

# Relationship Between Glucose Tolerance and Glucose-Stimulated Insulin Response in 65-Year-Olds

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**Background.** Decreased insulin secretion may contribute to the deterioration of glucose tolerance associated with aging.

**Methods.** We studied the insulin response to a 3-hour hyperglycemic clamp (10 mM) of 19 young ( $24 \pm 1$  y) subjects with normal glucose tolerance and 60 older ( $65 \pm 1$  y) subjects with various levels of glucose tolerance.

**Results.** The noninsulin dependent diabetic (NIDDM) group had a diminished first phase immunoreactive (IR)-insulin response compared to young and nondiabetic older groups ( $p < .05$ ). The older groups had a lower rate of change in IR insulin concentration during the third hour of hyperglycemia compared to the young group ( $p < .05$ ). This was not, however, a universal finding, because a decreased third hour response was not seen in a subgroup of older subjects whose glucose tolerance was similar to that of the young group. Another subgroup of older subjects with a decrease in glucose tolerance mild enough to be considered normal by the National Diabetes Group Criteria tended to have both an increase in the early insulin response and a decrease in the third hour response. More severe decreases in glucose tolerance were associated with blunting of the early response.

**Conclusion.** Aberrations in early and late phase glucose-stimulated insulin responses appear to be present in older subjects with even mildly decreased glucose tolerance. Some individuals, however, show no evidence of deterioration of glucose tolerance or insulin response to glucose with aging, at least up to age 70 years.

GLUCOSE tolerance frequently decreases with advancing age, and this may contribute to the development of noninsulin dependent diabetes (NIDDM) (1-4). The mechanisms responsible for the decrease in glucose tolerance have not been clearly defined. The development of insulin resistance with aging appears to play a major role in the decrease in glucose tolerance (3,5). In addition, there is evidence suggesting the development of a concurrent disturbance in glucose-stimulated insulin secretion that prevents the insulin response from increasing sufficiently to overcome the insulin resistance (6,8-10). Changes with age in islet sensitivity to gut-released stimulants of insulin secretion such as gastric inhibitory polypeptide may also affect oral glucose tolerance (6). To evaluate glucose-stimulated insulin release independently of gut factors, a number of investigators have used controlled, intravenous glucose stimulation of insulin secretion (7-10). DeFronzo (7) used the hyperglycemic clamp technique, in which blood glucose was maintained for 2 hours at 6.9 mM above basal concentration, to study the insulin response of 48 healthy nonobese subjects of varying age, but unknown glucose tolerance. He found no difference in the insulin response between young ( $24 \pm 1$  y), and two middle-aged groups ( $43 \pm 1$  y and  $54 \pm 1$  y). More recent studies, however, suggest that aging may be associated with decreased glucose-stimulated insulin secretion (8-10). Additional evidence for a decrease in pancreatic islet response to glucose with age has been provided by animal studies (11-13).

To better define the relationships between aging, glucose tolerance, and glucose-stimulated insulin response, we uti-

lized the hyperglycemic clamp technique to study a large number of older individuals with various levels of glucose tolerance, and we compared the results with those of a group of young normal subjects. We found that even mildly reduced glucose tolerance is associated with an abnormal plasma insulin response.

## METHODS

**Subjects.** — The 79 volunteers were healthy nonsmokers who were screened for participation on the basis of a normal physical examination, blood chemistry, urinalysis, blood cell counts, chest radiograph, and maximal treadmill stress test using the Bruce protocol with continuous ECG monitoring. All subjects were sedentary (defined as less than 30 minutes of vigorous physical activity twice a week for more than 6 months). All older subjects were community-dwelling, and 67% were retired or unemployed. Young subjects were recruited from the university community; 10 were graduate students and 9 were employees. Some characteristics of the subject groups are shown in Table 1. This study was approved by the Human Studies Committee of Washington University School of Medicine.

**Estimation of fat-free mass.** — In 67 subjects, fat-free mass was estimated from body density determined by hydrostatic weighing (14) after determination of residual lung volume by the oxygen dilution technique (15).

