# Glucose Metabolism in Older Adults: A Study Including Subjects More Than 80 Years of Age

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**OBJECTIVE:** This study was undertaken to understand the dynamics of glucose metabolism in healthy non-diabetic subjects older than age 80 (old-old) compared with subjects aged 61 to 79 (young-old), as well as to compare healthy older subjects with impaired glucose tolerance (IGT) with older subjects with normal glucose tolerance (NGT).

**DESIGN:** A cross sectional, observational study.

**SETTING:** A university hospital clinical research center.

**PARTICIPANTS:** There were 28 community-dwelling adults, 10 older than age 80 and 18 aged 61 to 79. Thirteen of these people had NGT and 15 had IGT. Subjects were not taking any medication that interfered with glucose tolerance.

**MEASUREMENTS:** Status of glucose tolerance was determined by an oral glucose tolerance test categorized as NGT or IGT according to WHO criteria. Insulin sensitivity ($S_I$) and glucose effectiveness ($S_G$) were assessed using a tolbutamide-assisted intravenous glucose tolerance test (IVGTT). The data were analyzed using the Minmod modeling program. Glucose tolerance ($K_g$) and the acute insulin response to glucose ($AIR_g$) were calculated from the IVGTT.

**RESULTS:** There were no significant differences between the young-old and old-old in body mass index or in plasma glucose, insulin, or C-peptide levels in the fasting state or during the OGTT. Values for $K_g$, $S_I$, $S_G$, and AIRg from the IVGTT were similar in the two age groups. When the subjects were classified by glucose tolerance status, the subjects with NGT had age, gender, and body mass index similar to the subjects with IGT. Older people with IGT had a lower Kg and tended to have higher fasting glucose and similar fasting insulin compared with people with NGT. IGT subjects had lower $S_I$ and tended to have lower $S_G$. The AIRg in IGT subjects tended to be low rather than high when compared with older people with NGT.

**CONCLUSION:** Otherwise healthy adults more than 80 years of age have measures of glucose metabolism similar to people aged 61 to 79. The presence of IGT in older adults is associated with insulin resistance, regardless of patient age. We hypothesize that the lack of pancreatic islet compensation for insulin resistance may contribute to impaired glucose tolerance in older adults. **J Am Geriatr Soc 45:813–817, 1997.**

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The prevalence of diabetes and impaired glucose tolerance increases with age.[1] More than 40% of individuals aged 65 to 74 years of age have impaired glucose tolerance (IGT) or diabetes mellitus.[2] Despite the prevalence of glucose intolerance and diabetes in the older population, the pathophysiological mechanisms involved in these disorders have not been studied in the oldest age group. Previous studies of mechanisms contributing to age-related glucose intolerance have focused on people aged 60 to 75 years. This present study was undertaken to understand the dynamics of glucose metabolism in healthy non-diabetic subjects more than 80 years of age (old-old) compared with subjects aged 61 to 79 (young-old), as well as to compare healthy older subjects who have IGT with older subjects who have normal glucose tolerance.

## METHODS

### *Research Design*

The subjects were community-dwelling adults older than age 60 listed in the registry of the Human Subjects Core maintained by the Claude Pepper Older Americans Independence Center at the University of Michigan. A total of 28 subjects were recruited: 18 young-old (61–79 years) and 10 old-old (80–88 years). Subjects with a body mass index greater than 30 kg/m$^2$ were excluded. All subjects were in good general health, with no personal history of diabetes, nor were they taking medications known to interfere with glucose tolerance. No subject reported participating in a formal exercise training program. Subjects gave no history of significant illness in the 6 months before the study; no biochemical or hematological abnormalities were found on routine laboratory screening tests.

