Cross-Sectional and Longitudinal Changes of Glucose Effectiveness in Relation to Glucose Tolerance

The Insulin Resistance Atherosclerosis Study

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OBJECTIVE—Glucose effectiveness (S_G), the capacity of glucose to enhance its own disposition, is an independent predictor of future diabetes. However, there are data on cross-sectional and longitudinal changes of S_G and its components, basal insulin effect on S_G (BIE) and S_G at zero insulin (GEZI), but the natural course of S_G has not been described in a large population.

RESEARCH DESIGN AND METHODS—S_G was measured at baseline in 1,265 participants (aged 40–69 years) and at the 5-year examination in 827 participants in the Insulin Resistance Atherosclerosis Study (IRAS) using the frequently sampled intravenous glucose tolerance test. None of these participants were treated with glucose-lowering agents.

RESULTS—In cross-sectional analyses, S_G, BIE, and GEZI deteriorated with worsening of glucose tolerance ($P < 0.001$ for all three associations). In longitudinal analyses among subjects with normal glucose tolerance (NGT) at baseline, S_G, BIE, and GEZI declined in those who progressed to impaired glucose tolerance (IGT) or diabetes ($P < 0.001$ for all three measures). More modest longitudinal changes were demonstrated in individuals with IGT. The transition back to NGT (as opposed to no change) compared with the transition to diabetes was statistically significant for S_G ($P = 0.049$) and BIE ($P = 0.042$) and was not a statistically significant trend for GEZI ($P = 0.332$). In individuals with diabetes, only BIE had a significant decline ($P = 0.003$).

CONCLUSIONS—S_G, BIE, and GEZI decline in subjects whose glycemic status worsens. S_G and GEZI deteriorate more in the initial stages of the disease process.

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Insulin sensitivity tends to decrease with time (1), but the directional change in insulin secretion is a major factor for future glucose tolerance status in the Insulin Resistance Atherosclerosis Study (IRAS) (2). Along with insulin sensitivity and insulin secretion, the insulin-independent component of glucose tolerance (i.e., glucose effectiveness [S_G]) is an independent determinant of future diabetes in different ethnic groups and varying states of glucose tolerance, family history of diabetes, and obesity (3). S_G represents the capacity of glucose, per se, to enhance glucose cellular uptake and to suppress endogenous glucose production (4). These properties of glucose are influenced by basal insulin concentration, the basal insulin effect (BIE), in insulin-dependent tissues. Consequently, the ability of glucose to promote glucose disappearance by insulin-dependent tissues (independently of the BIE) and insulin-independent tissues is known as S_G at zero insulin (GEZI) (4).

S_G is an important determinant of glucose tolerance status even in conditions of significant insulin resistance (5). It is reduced in those with impaired glucose tolerance (IGT) and diabetes (6,7), in healthy individuals after an infusion of cortisol (8) or glucagon (9), in states of very low caloric intake (10), in women with polycystic ovary syndrome (11), and in the elderly (12). S_G may be little influenced by weight-loss interventions (13) but may improve with physical training (14) and treatment with thiazolidinediones (15). There are data on cross-sectional and longitudinal changes of S_G, but the natural course of S_G has not been described in a large population.

We aimed to analyze changes in S_G and its components relative to the change in glucose tolerance status in the IRAS, a multicenter observational epidemiologic study in different ethnic groups and varying states of glucose tolerance (16). Insulin sensitivity index (S_I), first-phase acute insulin response (AIR), and S_G were directly measured by the frequently sampled intravenous glucose tolerance test.

RESEARCH DESIGN AND METHODS

The design and methods of the IRAS have been described elsewhere (16). In brief, enrollment was conducted at four clinical centers: non-Hispanic whites and African Americans were recruited in Oakland and Los Angeles, CA, and non-Hispanic whites and Hispanics were recruited in San Antonio, TX, and San Luis Valley, CO. A total of 1,624 individuals were enrolled (56% women) between October 1992 and April 1994. A follow-up examination was performed 5 years after the baseline examination (mean 5.2 years [range 4.6–6.6]). The response rate was 81%. Identical for both examinations, protocols were approved by local institutional review committees.

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All participants gave written informed consent.