In 12 subjects, for whom hydrostatic weights were not available, skinfold measurements were made at 6 sites using

Table 1. Subject Characteristics

Group	n	Age (years)	Weight (kg)	Body Fat (%)	Incr OGTT <sub>area</sub> (glc mM•min)	$\dot{V}O_2$ max (ml•kg <sup>-1</sup> •min <sup>-1</sup> )
Young	19	24 ± 1	71.9 ± 2.2	20.9 ± 2.0	141 ± 19	45.2 ± 1.8
Men	14	24 ± 1	74.0 ± 2.3	17.7 ± 1.3	156 ± 23	48.8 ± 1.4
Women	5	24 ± 1	65.9 ± 4.5	25.8 ± 1.5	97 ± 25	35.3 ± 2.4
Normal	23	65 ± 1	75.5 ± 3.2	34.8 ± 1.8*	264 ± 19*	23.6 ± 1.1*
Men	9	65 ± 1	86.4 ± 5.6	26.2 ± 1.7*	265 ± 23*	28.7 ± 1.7*
Women	14	64 ± 1	70.9 ± 3.8	40.4 ± 1.2	264 ± 38*	20.3 ± 0.6*
ND/IGT	24	65 ± 1	71.8 ± 2.1	30.7 ± 1.3*	595 ± 23*	24.1 ± 0.8*
Men	12	64 ± 1	76.6 ± 2.9	28.3 ± 2.6*	627 ± 31*	25.7 ± 0.7*
Women	12	66 ± 1	67.0 ± 2.5	34.8 ± 1.6	565 ± 33*	22.5 ± 1.3*
Diabetic	13	65 ± 1	82.6 ± 4.5	34.6 ± 3.6*	912 ± 50*†	23.2 ± 1.0*
Men	8	65 ± 1	86.4 ± 5.6	28.2 ± 2.5*	870 ± 64*†	23.7 ± 1.0*
Women	5	64 ± 1	76.5 ± 7.5	44.6 ± 6.6	979 ± 76*†	22.4 ± 2.3*

Note. Values are expressed as mean ± SE. Incr OGTT<sub>area</sub> represents area under the glucose curve above baseline, 0 to 180 minutes.

\*Significantly different from young ( $p < .05$ ).

†Significantly different from nondiabetic groups ( $p < .05$ ).

a Lange caliper (Cambridge [MD] Scientific Industries). In males, the 6 sites measured were at the triceps, subscapular, pectoralis, suprailiac, umbilicus, and front thigh. Percent body fat was estimated according to the formulas of Yuhasz (16) for men, and Behnke and Wilmore (17) for women.

**Oral glucose tolerance test (OGTT).** — Subjects were instructed to eat a weight-maintaining diet containing at least 150 g of carbohydrate per day for the week before the OGTT. Oral 75 g glucose tolerance tests were performed in the morning about 14 hours after the previous meal. Venous blood samples for glucose analysis were obtained in the fasting state and 0.5, 1, 1.5, 2, and 3 hours after glucose ingestion. Classification was performed according to the recommendations of the National Diabetes Data Group (18).

**Determination of oxygen uptake capacity.** —  $\dot{V}O_2$ max was determined during graded treadmill walking or running by a previously described method (19). The protocol was designed to increment exercise intensity by approximately 3 to 4 ml•kg<sup>-1</sup>•min<sup>-1</sup> every 2 minutes and to elicit fatigue in 6 to 12 minutes. Speed and grade increments were therefore varied according to the exercise capacity of the individual, which was estimated from the results of the treadmill test performed during the medical evaluation. Cardiorespiratory data were collected using a computerized system.

**Hyperglycemic clamp procedure.** — Within 4 weeks of the OGTT, a hyperglycemic clamp procedure was performed as described by DeFronzo et al. (20). Subjects were instructed to eat a weight-maintaining diet containing at least 150 g of carbohydrate per day for the week before the procedure. Subjects reported to the General Clinical Research Center at Washington University Medical Center at 0700 h after an overnight fast. A polyethylene catheter was placed into an antecubital vein for infusion of 20% glucose. A second catheter was inserted in a retrograde manner into a dorsal hand vein. The subject's hand was placed in a box heated to 70°C for sampling of arterialized blood (21). After

allowing 30 minutes for temperature equilibration, 3 blood samples were withdrawn over a 10-minute period for determination of postabsorptive glucose and immunoreactive (IR)-insulin concentrations.