All studies were performed in the Clinical Research Center (CRC) at University of Michigan Hospitals after informed written consent was given. This study was approved by the University of Michigan Human Use Committee. All subjects received a history and physical examination,



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EKG, and an oral glucose tolerance test (OGTT). The CRC dietitian provided instruction to each subject regarding an adult glucose tolerance preparatory diet including 250 gm of carbohydrate per day for 3 days before the OGTT. After a 12-hour overnight fast, an antecubital intravenous line was inserted, and the subjects ingested 75 g of a standard glucose solution within 2 minutes. Blood samples for plasma glucose were drawn before and 30, 60, 90, and 120 min after glucose ingestion. Results of the OGTT were interpreted using World Health Organization (WHO) criteria.[3] Subjects meeting criteria for non-insulin-dependent diabetes mellitus were excluded. IGT is defined as a fasting plasma glucose level less than 140 mg/dL and a 2-hour value ≥ 140 mg/dL but less than 200 mg/dL. Normal glucose tolerance (NGT) is defined by not meeting criteria for either diabetes or IGT.

Subjects meeting WHO criteria for IGT or NGT were scheduled to have a frequently sampled tolbutamide-assisted intravenous glucose tolerance test (IVGTT) using a standard protocol described previously.[3] Subjects were asked to follow the glucose tolerance preparatory diet for 3 days before the IVGTT. Each IVGTT was performed after a 12-hour overnight fast. With the subjects in the supine position, one intravenous catheter was placed in an antecubital vein for infusion of 50% glucose or normal saline and another was placed retrogradely into a dorsal vein of the contralateral hand. This hand was then placed in a warming box heated to 60°C to obtain arterialized venous blood samples. The catheters were kept patent with 0.9% NaCl mixed with sodium heparin 2000 units/L.

After a 20 min recovery period, three baseline samples were drawn at 5 min intervals for measurement of fasting glucose, insulin and catecholamine levels. Then 50% dextrose (300 mg/kg) was given as an intravenous bolus over 20 seconds. Blood samples (3 ml) were then drawn at frequent intervals for 180 min after the start of the glucose bolus according to the IVGTT protocol.[4] Twenty min after glucose administration, tolbutamide 135 mg/m$^2$ was given intravenously to further stimulate insulin secretion.[4,5] Heart rate and blood pressure were monitored at 15 min intervals throughout the study. The IVGTT protocol was well tolerated by all subjects. No adverse effects were observed.

### *Laboratory Methods*

Plasma was stored at -20°C until assayed. Plasma glucose concentration was measured by the Auto Analyzer glucose oxidase method, and the plasma insulin and C-peptide concentrations were measured by radioimmunoassay in the ligand core laboratory of the Michigan Diabetes Research and Training Center. Plasma catecholamine levels were measured using a radioenyzmatic assay as previously described.[6]

### *Data Analysis*

The IVGTT results were analyzed using the MinMod algorithm,[5] which includes estimation of $S_I$ (insulin sensitivity index), the increase in fractional glucose disappearance divided by the increase in effective insulin concentration ($10^{-4}$)/min/$\mu$U/mL. The algorithm also estimates $S_G$ (glucose effectiveness), which is the fractional disappearance rate of glucose at the basal insulin level ($10^{-2}$)/min. Insulin secretion was assessed as the acute insulin response to glucose ($AIR_g$, $\mu$U/mL) or first phase insulin secretion, the mean of the values of insulin levels at 3, 4, and 5 min after the iv glucose bolus minus the basal insulin level. The assessment of glucose tolerance ($K_g$) is the rate of plasma glucose disappearance from 5 to 19 minutes after iv glucose (%/min).

All data were analyzed using analysis of covariance with the SAS computer program. A $P$ value less than .05 was considered significant. Univariate analysis was carried out to compare individual parameters of interest between groups. To adjust for the influence of potential confounding variables, linear regression models were developed separately for $S_I$, $S_G$, $K_g$, and $AIR_g$. Regression models considered in this analysis are equivalent to analysis of covariance. The key independent variables in the regression included age and glucose tolerance status. The age by glucose tolerance interaction was also considered, but the results were not significant in all models. The remaining covariates in the model, such as gender, BMI, plasma norepinephrine and epinephrine, and systolic and diastolic blood pressure, were used to adjust for potential confounding. Age was considered in the model both as a continuous and as a categorical variable. The effects of interest were tested using an F-ratio test by comparing nested regression models with and without the tested effect.