Race/ethnicity, dietary intake, macronutrient composition, and energy expenditure from moderate and vigorous activities were assessed by self-report. Family history of diabetes was defined as diabetes in parents or siblings. Anthropometric variables and blood pressure were gathered by trained personnel. Plasma glucose and insulin concentrations were determined by the glucose oxidase and dextran-charcoal radioimmunoassay methods, respectively. The insulin assay displayed a high degree of cross-reactivity with proinsulin.

Baseline and follow-up examinations required two visits 1 week apart. During the first visit, a 75-g oral glucose tolerance test was administered to assess glucose tolerance status. During the second visit, insulin sensitivity and first-phase insulin secretion were measured by the frequently sampled intravenous glucose tolerance test with two modifications to the original protocol. First, an injection of regular insulin was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance. Second, the reduced sampling protocol (12 samples) was used because of the large number of subjects. Estimates of insulin sensitivity derived from this technique correlated significantly with those derived from the glucose clamp technique (16). S_I and S_G at basal insulin were calculated using mathematical modeling methods (MINMOD version 3.0, 1994; courtesy of Richard Bergman, PhD, Los Angeles, CA). BIE was computed as the product of S_I and basal insulin concentration and GEZI as the difference between total S_G and BIE (4). AIR was calculated as the mean of 2- and 4-min insulin concentrations after glucose administration.

In cross-sectional analyses, we defined normal glucose tolerance (NGT) as a fasting glucose concentration <5.6 mmol/L and a 2-h glucose concentration <7.8 mmol/L, impaired fasting glucose (IFG) as a fasting glucose concentration ≥5.6 and <7.0 mmol/L, IGT as a 2-h plasma glucose concentration ≥7.8 and <11.1 mmol/L, and diabetes as a fasting glucose concentration ≥7.0 mmol/L or a 2-h plasma glucose concentration ≥11.1 mmol/L. Because of the many possibilities of future change in glucose tolerance status, we carried out longitudinal analyses with three glucose tolerance categories: NGT, defined as a 2-h glucose concentration <7.8 mmol/L; IGT; and diabetes. Individuals treated with glucose-lowering medications were excluded from all analyses.

The present report includes cross-sectional and longitudinal data on 1,265 and 827 participants, respectively. We excluded 359 individuals from cross-sectional analyses (244 for taking glucose-lowering medications, 114 for having missing data, and 1 for having an extreme outlier value of S_G). We excluded 438 additional individuals from longitudinal analyses (24 died, 74 for taking glucose-lowering medications, 337 for not attending the follow-up examination, and 3 for having extreme outlier values of S_G).

Statistical analyses

Analyses were carried out using the SAS statistical software (version 9.1; SAS Institute, Cary, NC). In cross-sectional analyses, we used one-way ANCOVA (or logistic regression analysis) to compare differences for continuous (or dichotomous) variables between glucose tolerance categories to adjust for the effect of age, sex, race/ethnicity, and research center. Linear regression analyses were used to examine the relationship between demographic, lifestyle, and metabolic variables to S_G, BIE, and GEZI. Independent associations with S_G, BIE, and GEZI also were assessed by mutivariate linear regression models. The MIXED procedure, a generalization of the standard linear model used in the GLM procedure, was used to examine independent relationships of longitudinal changes in BMI, S_I, and AIR with changes in S_G, BIE, and GEZI. Log-transformed values of fasting insulin, S_I, AIR, and BIE were used to improve discrimination and calibration of the models and to minimize the influence of extreme observations. Given that some individuals had an S_I equal to 0, we used the natural logarithms of $S_I + 1$ as the transformation for S_I. We considered significant a two-sided P value < 0.050.

RESULTS—In cross-sectional analyses, glucose tolerance categories differed little in terms of dietary intake and macronutrient composition, but diabetes was associated with lower energy expenditure (Table 1). All metabolic traits deteriorated with worsening of glucose tolerance. S_I, AIR, S_G, and GEZI already were decreased in individuals with isolated IFG. S_I, S_G, BIE, and GEZI were lower in participants with isolated IGT. Participants with isolated IFG and isolated IGT did not differ in terms of S_G and GEZI; however, those with isolated IGT tended to have lower S_I and BIE and higher AIR. The decline in S_I, AIR, S_G, BIE, and GEZI with worsening of glucose tolerance by sex and race/ethnicity is shown in Supplementary Figs. 1 and 2.

