Insulin Resistance in Aging Is Related to Abdominal Obesity

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Studies have shown that insulin resistance increases with age, independent of changes in total adiposity. However, there is growing evidence that the development of insulin resistance may be more closely related to abdominal adiposity. To evaluate the independent effects of aging and regional and total adiposity on insulin resistance, we performed hyperinsulinemic euglycemic clamps on 17 young (21–33 yr) and 67 older (60–72 yr) men and women. We assessed FFM and total and regional adiposity by hydrodensitometry and anthropometry. Insulin-stimulated GDRs at a plasma insulin concentration of ~450 pM averaged 45.6 ± 3.3 μmol · kg FFM^{-1} · min^{-1} (mean ± SE) in the young subjects, 45.6 ± 10.0 μmol · kg FFM^{-1} · min^{-1} in 24 older subjects who were insulin sensitive, and 23.9 ± 11.7 μmol · kg FFM^{-1} · min^{-1} in 43 older subjects who were insulin resistant. Few significant differences were apparent in skin-fold and circumference measurements between young and insulin-sensitive older subjects, but measurements at most central body sites were significantly larger in the insulin-resistant older subjects. Waist girth accounted for >40% of the variance in insulin action, whereas age explained only 10–20% of the total variance and <2% of the variance when the effects of waist circumference were statistically controlled. These results suggest that insulin resistance is more closely associated with abdominal adiposity than with age. *Diabetes* 42:273-81, 1993

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Received for publication 11 June 1992 and accepted in revised form 21 September 1992.

FFM, fat-free mass; GDR, glucose disposal rate; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data Group; VO_{2max}, maximal oxygen uptake; HGP, hepatic glucose production; SSGIR, steady-state glucose infusion rate; R_a, rate of glucose appearance; R_d, rate of glucose disappearance; ANOVA, analysis of variance; FPG, fasting plasma glucose; WHR, waist-to-hip ratio; CV, coefficient of variation; HGO, hepatic glucose output; NIH, National Institutes of Health.

Aging often is associated with a deterioration in glucose tolerance. Population studies indicate that the plasma glucose concentration 2 h after an oral glucose challenge increases by ~0.3–0.5 mM per decade in apparently healthy people (1–3). Whether this deterioration is attributable to the aging process or to other factors such as increasing adiposity, abdominal obesity, and/or physical inactivity remains equivocal. Zavaroni et al. (3) found that the effect of aging on glucose tolerance was either eliminated or markedly reduced after adjusting for the effects of obesity and physical activity level. Shimokata et al. (1) also found that the decline in glucose tolerance from young to middle age could be explained by indexes of body composition and activity level, but determined that age remained an independent risk factor for glucose intolerance in older people.

The decline in glucose tolerance with age appears to be attributable in large measure to the increased resistance of skeletal muscle to the action of insulin (4–10). Insulin resistance is common in obese individuals (11–13). Although total adiposity (14,15) and visceral fat mass (16,17) increase with age, studies that used the hyperinsulinemic euglycemic clamp procedure to quantify insulin action have suggested that total adiposity does not explain the age-related increase in insulin resistance (8–10). To the best of our knowledge, the associations among aging, insulin resistance, and regional adiposity have not been examined. Therefore, this study examined the interactions of age, total and regional adiposity, and insulin action in young and older men and women.

RESEARCH DESIGN AND METHODS

Sixty-seven older subjects (34 men, 33 women; age 65 ± 1 yr) and 17 young subjects (11 men, 6 women; age 24 ± 1 yr) provided informed written consent to partici-

pate in this study, which was approved by the Washington University Human Studies Committee. Subjects were recruited from a pool of volunteers being screened for entry into another research project.

All subjects were normally active but had not engaged in regular endurance exercise (defined as ≥30 min of aerobic activity ≥2 days/wk) for a minimum of 6 mo before the study. Participants were nonsmokers and, with the exception of mild NIDDM in 19 subjects, were apparently healthy, as determined by medical history, physical examination, routine blood and urine chemistries, OGTT, and graded exercise stress test. None of the participants was taking medications known to affect glucose tolerance. One of the subjects with NIDDM was aware of the condition prior to entering the project but was not receiving treatment for NIDDM.