## RESULTS

The subjects were classified by age and glucose tolerance status (see Table 1). The young-old group included nine men and nine women, and the old-old group one man and nine women. There were no significant differences between the young-old and old-old groups in body mass index, fasting plasma glucose, insulin, C-peptide, and norepinephrine or epinephrine levels. Systolic, but not diastolic, blood pressure was significantly higher in the old-old compared with the young-old group. As shown in Figure 1, plasma glucose, insulin, and C-peptide levels during the OGTT were similar in the two age groups ($P$ = .95, .63, and .35, respectively by ANOVA). As shown in Figure 2, measures of dynamics of glucose metabolism from the IVGTT, represented by Kg, $S_I$, $S_G$ and AIRg, were also similar in the young-old group and the old-old group. No age group difference was detected when the analysis was limited to the nine old-old women compared with the nine young-old women (all $P$ values > 0.35).

When the subjects were classified by glucose tolerance status, the 13 subjects with NGT had age, gender, body mass index, blood pressure, and plasma catecholamine levels similar to the 15 subjects with IGT (see Table 1). The IGT subjects tended to have higher fasting glucose and similar fasting insulin and C-peptide compared with people with NGT. Although plasma glucose levels were higher during the OGTT in those with IGT (by definition), plasma insulin and C-peptide levels were similar in IGT and NGT groups ($P$ = .54 and .67, respectively, by ANOVA). As shown in Figure 3, the IGT subjects had lower Kg and $S_I$ values and tended to have a lower $S_G$. The evaluation of acute insulin secretion showed that people with IGT tended to have lower rather than higher AIRg when compared with older people with NGT (see Figure 3).

The results from the regression models adjusting for other covariates are consistent with the univariate analysis presented above. This analysis confirms that the significant difference in $S_I$ between NGT and IGT subjects is independent of other covariates ($P$ = .02). After adjusting for other covariates, the difference between NGT and IGT groups in $K_g$ is of borderline significance ($P$ = .09), suggesting that other

**Table 1. Characteristics of Study Subjects**

| | Subjects Grouped by Age | | Subjects Grouped by Oral Glucose Tolerance+ | |
|---|---|---|---|---|
| | Young-old | Old-old | NGT+ | IGT+ |
| n | 18 | 10 | 13 | 15 |
| Age (years) | 69 ± 1 | 85 ± 1** | 72 ± 3 | 76 ± 2++ |
| Gender (M/F) | 9/9 | 1/9 | 5/8 | 5/10 |
| Body mass index (kg/m$^2$) | 26 ± 1 | 24 ± 1 | 24 ± 1 | 26 ± 1 |
| Systolic blood pressure (mm Hg) | 135 ± 3 | 153 ± 8* | 139 ± 7 | 144 ± 4 |
| Diastolic blood pressure (mm Hg) | 73 ± 2 | 76 ± 3 | 74 ± 2 | 74 ± 2 |
| Heart rate (beats/min) | 67 ± 2 | 65 ± 2 | 66 ± 2 | 66 ± 1 |
| Fasting plasma glucose (mg/dL) | 105 ± 2 | 103 ± 4 | 99 ± 2 | 108 ± 3++ |
| Fasting plasma insulin (μU/mL) | 15 ± 1 | 14 ± 1 | 14 ± 1 | 15 ± 1 |
| Fasting plasma C-peptide (ng/mL) | 2.6 ± 0.2 | 2.1 ± 0.3 | 2.3 ± 0.2 | 2.5 ± 0.2 |
| Plasma norepinephrine (pg/mL) | 362 ± 28 | 383 ± 32 | 376 ± 34 | 364 ± 28 |
| Plasma epinephrine (pg/mL) | 66 ± 6 | 71 ± 7 | 66 ± 4 | 70 ± 7 |

Values are mean ± SEM.
+By WHO criteria: NGT = normal glucose tolerance; IGT = impaired glucose tolerance.
++$P \leq .015$ NGT vs IGT.
*$P = .025$ old-old vs young-old.
**$P < .001$ old-old vs young-old.

factors may contribute to the observed difference. The differences between NGT and IGT groups for $AIR_g$ and $S_g$ are also of borderline significance after adjustment for covariates ($P = .09$ and 0.12, respectively). Similarly, this analysis confirmed the lack of significance of the differences between old-old and young-old groups for $S_I$, $K_g$, $AIR_g$, and $S_G$ (all $P \geq 0.35$).

