Glucose Clearance Is Delayed after Hyperglycemia in Healthy Elderly Men

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ABSTRACT Delayed glucose clearance after hyperglycemia may contribute to insulin resistance. Rates of glucose and insulin decay were measured after 3 h of sustained hyperglycemia (10 mmol/L) in 8 healthy older men (66 ± 2 y) and were compared with those of 8 younger men (22 ± 1 y). Fractional glucose clearance rates were calculated by regression analysis. Insulin decay was estimated from insulin levels through 30 min postinfusion. Abdominal adiposity was estimated from waist-to-hip ratios. Body weight and basal plasma glucose, insulin and C-peptide concentrations did not differ between groups. Fat mass, abdominal adiposity, fasting serum triglycerides and total cholesterol, although normal, were higher (P < 0.05) in the older group. The elderly group experienced lower glucose clearance rates (1.9 ± 0.2 vs. 2.9 ± 0.1%/min, P < 0.002) and higher plasma insulin after hyperglycemia (P < 0.03). Glucose and insulin decay correlated with glucose infusion rates (r = 0.88, P < 0.0002 and r = 0.51, P < 0.05). Delayed glucose clearance was associated with greater abdominal adiposity (r = −0.56, P < 0.03), higher serum triglycerides (r = −0.73, P < 0.003) and elevated serum cholesterol (r = −0.56, P < 0.04). In conclusion, modest increases in abdominal adiposity and circulating lipids are associated with abnormal glucose clearance in clinically healthy older men; this may be a precursor to the development of insulin resistance and related complications that arise from prolonged postprandial hyperglycemia.


KEY WORDS: • aging • obesity • diabetes
• insulin resistance

Human aging is associated with the development of glucose intolerance (1), abnormal pancreatic β-cell secretion (2,3) and insulin resistance (4–8), although these observations are not universal (9). In contrast, some healthy elderly men and women maintain normal fasting glucose and insulin levels, and a normal response to ingested glucose. However, it has also been suggested that they may be unable to adequately clear circulating glucose under postprandial conditions (3). The mechanisms responsible for these abnormalities in carbohydrate metabolism are unknown.

Older age leads to changes in body composition that include increases in body weight, fat mass and abdominal adiposity. These age-related changes are thought to contribute to a deterioration in carbohydrate metabolism and insulin action (10). Other factors such as dyslipidemia (11), chronic disease and the use of medications may also add to poor glucose regulation in the elderly (12). Further study is required to explain the extent to which these metabolic changes are part of a continuum of dysmetabolism throughout the adult lifespan, beginning with increased adiposity and decreased insulin sensitivity, and proceeding to progressive impairments and related complications in later life.

The purpose of this investigation was to examine carbohydrate metabolism in healthy sedentary older men after a period of sustained hyperglycemia. We used the hyperglycemic clamp as the stimulus because it allowed us to control the metabolic and hormonal milieu to a much greater extent than a mixed meal, or glucose ingestion. The decay profile for glucose and insulin concentrations after the termination of glucose infusion in the older group was compared with that of a group of healthy sedentary young men. In addition, we were interested in the potential contribution of metabolic disorders such as hyperlipidemia and abdominal obesity to the regulation of glucose metabolism with advancing age.

SUBJECTS AND METHODS

Subjects. Sixteen men (8 older, age 59–75 y and 8 younger, age 21–28 y) participated in this investigation. These subjects were part of a larger study examining the effects of resistance exercise on glucose metabolism in the elderly (13). The experimental protocol was approved by the Institutional Review Board at Penn State University and all subjects provided written informed consent before enrollment in the study. All of the subjects were healthy, were free of any acute/chronic disease and did not use any medications that would affect carbohydrate or lipid metabolism. In addition, all of the subjects were sedentary, with a similar activity level between groups, as assessed by a physical activity questionnaire. None of the participants were engaged in any regular exercise regimen for at least 6 mo before testing. All subjects had a normal plasma glucose response to a 75-g oral glucose tolerance test (14) and did not have a family history of type 2 diabetes.

Height without shoes was measured to the nearest 1.0 cm. Body weight was measured to the nearest 0.1 kg. Body circumferences were measured to the nearest 1.0 cm for the waist (at the level of umbilicus) and hip (at the point of widest circumference around the buttocks). Waist-to-hip ratio (WHR) was calculated to estimate

Abbreviations used: FFA, free fatty acid; FFM, fat-free mass; QG, fractional glucose clearance; I, insulin; M, glucose infusion rate; WHR, waist-to-hip ratio.
abdominal adiposity (10). Body density and body fat were determined by hydrostatic weighing (13).