S_I decreased rapidly within the normal range of fasting and 2-h plasma glucose levels and to a lesser degree through the IFG, IGT, and the diabetic range of glucose levels (Fig. 1). AIR did not decline within the normal range of fasting glucose concentration and remained elevated within the normal range of 2-h glucose concentration. AIR had a steep decline through the IFG and IGT range of glucose levels. S_G and GEZI were very similar in their steady deterioration, which seemed to be more prominent within the normal range of fasting and 2-h glucose concentrations. BIE decreased throughout the entire range of fasting and 2-h glucose levels, although less pronounced within the normal range of fasting glucose concentration.

S_G, BIE, and GEZI were negatively related to age, adiposity, and plasma glucose levels and positively related to energy expenditure and S_I (Supplementary Table 1). S_G and GEZI also were negatively related to fasting insulin concentration and positively related to AIR. BIE had a positive association with fasting insulin concentration. In multiple linear regression models, we observed the following independent relationships: age and BMI were negatively and S_I and AIR positively related to S_G; age and BMI were negatively and AIR positively associated with GEZI; and age, BMI, 2-h glucose, and AIR were negatively related to BIE (Supplementary Table 2).

In longitudinal analyses, S_I decreased and adiposity, fasting and 2-h glucose levels, and AIR increased during the follow-up period (Table 2). BIE decreased, but S_G and GEZI did not significantly change.

Older age, higher baseline BMI and S_G, and lower baseline S_I and AIR were independently associated with a greater decline in S_G during the follow-up period (Supplementary Tables 3 and 4). Weight gain and higher decreases in S_I or AIR also were independently related to a greater decline in S_G. Similar results were obtained for the correlates of the longitudinal change in GEZI except for the absence of a relationship between change in S_I and change in GEZI. Baseline BMI, 2-h glucose, and BIE and longitudinal changes

in BMI, 2-h glucose, and AIR all were negatively associated with change in BIE.

In individuals with NGT at baseline, the transition to IGT or to diabetes was directly related to the declines in S_G ($P < 0.001$), BIE ($P = 0.009$), and GEZI ($P < 0.001$) (Fig. 2). S_G and GEZI declines also were statistically significant after adjusting for S_I and AIR ($P < 0.001$ and 0.011, respectively). In individuals with IGT at baseline, longitudinal changes in glucose tolerance status were accompanied by changes of borderline statistical significance for S_G ($P = 0.049$) and BIE ($P = 0.042$). Changes in GEZI were not significant ($P = 0.332$). S_G ($P = 0.327$) and GEZI ($P = 0.148$) did not significantly change in individuals with diabetes, but BIE further declined ($P = 0.003$). We obtained similar results using glucose tolerance categories defined by fasting glucose levels (Supplementary Fig. 3). S_G, in relation to AIR, or S_I, by glucose tolerance status at baseline and follow-up, is presented in Supplementary Fig. 4.

CONCLUSIONS

In cross-sectional analyses, S_G and its components, BIE and GEZI, are directly related to glucose tolerance. S_G and GEZI are not as severely compromised in subjects with significant deterioration of glucose tolerance (including those with type 2 diabetes) as are BIE, insulin sensitivity, and insulin secretion. Age, BMI, and AIR are independent correlates of S_G and GEZI. S_I also is an independent correlate of S_G because of the strong relationship between S_I and BIE. In longitudinal analysis, weight gain and worsening AIR correlate with declines in S_G and GEZI. Worsening S_I also is related to S_G decline. S_G and GEZI significantly decline in individuals with NGT whose glycemic status deteriorates. Changes in S_G and GEZI are more modest in individuals who already have IGT or diabetes, but BIE deterioration may occur at all stages of glucose tolerance.

