin sensitivity using the euglycemic, hyperinsulinemic clamp technique in Pima Indians and found IFG individuals to have significantly lower insulin sensitivity values compared with NGT individuals and similar values with IGT or IFG/IGT individuals (11). In contrast, three other studies using the hyperinsulinemic clamp technique (2-4) found no significant differences in insulin sensitivity between the IFG and NGT groups. In two of these studies (2,4), individuals with IFG were more insulin sensitive compared with those with NGT (although not statistically significant). Comparison with IGT group yielded different results; in two studies, insulin sensitivity values were similar between IFG and IGT groups (3,11) and in two other studies IFG individuals were more insulin sensitive than those with IGT (2,4).

A possible explanation for such discordant results when similar techniques are used to address the same question is that it results from a combination of the heterogeneity of insulin sensitivity values in IFG individuals, and the relatively few such individuals in the reports discussed above (2-4,11). Specifically, in those four studies, measurements of insulin sensitivity were performed in 10 (2), 21 (3),10 (4) and 11 (11) individuals with IFG; this represents a total of 52 patients with IFG as compared with the 63 individuals with IFG in this study. Furthermore, while 57% of IFG individuals were insulin resistant, there were 43% who were in the most insulin sensitive and intermediate tertiles. Therefore, it seems obvious that conclusions about the degree of peripheral insulin resistance in individuals

with IFG could vary dramatically as a function of which members of this heterogeneous population was enrolled in experimental groups of ~10 individuals.

In conclusion, our results are consistent with many previous reports in that our subjects with IFG, IGT, and IFG/IGT tend to be older, heavier and with more metabolic abnormalities than those with NGT (2,3,5-8,10,11). Our results are also in general agreement that peripheral insulin resistance is increased in individuals with IGT and IFG/IGT as compared with those with NGT (2-12). However, they are somewhat in conflict with the recent ADA statement (22) that "people with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity." Although hepatic glucose output is likely to be suppressed during measurement of insulin sensitivity (SSPG) (16), we cannot comment upon that aspect of the ADA statement as we did not specifically quantify hepatic glucose output. Nonetheless, at the simplest level we have shown that insulin sensitivity values are heterogeneous in all four glucose tolerance groups (Table 3), and there are both insulin sensitive and resistant individuals with NGT, IFG, IGT, and IFG/IGT; what distinguishes these four groups from each other is the relative number of individuals who fall into each category. The greatest degree of homogeneity is seen in the IFG/IGT group (94% insulin resistant, 3% insulin sensitive) and IGT group (76% insulin resistant, 3% insulin sensitive), explaining why there is no disagreement about the presence of insulin resistance in either group. In contrast, there is considerable heterogeneity in the NGT and IFG groups, and this very likely contributes to different findings when these groups are compared. However, despite this heterogeneity, and irrespective of how the population is divided, the majority of IFG individuals are insulin resistant and the minority are insulin sensitive when compared with NGT individuals. Based upon these findings, it appears that considerable caution needs to be expressed when generalizing about peripheral insulin resistance in IFG individuals based on the findings in relatively few patients.

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**TABLE 1. Demographic and laboratory characteristics of individuals with NGT, IFG, IGT, or IFG/IGT**

| | NGT | IFG | IGT | IFG/IGT | P values* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | NGT,IFG | NGT,IGT | NGT,IFG/IGT | IFG,IGT | IFG,IFG/IGT | IGT, IFG/IGT |
| n | 318 | 63 | 33 | 32 | | | | --- | | |
| Age (years) | 46 ± 14 | 51 ± 11 | 55 ± 8 | 57 ± 11 | 0.04 | 0.003 | <0.001 | 1.0 | 0.14 | 1.0 |
| Gender (% male/female) | 43/57 | 57/43 | 42/58 | 62/38 | | | | --- | | |
| Non-Hispanic White (%) | 89 | 86 | 82 | 81 | | | | --- | | |
| BMI (kg/m$^2$) | 25.5 ± 4 | 28.5 ± 5 | 27.7 ± 4 | 29.5 ± 4 | <0.001 | 0.02 | <0.001 | 1.0 | 1.0 | 0.56 |
| SBP (mmHg) | 123 ± 18 | 137 ± 21 | 135 ± 20 | 146 ± 18 | <0.001 | 0.004 | <0.001 | 1.0 | 0.10 | 0.08 |
| DBP (mmHg) | 76 ± 12 | 83 ± 13 | 84 ± 11 | 86 ± 10 | <0.001 | 0.001 | <0.001 | 1.0 | 0.78 | 1.0 |
| Total Cholesterol (mmol/L) | 4.8 ± 0.9 | 5.4 ± 0.8 | 5.0 ± 0.9 | 5.1 ± 0.7 | <0.001 | 0.52 | 0.32 | 0.16 | 0.28 | 1.0 |
| Triglyceride (mmol/L) | 1.0[1.0,1.1] | 1.6[1.4,1.8] | 1.6[1.3,1.8] | 1.8[1.5, 2.1] | <0.001 | <0.001 | <0.001 | 1.0 | 1.0 | 1.0 |
| HDL-C (mmol/L) | 1.33 ± 0.36 | 1.17 ± 0.34 | 1.21 ± 0.28 | 1.10 ± 0.21 | 0.003 | 0.34 | 0.001 | 1.0 | 1.0 | 0.94 |
| LDL-C (mmol/L) | 2.9 ± 0.8 | 3.4 ± 0.8 | 3.0 ± 0.8 | 3.1 ± 0.7 | <0.001 | 1.0 | 0.93 | 0.13 | 0.28 | 1.0 |
| Fasting Plasma Glucose (mmol/L) | 4.8 ± 0.5 | 5.9 ± 0.3 | 5.1 ± 0.4 | 6.1 ± 0.4 | <0.001 | 0.008 | <0.001 | <0.001 | 0.55 | <0.001 |
| 2-hr Glucose (mmol/L) | 5.3 ± 1.2 | 6.1 ± 1.0 | 8.9 ± 0.9 | 9.1 ± 0.8 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 1.0 |
| Fasting Plasma Insulin (pmol/L) | 61[58,65] | 84[74,97] | 84[69,101] | 127[105,154] | <0.001 | 0.01 | <0.001 | 1.0 | 0.003 | 0.01 |
| 2-hr Insulin (pmol/L) | 278[257,301] | 389[319,476] | 712[571, 888] | 761[622, 930] | 0.004 | <0.001 | <0.001 | 0.001 | <0.001 | 1.00 |