A priming dose of glucose was given over 15 minutes to raise the arterialized plasma glucose concentration to 10 mM (180 mg•dl<sup>-1</sup>). Plasma glucose was then maintained at this level for an additional 165 minutes by determining the plasma glucose concentration at 5-minute intervals by an automated glucose oxidase method (Beckman Instruments, Fullerton, CA) and adjusting the rate of glucose infusion. Blood samples were taken at -10, -5, 0, 2, 4, 6, 8, 10, and 15 minutes, and every 15 minutes thereafter, placed in chilled tubes containing 1000 kallikrein units of aprotinin and 6.0 mg ethylenediaminetetraacetic acid, and centrifuged. Plasma was separated and stored at -20°C until determination of IR-insulin concentrations by a double antibody radioimmunoassay (22). All urine was collected during the clamp for determination of glucose concentration. Urinary glucose loss did not significantly contribute to glucose disposal in any of the subjects.

**Calculations and statistics.** — Data were managed and analyzed using the CLINFO Data Analysis System (Biomedical Computer Program, Los Angeles). Rates of glucose disposal were calculated for each 30-minute period by correcting the mean infusion rate for glucose that was added to, or removed from, the glucose space (20). Areas for glucose response during the OGTT and early (0–10 min) and late (15–180 min) plasma IR-insulin responses during the clamp were calculated using a trapezoidal model. Comparisons between groups were performed using analysis of variance. Significant differences were located using the Neuman-Keuls post-hoc test. Correlations were assessed by univariate linear regression analysis.

## RESULTS

Nineteen young (19–30) and 60 older (60–72) subjects were studied by the hyperglycemic clamp procedure. Body

Table 2. Hyperglycemic Clamp Data

Group	Glucose <sub>0</sub> (mM)	Insulin <sub>0</sub> (pM)	Mean Glucose 0–180 min (mM)	CV Glucose %	Glucose Disposal	
					15–180 minutes (mmol•kgFFM <sup>-1</sup> )	150–180 minutes (mg•kgFFM <sup>-1</sup> •min <sup>-1</sup> )
Young	5.15 ± 0.09	37 ± 4	9.89 ± 0.02	3.2 ± 0.2	7.55 ± 0.46	12.2 ± 0.90
Normal	5.59 ± 0.08*	44 ± 8	9.97 ± 0.01*	3.4 ± 0.4	5.41 ± 0.33*	7.48 ± 0.57*
ND/IGT	5.81 ± 0.07*	48 ± 5	9.94 ± 0.01*	2.6 ± 0.2	4.50 ± 0.23*	5.68 ± 0.26*
Diabetic	6.65 ± 0.26*†	72 ± 12*†	9.96 ± 0.03*	2.0 ± 0.4	3.15 ± 0.32*†	3.98 ± 0.44*†

Notes. Values are expressed as mean ± SE. Glucose<sub>0</sub> and insulin<sub>0</sub> represent fasting plasma concentration at time 0 minutes. CV glucose represents the coefficient of variation in glucose concentration, 0–180 minutes.

\*Value significantly different from young ( $p < .05$ ).

†Value significantly different from nondiabetic groups ( $p < .05$ ).

weight, percent body fat, and incremental OGTT glucose areas are summarized in Table 1. All young subjects had normal glucose tolerance, whereas older subjects had various levels of glucose tolerance, i.e., 23 normal, 10 nondiagnostic (abnormal, but lacking criteria for impaired), 14 impaired, and 13 diabetic. For purposes of analysis, subjects with nondiagnostic and impaired glucose tolerance tests were grouped together (ND/IGT). In general, compared to young control subjects, older individuals did not differ significantly in weight. Older subjects did have greater percent body fat overall, but when analyzed by gender, the differences were only significant for the men. Among the older subjects, there was no correlation between body fat and glucose tolerance when analyzed overall or by gender.

A summary of data from the hyperglycemic clamp procedures is presented in Table 2. Compared to young subjects, older individuals had higher postabsorptive plasma glucose concentrations. The mean postabsorptive plasma IR-insulin concentration was also elevated in the NIDDM group. Plasma IR-insulin responses to the hyperglycemic clamp are presented in Figure 1, and are divided to demonstrate the periods of early (0–10 min) and late (15–180 min) response. Glucose disposal is presented in Table 2 as total glucose disposed during steady state hyperglycemia (15–180 min). To allow direct comparison with results from previous studies, glucose disposal was also calculated as the average rate of glucose disposal in  $\text{mg} \cdot \text{kgFFM}^{-1} \cdot \text{min}^{-1}$  for the last half-hour (150–180 min) of the clamp. The correlation coefficient between these two periods of glucose disposal, i.e., 15–180 and 150–180 min, was 0.96 ( $p < 10^{-8}$ ). The older groups exhibited lower mean glucose disposal rates per kilogram fat-free mass during the clamp (Table 2).