S_G is an important determinant of glucose metabolism (5) and an independent predictor of the development of diabetes (3,6). Some studies have described that S_G is reduced in people with IGT and diabetes (6,7). S_G may be similar in these two groups of individuals (7). S_G seems to be higher in the first-degree offspring of individuals with type 2 diabetes who are more insulin resistant than matched subjects without any family history of diabetes (17). In addition, the ability of glucose to enhance its own utilization may not be impaired in diabetic subjects who are insulin

Table 1—*Cross-sectional analysis of baseline characteristics by glucose tolerance status in the IRAS*

	NGT	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes	*P* trend
n	467	196	108	209	285	—
Age (years)	53.4 ± 0.4	54.6 ± 0.6*	57.1 ± 0.8†	57.0 ± 0.6†	57.1 ± 0.5†	<0.001
Female (%)	60.0 (55.4–64.3)	35.7 (29.3–42.7)†‡	71.3 (62.1–79.0)§	55.5 (48.7–62.1)‖	55.4 (49.6–61.1)‖	0.903
Ethnicity (%)						
Hispanics	35.1 (30.9–39.6)	32.1 (26.0–39.0)*	44.4 (35.4–53.9)	32.1 (26.1–38.7)*	29.1 (24.1–34.7)‖	0.141
African Americans	24.6 (20.9–28.7)	26.5 (20.8–33.1)‖	12.0 (7.1–19.6)¶	32.1 (26.1–38.7)‡§	35.1 (29.8–40.8)‡¶	0.002
Non-Hispanic whites	40.3 (35.9–44.8)	41.3 (34.6–48.3)	43.5 (34.5–53.0)	35.9 (29.7–42.6)	35.8 (30.4–41.5)	0.142
BMI (kg/m^2)	26.9 ± 0.2	28.4 ± 0.4§	28.3 ± 0.5†	31.6 ± 0.4†‡	31.7 ± 0.2†‡	<0.001
Waist circumference (cm)	86.8 ± 0.5	90.5 ± 0.8¶	91.3 ± 1.1†	98.3 ± 0.8†‡	99.5 ± 0.7†‡	<0.001
Fasting glucose (mmol/L)	5.01 ± 0.06	5.86 ± 0.09†‡	5.24 ± 0.12†	6.08 ± 0.09†‡	8.32 ± 0.08†‡	<0.001
2-h Glucose (mmol/L)	5.70 ± 0.10	6.19 ± 0.16†‡	8.87 ± 0.21†	9.13 ± 0.15†	15.0 ± 0.13†‡	<0.001
Fasting insulin (μU/mL)#	10.6 ± 0.2	14.0 ± 0.4†	13.1 ± 0.7	17.3 ± 0.5†‡	20.5 ± 0.6†‡	<0.001
S_I ($\times 10^{-4}$ min^{-1} • μU^{-1} • mL^{-1})#	2.29 ± 0.07	1.80 ± 0.09‡¶	1.23 ± 0.11†	0.99 ± 0.10*†	0.44 ± 0.06†‡	<0.001
AIR (μU/mL)#	58.6 ± 1.8	42.1 ± 2.2*†	53.0 ± 3.8	39.3 ± 2.0†‡	24.8 ± 1.0†‡	<0.001
S_G ($\times 10^{-2}$ min^{-1})	2.16 ± 0.03	1.83 ± 0.05¶	1.76 ± 0.07†	1.64 ± 0.05†	1.50 ± 0.04†‖	<0.001
BIE ($\times 10^{-2}$ min^{-1})#	0.28 ± 0.01	0.27 ± 0.02‡	0.18 ± 0.02†	0.20 ± 0.01†	0.10 ± 0.01†‡	<0.001
GEZI ($\times 10^{-2}$ min^{-1})	1.89 ± 0.04	1.57 ± 0.05¶	1.59 ± 0.07¶	1.46 ± 0.05†	1.41 ± 0.07*†	<0.001
Dietary intake (kcal)	1,839 ± 34	1,863 ± 52	1,932 ± 72	1,914 ± 50	1,919 ± 43	0.097
Carbohydrates (% of intake)	47.6 ± 0.36	47.0 ± 0.56	47.5 ± 0.78	46.3 ± 0.53§	46.7 ± 0.46	0.061
Fat (% of intake)	34.6 ± 0.32	34.8 ± 0.49	34.5 ± 0.66	34.7 ± 0.47	35.1 ± 0.40	0.327
Energy expenditure (kcal/kg/year)	4,290 ± 164	4,335 ± 253	3,507 ± 339	3,891 ± 243	3,377 ± 210†	<0.001

Data are *n*, percentage (95% CI), or means ± SE. Results were adjusted for age, sex, race/ethnicity, and research center. *P* value for test of difference with NGT as the category of comparison: †$P < 0.001$; §$P < 0.05$; ¶$P < 0.01$. *P* value for test of difference with IGT as the category of comparison: *$P < 0.05$; ‡$P < 0.001$; ‖$P < 0.01$. #Log-transformed variables and back-transformed to their units for presentation.