Data presented as mean ± SD or geometric means and [95%CI]. *P values represent post-hoc pairwise comparisons which were adjusted for multiple comparisons within the variable but not for all comparisons made in the study.

**TABLE 2. Indices of insulin resistance**

| | NGT | IFG | IGT | IFG/IGT | P values* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | NGT, IFG | NGT, IGT | NGT, IFG/IGT | IFG, IGT | IFG, IFG/IGT | IGT, IFG/IGT |
| n | 318 | 63 | 33 | 32 | | | --- | | | |
| **Unadjusted** | | | | | | | | | | |
| SSPG | 7.2[6.8,7.6] | 9.9[8.8,11.0] | 11.6[10.2,12.9] | 14.1[12.9,15.3] | <0.001 | <0.001 | <0.001 | 0.23 | <0.001 | 0.03 |
| HOMA-IR | 1.9[1.8,2.0] | 3.2[2.7,3.7] | 2.7[2.2,3.3] | 4.9[4.0, 6.0] | <0.001 | 0.003 | <0.001 | 1.0 | 0.003 | <0.001 |
| **Adjusted for age, gender, and BMI** | | | | | | | | | | |
| Adjusted SSPG | 7.6[7.3,8.0] | 8.9[8.1,9.7] | 10.9[9.8,12.0] | 12.7[11.5,13.8] | 0.03 | <0.001 | <0.001 | 0.03 | <0.001 | 0.15 |
| Adjusted HOMA-IR | 2.0[1.9,2.1] | 2.8[2.4,3.1] | 2.5[2.1,3.0] | 4.1[3.4,4.8] | <0.001 | 0.06 | <0.001 | 1.0 | 0.002 | 0.001 |

Arithmetic means [95% CI] are presented for SSPG, and geometric means are presented for HOMA-IR. *P values represent posthoc pairwise comparisons which were adjusted for multiple comparisons within the variable but not for all comparisons made in the study.

**TABLE 3. Proportion (%) of individuals in SSPG tertiles, quartiles, and quintiles in the four glucose tolerance groups**

| | NGT | IFG | IGT | IFG/IGT |
|---|---|---|---|---|
| **SSPG Tertiles** | | | | |
| Tertile 1 (SSPG <4.9 mmol/L) | 33 | 13 | 3 | 3 |
| Tertile 2(SSPG 4.9-8.4 mmol/L) | 34 | 30 | 21 | 3 |
| Tertile 3 (SSPG >8.4 mmol/L) | 33 | 57 | 76 | 94 |
| **SSPG Quartiles** | | | | |
| Quartile 1 (SSPG <4.1 mmol/L) | 25 | 6 | 3 | 0 |
| Quartile 2 (SSPG 4.1-6.3 mmol/L) | 25 | 19 | 9 | 3 |
| Quartile 3 (SSPG 6.4-9.7 mmol/L) | 25 | 22 | 18 | 9 |
| Quartile 4(SSPG >9.7 mmol/L) | 25 | 53 | 70 | 88 |
| **SSPG Quintiles** | | | | |
| Quintile 1(SSPG <3.8 mmol/L) | 20 | 6 | 3 | 0 |
| Quintile 2 (SSPG 3.8-5.3 mmol/L) | 20 | 13 | 6 | 3 |
| Quintile 3 (SSPG 5.4-7.7 mmol/L) | 20 | 21 | 12 | 0 |
| Quintile 4 (SSPG 7.8-10.6 mmol/L) | 20 | 16 | 15 | 19 |
| Quintile 5(SSPG >10.6 mmol/L) | 20 | 44 | 64 | 78 |

SSPG=steady-state plasma glucose, higher values represent greater degrees of insulin resistance. Tertiles, quartiles and quintiles were based on SSPG concentrations in the NGT group.

**FIGURE 1.** Box plots illustrating the median and range of steady-state plasma glucose (SSPG) concentrations by glucose tolerance categories. Higher SSPG concentrations represent greater degrees of insulin resistance. Boundaries of the box signify lower and upper quartiles. Circle (○) represents outliers with values between 1.5 and 3 box lengths from the boundaries of the box.