**Study design.** To control prior diet and physical activity, the subjects resided in the General Clinical Research Center for three nights and two consecutive days before testing. During residence, the subjects consumed a eucaloric diet (60% carbohydrate, 25% fat, 15% protein). Glucose infusions were performed on d 3 of residence.

**Hyperglycemic infusion.** Sustained hyperglycemia was achieved by using the hyperglycemic clamp (180 min, 10.0 mmol/L), as described previously (13). After an overnight fast (~12 h), baseline blood samples were drawn for plasma glucose, insulin and C-peptide determination. Subsequently, plasma glucose concentrations were raised to 10.0 mmol/L within 15 min by using a primed glucose infusion (200 g/L dextrose) with a variable-speed infusion pump (Harvard Apparatus, South Natick, MA). Plasma glucose concentrations were maintained at 10.0 mmol/L for another 165 min by a variable-rate infusion based on the prevailing glucose concentration. Blood samples (0.5 mL) were drawn every 5 min and glucose concentrations were used to adjust the infusion rate throughout the procedure. At the conclusion of the hyperglycemic stimulus, plasma glucose levels were measured every 5 min (180–210 min) for the assessment of fractional glucose clearance. Plasma insulin levels were measured at 15 and 30 min after the infusion (180–210 min).

**Analytical methods.** Plasma glucose concentrations were measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin and C-peptide concentrations were determined in duplicate by double antibody RIA (Linco Research, St. Charles, MO and Diagnostic Products, Los Angeles, CA). Serum triglycerides and total cholesterol were measured using enzymatic-colorimetric procedures (Hitachi 747, Roche, Indianapolis, IN).

**Glucose and insulin clearance.** Fractional glucose clearance (Gc, %/min) was calculated from plasma glucose concentrations at 180 min (mean, 150–180 min) and the prevailing glucose levels obtained every 5 min thereafter (time; t, 180–210 min), as described previously by Elahi et al. (3). Regression analysis was used to estimate Gc for each subject, using the following equation, where t = 180, 185, 190, 195, 200, 205 and 210 min.

\[
[\text{glucose}] = [\text{glucose}]_{180} \times (1 - Gc \times t)
\]

Insulin decay was estimated by calculating the changes (Δ) in plasma insulin concentrations at 15- and 30-min postinfusion, as indicated.

\[
\Delta [\text{insulin}]_{15} = [\text{insulin}]_{15} - [\text{insulin}]_{0}
\]

\[
\Delta [\text{insulin}]_{30} = [\text{insulin}]_{30} - [\text{insulin}]_{10}
\]

**Statistics.** The MIXED procedure for the Statistical Analysis System (SAS Institute, Cary, NC) was used for ANOVA by the rank transformation (nonparametric) approach. Primary dependent variables and descriptive data were analyzed by a one-way ANOVA. Glucose, insulin and C-peptide responses were analyzed by two-way repeated-measures ANOVA with two main effects, Group (Younger and Older) and Time (180–210 min). Model-adjusted P-values from a comparison of the least-squared means were used to determine differences at various time points. A Group-by-Time interaction was used to demonstrate group differences in overall response. A multiple stepwise regression analysis and univariate analyses (Spearman product-moment correlations) were performed to determine the relationships between glucose clearance, insulin decay, glucose infusion rate (M) values, triglycerides, cholesterol and body composition. All values are expressed as mean ± SEM. An α-level of 0.05 was used to determine significant differences.

**RESULTS**

Subjects did not differ in body weight, fat-free mass (FFM) and BMI, but the older group had a higher fat mass, WHR, fasting serum triglycerides and fasting serum total cholesterol (Table 1). All subjects had a normal response to an oral glucose tolerance test, as indicated by 2-h values (5.7 ± 0.5 and 6.0 ± 0.6 mmol/L for young and old subjects, respectively).

Baseline plasma glucose (Old 5.3 ± 0.1, Young 5.1 ± 0.1 mmol/L), insulin (I; Old 57 ± 4, Young 52 ± 2 pmol/L) and C-peptide (Old 0.4 ± 0.1, Young 0.3 ± 0.1 nmol/L) concentrations did not differ between the two age groups and were within normal limits. Both groups achieved similar glucose levels (Old 10.0 ± 0.0, Young 10.0 ± 0.1 mmol/L) during the infusion period and did not differ in insulin (Old 225 ± 35, Young 215 ± 28 pmol/L), and C-peptide (Old 1.4 ± 0.2, Young 1.3 ± 0.2 nmol/L) responses to hyperglycemia. The amount of glucose required to maintain hyperglycemia (M values, calculated from the glucose infusion rates and adjusted for the glucose equivalent space and urinary glucose loss, if any) was lower in older than in younger men [35.6 ± 3.3 vs. 56.7 ± 4.4 μmol/(kg FFM min), P < 0.002]. M-to-I ratios (M divided by the prevailing insulin levels for 150–180 min) were also lower in the older group [18.9 ± 2.8 vs. 30.0 ± 3.9 μmol·kg FFM·min−1·(pmol/L insulin)−1, P < 0.04].