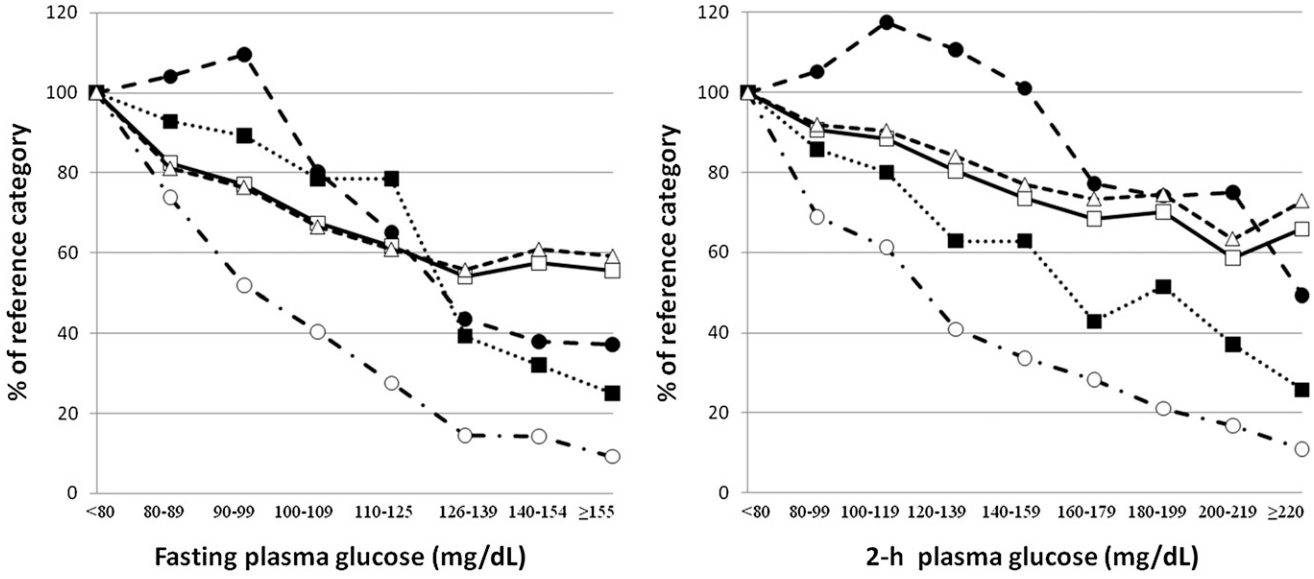

Figure 1—*Cross-sectional analysis of the relationship between S_I, AIR, S_G, BIE, and GEZI and fasting and 2-h glucose levels.* ○, S_I; ●, *AIR;* □, S_G; ■, *BIE;* △, *GEZI. All results were adjusted for age, sex, race/ethnicity, and research center.*

resistant (18). Our larger sample size has allowed us to carry out a more comprehensive assessment on the relation of S_G and its components to glucose tolerance. BIE has a significant deterioration with worsening of glucose tolerance. It is not lower in individuals with isolated IFG because the decrease in insulin sensitivity is compensated with an increase in fasting insulin concentration. S_G and GEZI have steady declines as glucose tolerance worsens but remain preserved, to a large extent, in states of significant insulin resistance, including diabetes. Consequently, the body seems to protect its last resort for glucose utilization when there is a severe impairment of glucose tolerance.

We have previously reported that African Americans and Hispanics have lower insulin sensitivity and higher insulin secretion than non-Hispanic whites, but S_G did not differ significantly by ethnic group (19). In a study among 32 individuals of African descent, Osei et al. (20) have described that S_G is preserved in those with IGT or diabetes despite having more insulin resistance and β-cell dysfunction. Our results indicate S_G and both S_G components deteriorate as glucose tolerance worsens in all three race/ethnic groups. The absence of statistical differences in S_G in African Americans with isolated IFG or isolated IGT relative to counterparts with NGT may be attributed to sample size. GEZI is significantly lower in African Americans with isolated IFG, and there is no interaction effect of race/ethnicity on the relationship between S_G and GEZI to glucose tolerance.