## DISCUSSION

This study was designed to compare the dynamics of glucose metabolism between healthy non-diabetic, non-obese subjects more than 80 years old and subjects 61 to 79 years old, as well as among healthy older adults classified by glucose tolerance status according to WHO criteria regardless of age. When groups were matched for glucose tolerance status, we did not detect poorer measures of glucose metabolism in the subjects more than 80 years old. Similarly, Paolisso et al. have recently reported no decrease of insulin action in a group of Italian centenarians with normal glucose tolerance compared with younger age groups.[7] These results raise the question of whether we studied a subgroup of older "survivors" who are especially healthy and physically fit. We recognize that with the limited size of our study population, small differences betwen groups could have been missed.

Factors such as increased adiposity, hypertension, decreases in physical activity, and/or modification of dietary factors, which can be associated with insulin resistance in older people,[1,8–12] were not specifically controlled for in our study although some were included in the statistical analysis. The centenarians studied by Paolisso et al. had lower body weight and better glucose tolerance than their young-old comparison group.[7] Obesity is not likely a confounding factor in our results since we excluded individuals whose BMI was greater than 30 kg/m$^2$. However, since we do not have measures of body composition or central adiposity, we cannot exclude the potential contribution of central adiposity to insulin resistance in our study population. Although we do not have formal measures of exercise performance, the subjects in our study were not participants in organized athletic programs for older adults. None of our subjects met diagnostic criteria for hypertension. However, supine systolic blood pressure of several of the old-old subjects obtained at baseline on the IVGTT study day exceeded 160 mm Hg. We did not observe a significant relationship between $S_I$ and either systolic or diastolic blood pressure in this study population ($r$ values = .028 and .031; each $P > .39$). Finally, to minimize dietary factors, subjects were instructed to consume a diet containing a minimum of 250 gm of carbohydrate before their IVGTT study.

When the data were analyzed according to the glucose tolerance status of the subjects, insulin sensitivity was significantly lower in the IGT group, and $K_g$ also tended to be lower, supporting the hypothesis that insulin resistance contributes to the etiology of IGT in this population. The trend toward a decrease of $S_G$ in IGT people suggests the possibility that diminished glucose-mediated glucose disposal is another factor in the deterioration of glucose metabolism in this group. A reduced value for $S_G$ has been observed in people with diabetes.[5] Studies in older people with NGT have reported an age-associated decrease in non-insulin-mediated glucose uptake[13] but no age group difference of $S_G$.[9,14] However these studies did not address mechanisms for IGT.

In our study, even though subjects with IGT had higher fasting and post- challenge glucose levels and lower $S_I$, their insulin and C-peptide levels were similar to NGT subjects, and the $AIR_g$ tended to be lower rather than increased. Studies of old animals have reported decreased indexes of pancreatic beta cell function.[1] However, in older humans, beta cell function has been reported to be normal, elevated, or decreased.[1] Because insulin secretion is normally regulated by a physiologic feedback control mechanism, the presence of insulin resistance and hyperglycemia should result in compensatory hyperinsulinemia if pancreatic beta cell function is normal.[1,15] Thus the lack of increase of insulin and C-peptide levels in older IGT subjects suggests a possible defect of the beta cell's ability to adapt to insulin resistance by developing