Although glucose was similar during hyperglycemia, glucose decay profiles differed between groups (Fig. 1). Indeed, Gc (%/min) was slower in the older compared with the younger group (1.9 ± 0.2 vs. 2.9 ± 0.1%/min, P < 0.002). In addition, insulin decay was also slower at 30 min postinfusion in older than in younger men (124 ± 22 vs. 73 ± 7%/min, P < 0.03). Univariate analysis revealed that both glucose clearance (Fig. 2; r = 0.88, P < 0.0002) and insulin decay (r = 0.51, P < 0.05) were related to glucose infusion rates. Furthermore, a lower Gc was associated with a greater WHR (Fig. 3; r = −0.56, P < 0.03), higher serum triglycerides (Fig. 3; r = −0.73, P < 0.003) and higher serum total cholesterol (r = −0.56, P < 0.04). Using stepwise regression analysis, the glucose infusion rate was found to be a primary predictor of glucose decay (r = 0.86, P < 0.0001) and explained >72% of the variance after adjusting for sample size and number of predictors in the model. Abdominal adiposity entered the regression analysis at the second step (r = 0.90, P < 0.0001), and contributed an additional 6% to the adjusted variance. However, serum triglyceride and cholesterol concentrations were not independent predictors of glucose decay.

**DISCUSSION**

Despite a normal response to an oral glucose challenge, the older men in this study displayed abnormal glucose clearance after the hyperglycemic stimulus. Insulin levels also remained higher in the elderly group at 30 min, resulting in moderate hyperinsulinemia. The reduced fractional clearance of glucose after hyperglycemia was directly related to the glucose infusion rate, or M-value, during the clamp. Furthermore, glucose infusion rates were lower in the older men, and insulin sensitivity estimated from the

| Table 1 Clinical characteristics of the men1 |
|-----------------|-----------------|
|                | Older           | Younger         |
| Age, y          | 66 ± 2*         | 22 ± 1          |
| Body weight, kg | 75.7 ± 4.2      | 76.1 ± 5.5      |
| BMI, kg/m²      | 25.5 ± 1.2      | 23.4 ± 1.9      |
| Fat-free mass, kg | 58.5 ± 2.9    | 63.9 ± 3.0      |
| Fat mass, kg    | 17.2 ± 1.7*     | 12.2 ± 3.0      |
| Waist-to-hip ratio | 0.91 ± 0.01*   | 0.83 ± 0.02     |
| Serum triglycerides, mmol/L | 13.6 ± 1.7* | 8.6 ± 0.8      |
| Serum total cholesterol, mmol/L | 4.9 ± 0.4* | 3.7 ± 0.2      |

1 Values are means ± SEM; n = 8. * Different from the younger group, P < 0.05.
2 Due to technical difficulties, there was insufficient blood to measure fasting lipids in one of the younger subjects (n = 7).
M/I ratios was also lower in the elderly. Because most of the glucose infused during the clamp is taken up by skeletal muscle, these data suggest that insulin resistance in skeletal muscle may be a major contributing factor to the delayed glucose clearance in the elderly. These data are consistent with a report by Elahi et al. (3) of a progressive decline in glucose decay after hyperglycemia in young healthy subjects compared with subjects that were middle-aged, old healthy, and old with impaired glucose tolerance. The physiologic effect of this delayed glucose clearance was not apparent in the older men in our study because they had normal clinical indices. However, prolonged chronic hyperglycemia may exacerbate insulin resistance and contribute to type 2 diabetes (15). In addition, hyperglycemia may induce glucose toxicity via the hexosamine pathway, which is also associated with the development of insulin resistance (16–18). In the elderly, particularly in those with type 2 diabetes, hyperglycemia may contribute to the formation of advanced glycation end products (19) and lead to a variety of related complications such as microvascular disease, nephropathy, retinopathy and neuropathy (20). Although it is clear that the subjects in our study did not have any of these complications, they did experience more prolonged hyperglycemia than the young control group. This places them at greater risk for developing such complications, and highlights the importance of understanding the mechanisms that contribute to the development of hyperglycemia and the identification of strategies to either alter insulin resistance, or the magnitude and duration of postprandial glycemia in this population.