Cnop et al. (21) already have described longitudinal changes in S_G in 33 first-degree relatives of non-Hispanic whites with type 2 diabetes. These individuals tended to be insulin resistant, which is a common trait in offspring of diabetic individuals. During the follow-up period, there was a significant deterioration in β-cell function but without a significant decline in either S_I or S_G. Among the 16 individuals with NGT at baseline, baseline S_G was lower in individuals who progressed to IGT, but the change in S_G during the period of observation was not statistically significant. Cnop et al. (21) recommended additional studies with larger sample sizes because a drop in S_G occurred in some individuals whose glucose tolerance status progressed to IGT. These results are not inconsistent with our article. In our large epidemiological study, S_G declines as glucose tolerance worsens, particularly early in the disease process.

Physical inactivity has been associated with lower S_I and S_G (14). Dietary fat has been linked to worsening of glucose tolerance in epidemiological studies (22). However, there is no evidence that isoenergetic replacement of saturated fat with monounsaturated fat or carbohydrates improves insulin sensitivity in studies with randomized diets (23). In our population, which is characterized by high rates of obesity, glucose tolerance abnormalities, and inactivity, diet and physical activity are not related to S_G. Insulin secretion, an important determinant of glucose tolerance status, tends to increase with weight gain and deterioration of insulin

Table 2—*Demographics and metabolic variables in 827 participants who had data from both assessments*

	Baseline assessment	Follow-up assessment	*P*
Age (years)	55.0 ± 0.3	60.2 ± 0.3	<0.001
BMI (kg/m^2)	28.6 ± 0.2	29.1 ± 0.2	0.042
Waist circumference (cm)	91.1 ± 0.4	93.3 ± 0.4	<0.001
Fasting glucose (mmol/L)	5.67 ± 0.05	5.96 ± 0.095	<0.001
2-h Glucose (mmol/L)	7.70 ± 0.13	8.81 ± 0.13	<0.001
Fasting insulin (μU/mL)*	13.4 ± 0.3	16.3 ± 0.3	0.002
S_I ($\times 10^{-4}$ min^{-1} · μU^{-1} · mL^{-1})*	1.59 ± 0.05	0.99 ± 0.04	<0.001
AIR (μU/mL)*	47.5 ± 1.4	56.8 ± 1.7	<0.001
S_G ($\times 10^{-2}$ min^{-1})	1.90 ± 0.03	1.87 ± 0.03	0.408
BIE ($\times 10^{-2}$ min^{-1})*	0.23 ± 0.01	0.17 ± 0.01	<0.001
GEZI ($\times 10^{-2}$ min^{-1})	1.67 ± 0.03	1.70 ± 0.03	0.466

Data are means ± SE. *Log-transformed variables and back-transformed to their units for presentation.