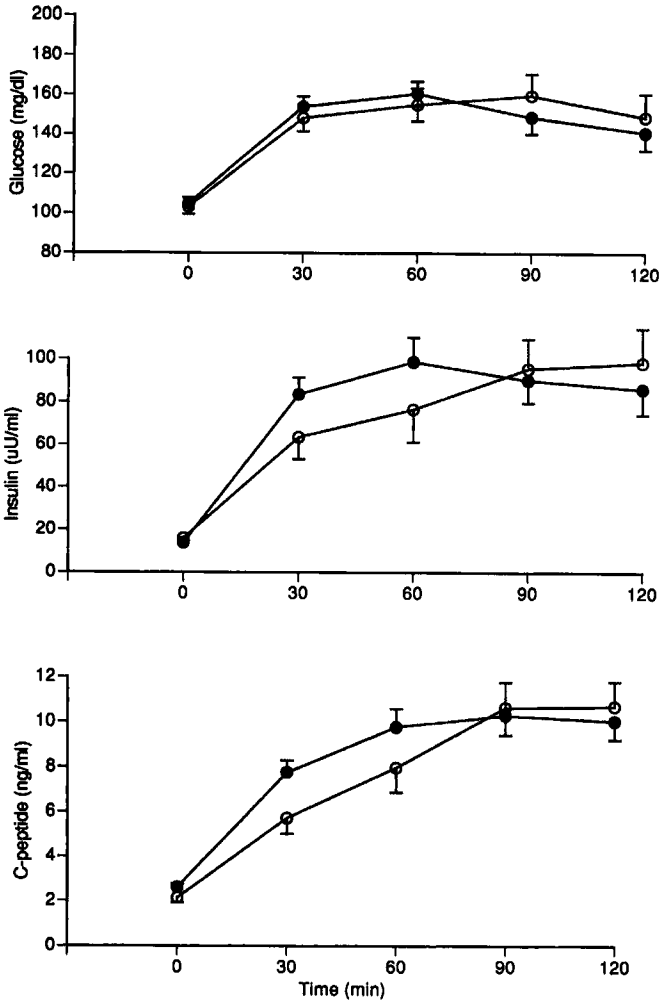


Figure 1. Comparison of plasma glucose, insulin, and C-peptide levels during a 75-g oral glucose tolerance test in subjects aged 61 to 79 years (young-old, n = 18, solid circles) and subjects more than age 80 years (old-old, n = 10, open circles). All values are mean ± SEM. No significant differences between groups were observed.

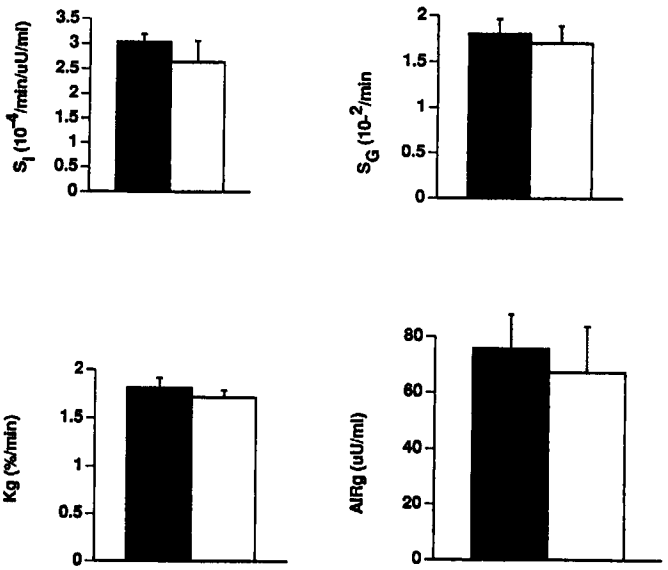


Figure 2. Comparison of findings in subjects aged 61–79 years (young-old, n = 18, solid bars) and subjects more than age 80 years (old-old, n = 10, open bars) for key parameters during a tolbutamide-assisted intravenous glucose tolerance test. $K_g$ is the rate of plasma glucose disappearance from 5 to 19 minutes after IV glucose; $S_I$ is the insulin sensitivity index, estimated by the Minmod algorithm as the increase in fractional glucose disappearance divided by the increase in effective insulin concentration; $S_G$ is glucose effectiveness, also estimated by the Minmod algorithm as the fractional disappearance rate of glucose at the basal insulin level; $AIR_g$ is the acute insulin response to glucose, or first phase insulin secretion, calculated as the mean of the values of plasma insulin levels at 3, 4, and 5 minutes after IV glucose minus the basal insulin level. All values are mean ± SEM. No significant differences between groups were observed.