There were differences among the groups in the pattern of IR-insulin response to sustained hyperglycemia as measured by the whole area or incremental area above baseline under the IR-insulin curve. The early response was blunted in the NIDDM group whether measured as the initial rate of increase in plasma IR-insulin concentration between 0 and 4 minutes, or the incremental IR-insulin area during the first 10 minutes (Figure 1). Young and older groups had similar patterns of late IR-insulin response until the third hour of glucose infusion, at which time the mean IR-insulin concentration of the young group continued to increase, while the mean IR-insulin-response of the older groups tended to flatten (Figure 1). Late phase responses were further ana-

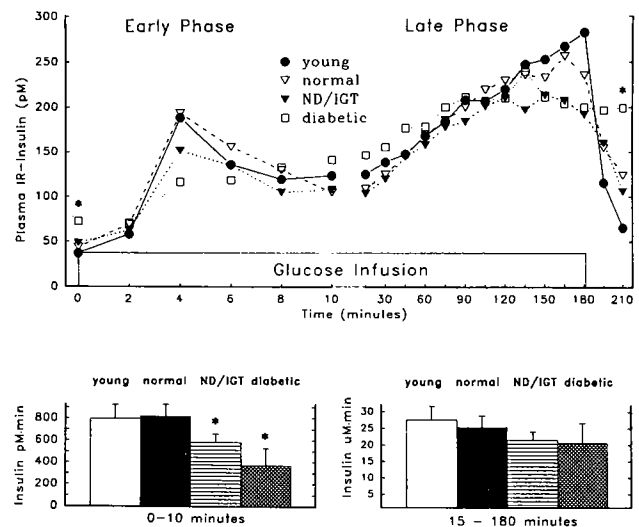


Figure 1. A. Mean plasma IR-insulin responses during a 3-hour hyperglycemic clamp and 30-minute recovery, divided to show early and late phases. B. Responses expressed as mean incremental area above baseline ± SE are presented in bar graphs. \*Different from young,  $p < .05$ .

lyzed as rates of change in plasma IR-insulin concentration for each hour. There were no significant differences in responses among groups for the first 2 hours, but during the third hour, older groups had lower mean rates of change in plasma IR-insulin (Figure 2).

When compared to the young group, older groups had slower rates of decline of plasma IR-insulin calculated as the rate of change in IR-insulin concentration during the 30-minute period following the glucose infusion (180–210 min, Figure 1,  $p < .05$ ). The rate of decline in insulin during this post-clamp period correlated with glucose disposal during the clamp ( $r = -.57$ ,  $p < 10^{-7}$ ), and the slower rate of decline was probably due to slower clearance of glucose and continued stimulus to insulin secretion.

Of the 23 older subjects with normal glucose tolerance, 12 had an incremental area under the glucose tolerance curve that was within 1 standard deviation of the mean of that of the young group ( $141 \pm 83$  (SD)  $\text{mM} \cdot \text{min}$ ). To identify characteristics in older people that might be responsible for maintenance of glucose tolerance comparable to that of normal young individuals, we analyzed separately this sub-

group of subjects designated strictly normal ( $157 \pm 14$  (SE)  $\text{mM}\cdot\text{min}$ ). The other 11 subjects in the older group with normal glucose tolerance were designated high normal ( $380 \pm 29$   $\text{mM}\cdot\text{min}$ ,  $p < .005$  vs strictly normal). There were no differences between the older strictly normal and high normal groups in age, gender, weight, body fat, or postabsorptive insulin or glucose concentration (Table 3). Glucose disposal during the clamp was also similar in the strictly normal and high normal groups ( $5.56 \pm .47$  vs  $5.23 \pm .48$   $\text{mmols}\cdot\text{kgFFM}^{-1}$  respectively, for 15–180 min). As it has been reported that glucose tolerance is associated with fitness as measured by oxygen uptake capacity (23), we determined that there was also no difference between the strictly normal and high normal groups in this parameter (Table 3).