OGTT. Glucose tolerance was determined using a 75-g OGTT, performed in the morning after a 12-h fast. Diet was monitored for 3 days before both the OGTT and the euglycemic clamp to ensure an intake of ≥150 g of cholesterol per day. Blood samples for the determination of glucose and insulin were taken immediately before and 30, 60, 90, 120, and 180 min after the glucose challenge. The total areas under the glucose and insulin curves were calculated using the trapezoidal rule.

We have defined the term "strictly normal" glucose tolerance in the older subjects to mean plasma glucose concentrations ± 2 SD of the values measured in the young subjects at all time points during the OGTT. Those older subjects classified as having "high normal" glucose tolerance had at least one glucose value that was >2 SD above the mean of the young subjects, but did not meet the criteria for impaired or diabetic glucose tolerance as defined by the NDDG (18). Subjects that had nondiagnostic glucose tolerance by NDDG standards were included in the high normal group.

Body composition. Hydrodensitometric and anthropometric measures of body composition and fat distribution were performed as described previously (14). Body fat percentage was estimated from body density using the equation of Brozek et al. (19). Skin-fold thickness was determined at the triceps, subscapula, pectoralis, umbilicus, suprailiac, and anterior thigh, and circumferences were measured at the chest, waist, abdomen, hips, and thigh (20). Skin-fold and circumference measures were obtained at each site, then duplicate measures were taken. If values did not agree within 1.0 mm for skin-fold thickness or 0.5 cm for girth, additional determinations were made. Outlying values (>4.0 mm for skin folds and >1.5 cm for girths) were eliminated, and remaining values were averaged.

$\dot{V}O_{2max}$. Using an incremental treadmill protocol, $\dot{V}O_{2max}$ was measured to determine whether insulin action was related to level of fitness, particularly among the older subjects. During a 5- to 10-min warm-up, subjects walked or jogged at a speed that elicited a heart rate of ~70% of age-predicted maximal heart rate. Speed was then kept constant, and grade was increased by 1–3% every 2 min until volitional exhaustion.

$\dot{V}O_2$ was measured continuously and calculated for each 30-sec interval using an automated open-circuit system consisting of an inspired gas meter (Parkinson-Cowan CD-4, Carl Poe, Houston, TX), a mixing chamber, and electronic O_2 (Applied Electrochemistry S3-A, Sunnyvale, CA) and CO_2 (Beckman LB-2, Fullerton, CA) analyzers. At least two of the following criteria were met during each test to establish $\dot{V}O_{2max}$ had been attained: a plateau in $\dot{V}O_2$ despite an increase in treadmill grade, attainment of age-predicted maximal heart rate, a respiratory exchange ratio ≥1.10.

Hyperinsulinemic, euglycemic clamp. The subjects were admitted to the Washington University General Clinical Research Center at 0700 after an overnight fast. They voided, were weighed, then remained supine for the duration of the procedure. A polyethylene catheter was inserted into an antecubital vein for the infusion of glucose (20% dextrose), insulin, and KCl. A second catheter was inserted retrograde into the distal portion of a dorsal hand vein. The hand was kept in a box warmed to 70°C for the duration of the euglycemic clamp for sampling of arterialized blood. Four baseline blood samples were drawn at 10-min intervals to determine fasting glucose and insulin concentrations and, in the older subjects, glucose kinetics (see below).

A two-stage hyperinsulinemic, euglycemic clamp assessed insulin action (21). The insulin infusates were prepared by diluting purified porcine insulin (Squibb Novo, Princeton, NJ) in 0.9% saline. Approximately 4 ml of the subject's blood was added to the infusate to minimize the adherance of insulin to glassware and tubing. After the baseline blood samples were obtained, two sequential, primed, continuous infusions of insulin at 40 and 400 (young) or 800 (older) mU · m^{-2} · min^{-1} were performed. Each stage lasted 120 min.