Abnormal clearance of glucose after hyperglycemia was also associated with abdominal adiposity. Although the older subjects clearly had more body fat than the younger men, they were not obese per se, but had a “normal” increase in adiposity, particularly in the abdominal region, which is representative of a sedentary older population (21). Because we did not find a correlation between body fat or BMI and glucose decay, we conclude that the distribution of body fat, rather than total body fat, is a more important determinant of dysmetabolism in these older men. Previous studies have shown that the insulin resistance of aging is related to greater central obesity, independent of chronological age (10,22). Clinically, body fat accumulation in the abdominal region has also been closely linked to increased risk for type 2 diabetes and cardiovascular disease (23). The present findings are unique in that we associate abdominal adiposity with glucose intolerance, as measured by postinfusion glucose decay. Thus, these data provide further support for the growing body of literature linking central obesity and abnormal glucose homeostasis.

![Figure 1](https://academic.oup.com/jn/article-abstract/133/7/2363/4688387)

**FIGURE 1** Glucose and insulin concentrations in older and younger men after termination of 180 min of sustained hyperglycemia. Fractional glucose clearance ($G_k$, %/min) was calculated for each subject by regression analysis of glucose concentrations from 180 to 210 min. *Different from the younger group at that time, $P < 0.001$. †Different from the younger group, $P < 0.002$. **Different insulin response than the younger group, $P < 0.02$.**

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![Figure 2](https://academic.oup.com/jn/article-abstract/133/7/2363/4688387)

**FIGURE 2** Fractional glucose clearance is related to the amount of glucose metabolized during hyperglycemia in 16 younger (□) and older (○) men with normal glucose tolerance. Fractional glucose clearance ($G_k$, %/min) was calculated for each subject by regression analysis of glucose concentrations from 180 to 210 min. Metabolized glucose was calculated from glucose infusion rates (M) for 150–180 min.

**FIGURE 3** Delayed glucose clearance after hyperglycemia is associated with abdominal adiposity (A) and fasting serum triglycerides (B) in 15 younger (□) and older (○) men with normal glucose tolerance. Fractional glucose clearance ($G_k$, %/min) was calculated for each subject by regression analysis of glucose concentrations from 180 to 210 min. Triglyceride concentrations were not available for one younger subject due to technical difficulties.
In addition, the present study may shed some light on the mechanisms by which abdominal adiposity in the older group affects glucose homeostasis. As noted in numerous reports, abdominal adiposity is related to dyslipidemia, including elevated triglycerides and free fatty acid (FFA) levels (24–27). In fact, the older men had elevated levels of serum triglycerides and total cholesterol compared with the younger group. However, all but one of the older subjects had serum triglycerides within normal limits (4.4–17.4 mmol/L) and three of the older subjects had slightly elevated total cholesterol (>5.18 mmol/L). Indeed, serum triglycerides and cholesterol levels were both correlated with delayed glucose clearance. These data suggest that subjects with higher circulating lipids are less able to clear glucose during the postinfusion period. In fact, Kelley et al. (26,27) and others (25,28) found strong relationships among insulin resistance, elevated triglycerides, skeletal muscle phospholipids and higher abdominal body fat. In addition, increased muscle triglycerides have been associated with insulin resistance and lower lipid oxidation rates (26). It is possible that the greater abdominal fat in older men leads to antilipolytic insulin resistance, increased lipolysis and FFA flux to the liver, which causes an overproduction of VLDL, resulting in hypertriglyceridemia and hypercholesterolemia (24,25). Moreover, other studies have demonstrated that higher circulating FFA levels cause hepatic insulin resistance, hyperinsulinemia and hyperglycemia (29). Thus, the present data suggest that hyperlipidemia, secondary to elevated abdominal fat, may contribute to delayed glucose clearance in otherwise healthy older men. Our findings provide additional support for the importance of aerobic and resistance exercise programs for the elderly, which have been shown by several investigators (8,30) to reduce obesity and improve insulin action in sedentary older adults.

In conclusion, these data demonstrate a subtle but clear difference in the efficiency of glucose disposal between younger and older men, and the lack of a sufficient compensatory response in insulin secretion to overcome the relative insulin resistance in the older group. When these deficiencies are placed in context with other indices of impaired fuel metabolism such as accretion of abdominal fat and elevated lipids, the data reinforce the concept of a continuum of dysmetabolism throughout the adult lifespan. This continuum may begin with increased adiposity and decreased insulin sensitivity in early life and proceed to progressive impairments with the passage of time until related complications manifest in mid- and especially late life. To prevent age-related complications associated with prolonged hyperglycemia, even clinically normal older adults should engage in a lifestyle that promotes healthy eating and exercise, to increase peripheral sensitivity to insulin, decrease abdominal adiposity, decrease circulating lipids and improve glucose clearance.

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LITERATURE CITED