In spite of these similarities to the strictly normal group, the high normal group had a different pattern of insulin response. Like the NIDDM group, the high normal group had a negative mean rate of change in plasma IR-insulin concentration during the third hour of hyperglycemic stimulus (Figure 3). In contrast, the insulin concentration of the strictly normal group continued to increase (Figure 3), and was not significantly different from that of the young group. Compared to the strictly normal group, the high normal group tended to have a more robust initial rate of increase in insulin between 0 and 4 minutes. The greater the initial rate of increase in insulin in the high normal subjects, the more pronounced was the later decline in insulin concentration between 120 and 180 minutes ( $r = -.77$ ,  $p < .01$ ). When subjects with strictly normal glucose tolerance were excluded, the decrease in glucose tolerance (i.e., increase in incremental glucose area) from high normal to nondiagnostic, impaired, and NIDDM correlated inversely with the magnitude of the initial rate of insulin response (Figure 4). Adding the rate of change during the third hour did not improve the correlation coefficient.

DISCUSSION

Glucose tolerance is determined by the balance between insulin secretion and insulin action. In previous studies that found no evidence of a decrement in insulin secretion with aging, it was concluded that a decrease in insulin action is responsible for the decline in glucose tolerance (5,7). In theory, this seems unlikely because diminished insulin action should result in an increase in blood glucose concentration and a compensatory increase in insulin secretion.

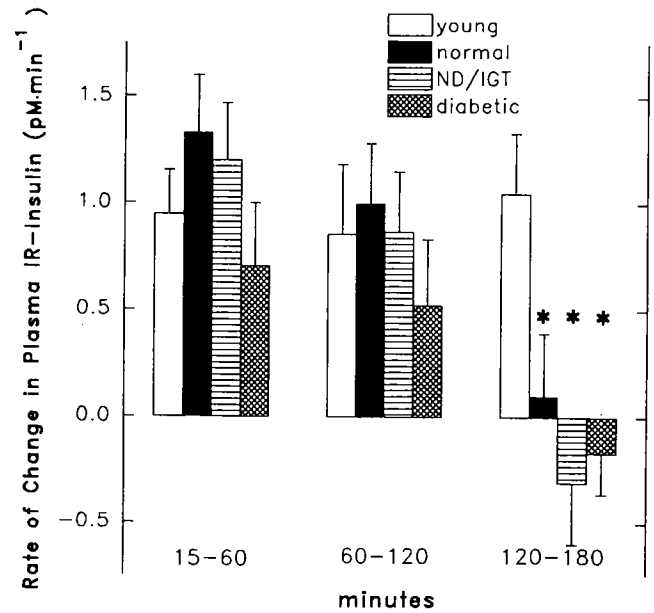


Figure 2. Rate of change in late plasma IR-insulin concentration during each hour of the clamp expressed as mean  $\pm$  SE. \*Different from young,  $p < .05$ .

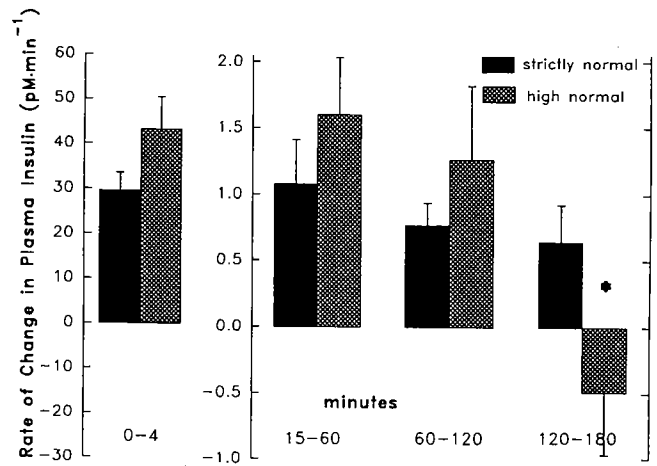


Figure 3. Initial rate of change in plasma IR-insulin concentration and rate of change during each hour of a hyperglycemic clamp expressed as mean  $\pm$  SE. \*Different from strictly normal,  $p < .05$ .