compensatory hyperinsulinemia. Indirect evidence of beta cell dysfunction in lean, older adults with normal glucose tolerance has also been suggested recently by the finding of an increased proinsulin/insulin ratio.[16]

Many studies have demonstrated an age-associated increase in plasma norepinephrine levels, inferring that there is an increase in sympathetic nervous system activity with age.[17] However, none of these studies has reported plasma catecholamine levels in the old-old. In our study population, there were no differences in either plasma norepinephrine or epinephrine levels between young-old and old-old subject groups. Consistent with previous studies, the mean plasma norepinephrine levels of the young-old and old-old groups were elevated above values reported in younger populations; however, there was no significant association between age and plasma norepinephrine level observed in this population of subjects ranging in age from 61 to 88 years ($r$ = .132, $P$ = .51). These results suggest that there may be no further increase in plasma norepinephrine levels in healthy, nondiabetic old-old compared with young-old subjects. Additional studies of norepinephrine kinetics would be required before inferring that there is also no difference in sympathetic nervous system activity. There was no difference in plasma norepinephrine level between NGT and IGT groups. In addition, we did not observe a relationship between $S_I$ and plasma norepinephrine in this study population ($r$ = .124; $P$ = .54). This result is consistent with our previous study, which concluded that there was no association between heightened sympathetic nervous system activity and insulin resistance in aging.[18]

We need to emphasize that there are limitations because of the cross-sectional design of this study. A longitudinal study would be required to evaluate whether there is a progressive decrease of glucose metabolism with advancing age. The young-old and old-old groups were not well matched for gender, with a higher proportion of women represented in the old-old group. However, no significant gender differences in either glucose clamp or IVGTT derived measures of insulin action have been observed in previous studies.[9,19]

In summary, measurements of glucose metabolism do not appear to be worse in healthy people more than 80 years old than in people aged 61 to 79. The presence of IGT in healthy older people regardless of age is associated with insulin resistance and variable decreased glucose effectiveness. Despite the presence of higher plasma glucose during the OGTT and insulin resistance, older people with IGT do not have increased basal or stimulated insulin levels. Therefore, we hypothesize that lack of pancreatic islet compensa-

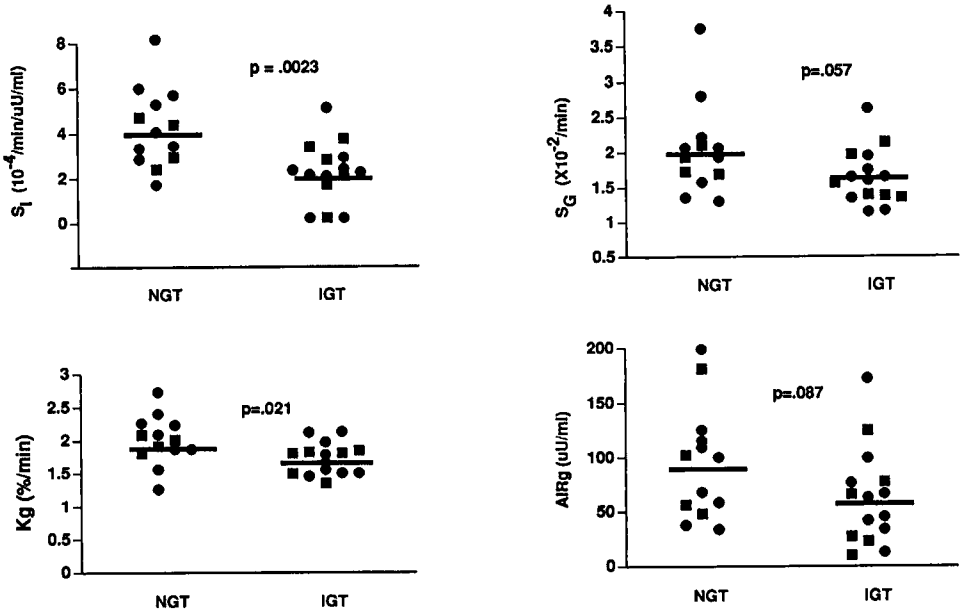


Figure 3. Comparison of key parameters during IV glucose tolerance testing of study subjects grouped by results of oral glucose tolerance testing using WHO criteria: NGT = normal glucose tolerance; IGT = impaired glucose tolerance. The solid circles represent people aged 61 to 79 (young-old) and the solid squares represent people more than age 80 (old-old). For definitions of $S_I$, $S_G$, $K_g$, and $AIR_g$, see legend to Figure 1.