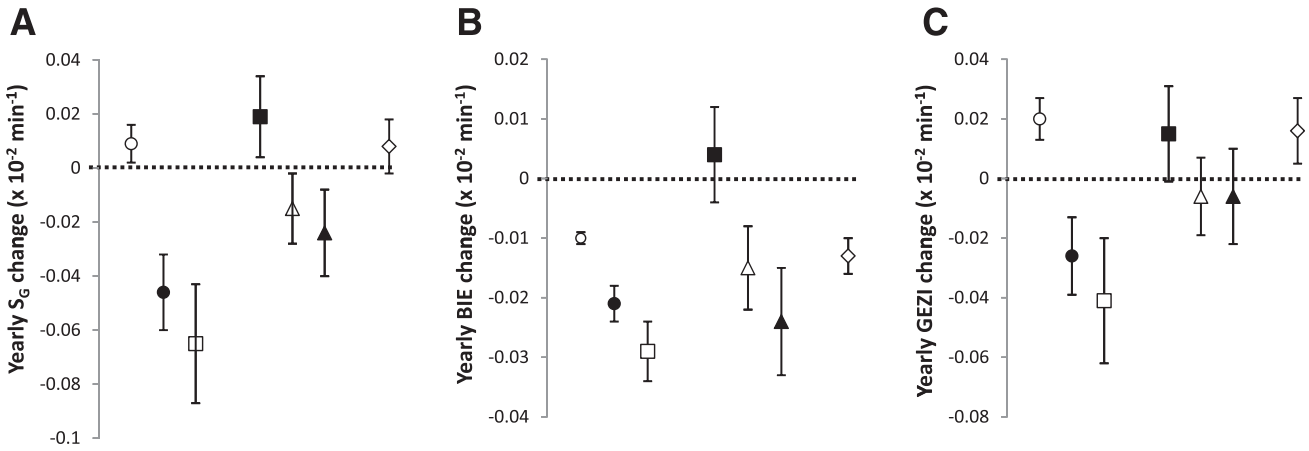

Figure 2—*Yearly changes in S_G, BIE, and GEZI relative to the change in glucose tolerance status.* A: *Yearly changes in S_G. Results were adjusted for age, sex, race/ethnicity, research center, and baseline S_G.* B: *Yearly changes in BIE. Results were adjusted for age, sex, race/ethnicity, research center, and baseline log BIE.* C: *Yearly changes in GEZI. Results were adjusted for age, sex, race/ethnicity, research center, and baseline GEZI. Results were stratified by glucose tolerance status at the baseline and follow-up examinations: ○, NGT at baseline and follow-up; ●, NGT at baseline and IGT at follow-up; □, NGT at baseline and diabetes at follow-up; ■, IGT at baseline and NGT at follow-up; △, IGT at baseline and follow-up; ▲, IGT at baseline and diabetes at follow-up; ◇, diabetes at baseline and follow-up.*

sensitivity (2,3). Although not declined in the whole IRAS cohort, longitudinal changes in S_G occur in parallel with those in adiposity, insulin sensitivity, and β-cell function. BIE partially explains the relationship between insulin sensitivity and S_G.

In most tissues, glucose uptake is regulated by the expression of specific glucose transporter proteins at the plasma membrane. Two of them, GLUT-1 and GLUT-4, are of particular importance for whole-body glucose homeostasis. Expressed in insulin-responsive tissues, GLUT-4 is located in intracellular membrane compartments in the basal non–insulin-stimulated state (24). GLUT-4 is translocated to the cell's surface by insulin and exercise and accounts for the insulin-dependent glucose uptake. Intracellular GLUT-4 depletion and interference in its translocation in response to insulin occurs in insulin-resistant states (25). GLUT-1 is much more widely distributed. GLUT-1 is located in the plasma membrane in the basal state and may account, at least partially, for the insulin-independent glucose uptake (17,24). There is experimental evidence that exercise training, inflammation, and insulin resistance are associated with an increase in GLUT-1 content in skeletal muscle (24). Thus, upregulation of GLUT-1 could mediate the preservation of S_G in states of severe impairment of glucose tolerance.

In conclusion, S_G declines in subjects whose glycemic status worsens, but our study cannot determine whether glucose uptake by tissues and suppression of endogenous glucose production by the liver are equally affected in each of the glucose tolerance categories. Age, adiposity, insulin resistance, and β-cell dysfunction largely explain the relationship of S_G to plasma glucose levels. The deterioration of BIE, the basal insulin effect component of S_G, is a steady process throughout the entire range of fasting and 2-h glucose levels and is driven by insulin resistance. BIE partially accounts for the relationship between S_G and insulin sensitivity. The decline of GEZI, the ability of glucose to promote its own disappearance independently of the BIE, is more prominent in the initial stages of the disease process leading to diabetes. It already is manifested in individuals with isolated IFG and IGT in men and women and across race/ethnic groups. Longitudinal changes in GEZI concur with weight and β-cell function changes.

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C.L. contributed to discussion and wrote, reviewed, and edited the manuscript. L.E.W. researched data, contributed to discussion, and reviewed and edited the manuscript. A.J.K. researched data and reviewed and edited the manuscript. A.J.G.H. contributed to discussion and wrote, reviewed, and edited the manuscript. M.J.R. and S.M.H. researched data, contributed to discussion, and reviewed and edited the manuscript.

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