Table 3. Characteristics of Subjects with Normal Oral Glucose Tolerance

Group	n	Age (years)	Glucose <sub>0</sub> (mM)	Insulin <sub>0</sub> (pM)	Weight (kg)	Body Fat (%)	$\dot{V}O_{2\text{max}}$ ( $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )
Strictly normal	12	64 $\pm$ 1	5.70 $\pm$ 0.14	37 $\pm$ 9	77.8 $\pm$ 3.4	36.3 $\pm$ 2.5	23.8 $\pm$ 1.8
Men	4	65 $\pm$ 1	6.13 $\pm$ 0.30	60 $\pm$ 24	86.8 $\pm$ 9.1	25.7 $\pm$ 3.6	30.7 $\pm$ 3.1
Women	8	64 $\pm$ 1	5.48 $\pm$ 0.09	26 $\pm$ 3	73.3 $\pm$ 3.9	41.5 $\pm$ 0.6	20.4 $\pm$ 0.7
High normal	11	65 $\pm$ 1	5.47 $\pm$ 0.08	51 $\pm$ 13	73.0 $\pm$ 5.0	33.3 $\pm$ 2.6	23.4 $\pm$ 1.4
Men	5	64 $\pm$ 2	5.43 $\pm$ 0.07	43 $\pm$ 6	79.3 $\pm$ 6.0	26.5 $\pm$ 2.0	27.1 $\pm$ 1.7
Women	6	65 $\pm$ 2	5.50 $\pm$ 0.14	58 $\pm$ 24	67.8 $\pm$ 7.3	38.9 $\pm$ 2.7	20.2 $\pm$ 1.0

Notes. Values are expressed as mean  $\pm$  SE. Glucose<sub>0</sub> and insulin<sub>0</sub> are fasting, plasma and concentrations.

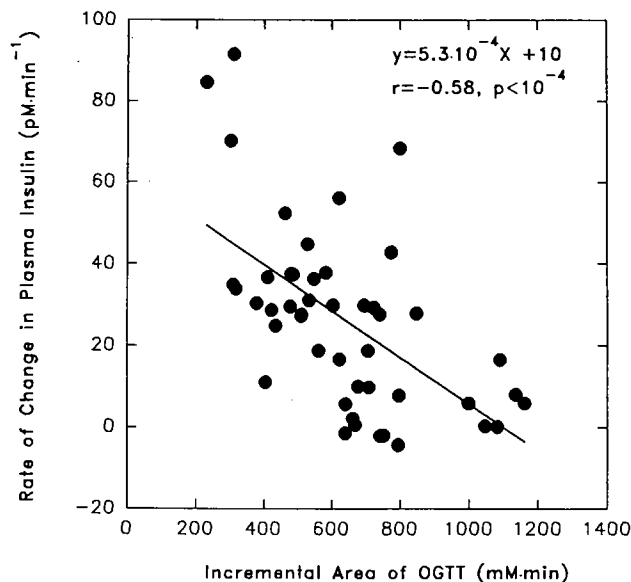


Figure 4. Correlation between glucose tolerance expressed as incremental area of OGTT over 0–180 minutes and initial rate of change in plasma IR-insulin for 0–4 minutes.

Two recent studies utilized an intravenous hyperglycemic challenge to evaluate the insulin response of glucose-intolerant, elderly men. Gumbiner et al. (9) performed an elegant study of 10 elderly men with abnormal glucose tolerance and 8 young subjects matched for body mass index. After analysis of c-peptide kinetics during a 180-minute hyperglycemic clamp and an intravenous glucose infusion modeled to the glycemic challenge of the oral glucose tolerance test, they concluded that the  $\beta$ -cell secretory response to intravenous glucose was relatively low in the glucose-intolerant older group. Chen et al. (8), who used Bergman's minimal mathematical model of a frequently sampled intravenous glucose and arginine infusion test, found that glucose intolerance in normal weight elderly men was associated with both insulin resistance and an abnormal insulin response characterized by a lower late insulin response to glucose and decreased arginine potentiation.