tion for insulin resistance may contribute to impaired glucose tolerance in older adults.

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## REFERENCES

1. Halter JB. Aging and carbohydrate metabolism. In: E.J. Masoro, ed. Handbook of Physiology, Volume on Aging. Oxford: Oxford University Press Inc., 1995, pp 119–145.
2. Harris MI, Hadden WC, Knowler WC et al. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in a U.S. population aged 30–74 yr. Diabetes 1987;36:523–534.
3. World Health Organization. WHO Expert Committee on Diabetes Mellitus: Second Report. Tech., Rep. Ser., No. 646. Geneva: World Health Organization, 1980.
4. Bergman RN, Finegood DT, Ader M. Assessment of insulin sensitivity in vivo. Endocr Rev 1985;6:45–86.
5. Bergman RN. Toward physiological understanding of glucose tolerance. Minimal-model approach. Lilly Lecture 1989. Diabetes 1989;38:1512–1527.
6. Evans MI, Halter JB, Porte D Jr. Comparison of double- and single-isotope enzymatic derivative methods for measuring catecholamines in human plasma. Clin Chem 1978;24:467–570.
7. Paolisso G, Gambardella A, Ammendola S et al. Glucose tolerance and insulin action in healthy centenarians. Am J Physiol 1996;270 (Endocrinol. Metab 33):E890–894.
8. Chen M, Bergman RN, Pacini G et al. Pathogenesis of age related glucose intolerance in man: Insulin resistance and decreased β- cell function. J Clin Endocrinol Metab 1985;60:13–20.
9. Chen M, Bergman RN, Porte D. Insulin resistance and beta-cell dysfunction in aging: The importance of dietary carbohydrate. J Clin Endocrinol Metab 1988;67:951–957.
10. Meyers DA, Goldberg AP, Bleecker ML et al. Relationship of obesity and physical fitness to cardiopulmonary and metabolic function in healthy older men. J Gerontol Med Sci 1991;46:M57–65.
11. Wang JT, Ho LT, Tang KT et al. Effect of habitual physical activity on age-related glucose intolerance. J Am Geriatr Soc 1989;37:203–209.
12. Supiano MA, Morrow LA, Hogikyan RV et al. Aging and insulin resistance: Role of sympathetic activity and blood pressure. J Gerontol Med Sci 1993;48:M237–243.
13. Meneilly GS, Elahi D, Minaker KL et al. Impairment of noninsulin-mediated glucose disposal in the elderly. J Clin Endocrinol Metab 1989;63:566–571.
14. Morrow LA, Morganroth GS, Herman WH et al. Effects of epinephrine on insulin secretion and action in humans. Interactions with aging. Diabetes 1993;42:307–315.
15. Porte D Jr. Beta-cells in Type II diabetes mellitus. Diabetes 1991;40:166–180.
16. Shimizu M, Kawazu S, Tomono S et al. Age-related alteration of pancreatic β-cell function. Diabetes Care 1996;19:8–11.
17. Linares OA, Halter JB. Sympathochromaffin system activity in the elderly. J Am Geriatr Soc 1987;35:448–453.
18. Supiano MA, Hogikyan RV, Morrow LA et al. Hypertension and insulin resistance: Role of sympathetic nervous system activity. Am J Physiol 1992;263:E935–948.
19. Franssila-Kallunki A, Schalin-Jantti C, Groop L. Effect of gender on insulin resistance associated with aging. Am J Physiol 1992;263 (Endocrinol. Metab:26):E780–785.