However, it is not clear from studies on glucose-intolerant subjects whether a reduction in glucose-stimulated insulin secretion follows or precedes glucose intolerance. This point is particularly important in view of evidence that glucose infusion and prolonged hyperglycemia cause suppression of glucose-stimulated insulin secretion even after blood glucose drops to near-normal levels (24). In this regard, Becaro et al. (10) recently used a frequently sampled intravenous glucose tolerance test to study nonobese Italian men with apparently normal glucose tolerance. They found no evidence for insulin resistance, but after analysis of c-peptide patterns, they concluded  $\beta$ -cell activity was lower in the older men.

In our study, we used a prolonged, uniform, intravenous glucose challenge to compare the glucose-stimulated insulin response of older men and women with various levels of glucose tolerance to that of young subjects. Our findings

confirm previous reports that the early insulin response of people with NIDDM is blunted (25,26). Although results from some studies support the suggestion that glucose intolerance in at least some aged individuals is associated with a lower early response (9,27,28), results of other studies of older subjects indicate first phase secretion is normal in nondiabetic subjects (7,8,26). In our study, the early insulin response was not significantly decreased in older subjects with normal glucose tolerance (strictly normal or high normal), but was decreased in those with nondiagnostic or impaired glucose tolerance or NIDDM (Figure 1). These findings suggest that the decrease in first phase response occurs late in the development of glucose intolerance and hyperglycemia. The correlation between glucose tolerance and the initial rate of insulin response suggests that development of severe glucose intolerance is associated with progressive blunting of the early response (Figure 4).

The mild decrease in glucose tolerance of the high-normal group was associated not with a blunt but with a surprisingly robust rate of insulin response initially and during the first 2 hours of the late response, before the rate dropped precipitously (Figure 3). Because the magnitude of the initial rate of increase in insulin correlated with the magnitude of the third hour decrease in rate of insulin response, one might speculate that mild postprandial hyperglycemia predisposes pancreatic islets to an exuberant initial response, depleting a pool of stored insulin that is responsible for the sustained response.

These results suggest that an early, small decrease in glucose tolerance may be associated with a relatively exuberant early insulin response which becomes gradually blunted as glucose tolerance decreases. It seems possible that the pattern of insulin secretion in the high normal group represents an early stage in the continuum of the development of impaired glucose tolerance in some individuals, with mild hyperglycemia initially resulting in an exaggerated early insulin response. Later, with progressive glucose intolerance, a blunted early response occurs.

The decline in rate of increase in plasma insulin concentration during the third hour of a hyperglycemic clamp was another abnormality in insulin response present in the subjects with mild and more severe glucose intolerance, but not in those with strictly normal oral glucose tolerance. Similar to our results, Gumbiner et al. (8) observed a flattening of the calculated insulin secretory response of their older glucose-intolerant subjects during the third hour of a hyperglycemic clamp. They also observed, however, a similar pattern in their younger control subjects. Their young subjects (age  $30 \pm 5$  years) were matched for BMI with older subjects and had reduced glucose tolerance, when compared to our young subjects. The 60 minute and 120 minute mean glucose concentrations were respectively 10.5 (189) and 7.3 mM (131 mg/dl) (8). The incremental area under the 180 minute oral glucose tolerance curve was approximately 380 mmols·min, which was more than 2 standard deviations above the mean of our young group (see Table 1), and outside the definition of strictly normal used in our study. In these subjects with relatively reduced glucose tolerance, a lack of continued increase in late insulin secretion is compatible with our results.

The physiological significance of abnormal early and late insulin responses to intravenous glucose administration and hyperglycemia is not clear, as neither has a clear equivalent after a normal meal. However, these findings do provide evidence that development of abnormal glucose tolerance in older individuals is associated with development of abnormalities of glucose-stimulated insulin secretion. It seems reasonable that progressive abnormalities of glucose-stimulated insulin secretion and the development of insulin resistance together are responsible for deterioration in glucose tolerance.

In summary, we have found a lack of a sustained insulin response to prolonged hyperglycemia in a group of older subjects with minimally decreased glucose tolerance. More severe deterioration in glucose tolerance, i.e., impaired glucose tolerance or NIDDM, was associated with blunting of the early insulin response, and a decreased insulin response during the third hour of hyperglycemia. These abnormalities were not present in some older individuals, who were indistinguishable from young, normal people in terms of glucose tolerance and pattern of insulin response to 3 hours of hyperglycemia. This finding provides evidence that a deterioration of glucose tolerance is not an inevitable concomitant of aging, at least up to 70 years of age.

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