During the second stage, the plasma insulin concentration was raised to a lower level in the young than in the older subjects because we previously have shown this insulin concentration yields a maximal insulin-stimulated GDR during euglycemia in young subjects with normal glucose tolerance (22). Plasma glucose concentration was determined every 5 min using the glucose oxidase method (Beckman) and was maintained at 5 mM during hyperinsulinemia by varying the glucose infusion rate (Harvard Apparatus, Millis, MA). Blood samples were obtained at 15-min intervals throughout the 240 min of hyperinsulinemia for the subsequent determination of plasma insulin concentration (23).

Mikines et al. (24) have shown that HGP is fully suppressed in young, untrained subjects at the insulin concentrations attained in this study. To determine HGP rates during hyperinsulinemia in the older subjects, the euglycemic clamp procedure included a primed (25 μCi bolus), continuous infusion (0.25 μCi/min) of [3-^{3}H]glucose (NEN-DuPont, Boston, MA) lasting ~6 h; the insulin infusions were performed during the final 4 h. Blood samples for the determination of glucose kinetics were obtained at 10-min intervals during the final 30 min of each stage, i.e., baseline, lower insulin concentration, and high insulin concentration. Plasma-specific activity was determined by liquid scintillation counting after deproteinization of plasma with 3.0 M perchloric acid (0.3 ml/1.2 ml plasma).

Calculations. In the young subjects, the GDR during the final 30 min of each insulin infusion was calculated from the SSGIR, adjusted for fluctuations in the plasma glucose space (21). In the older subjects, R_a and R_d (μmol · kg FFM^{-1} · min^{-1}) were calculated for the final 30 min of each stage using the non–steady-state equations of Steele (25). Fluctuations in R_a caused by random error in the determination of plasma-specific activity were minimized by using a three-point smoothing procedure (26). The isotopic determination of glucose kinetics sometimes resulted in an underestimation of R_d during hyperinsulinemia, as evidenced by negative values for HGP (27). When this occurred, the GDR was assumed to be the SSGIR.

Statistical analyses. The data were stored and analyzed using the CLINFO Data Analysis System of the Washington University General Clinical Research Center and BMDP software. Statistical differences among the groups were determined using a one-way ANOVA and the Newman-Keul post hoc test where appropriate. Univariate and multivariate linear regression analyses determined the relationships among variables of interest. Statistical significance was accepted at $P < 0.05$. All data are expressed as means ± SE.

RESULTS

Glucose tolerance. In the 67 older people, glucose tolerance was determined as strictly normal in 13, high normal in 12, impaired in 23, and NIDDM in 19. Seven of the subjects with impaired glucose tolerance and 4 with NIDDM were distinct in that their insulin response during the OGTT was markedly lower (insulin area, 35,544 ± 2,568 pM/min) than that of the other subjects in those two groups (insulin area, 107,754 ± 16,296 pM/min; $P < 0.05$). Because these 11 subjects appeared to be different both in terms of body composition and insulin sensitivity, they were studied separately and classified as insulin deficient. Fig. 1*A* shows the plasma glucose responses for all the groups.

Notable differences occurred among the groups in insulin response to the OGTT. The area under the OGTT insulin curve was significantly higher in the high normal, impaired glucose tolerance, and NIDDM groups than in the other groups (Fig. 1*B*). Although glucose values were not significantly different in the young and strictly normal groups, insulin concentrations tended to be higher ($P < 0.10$) in the strictly normal group after 30 min. The insulin-deficient group (*INS-DEF*) had a markedly blunted insulin response, particularly during the first hour of the test when the plasma glucose concentration increased sharply. At 30 and 60 min after glucose ingestion, the plasma insulin concentration was significantly lower in the insulin-deficient group than in all other groups of older subjects, and also was significantly lower at later time points compared with the high normal, impaired, and NIDDM groups (Fig. 1*B*).

Whereas the peak insulin concentration was attained within 60 min in the young subjects and strictly normal older group, the peak response was delayed in the other groups. Moreover, the peak insulin concentration was higher in the high normal and impaired groups than in the young subjects and the strictly normal and insulin-deficient older subjects ($P < 0.05$).

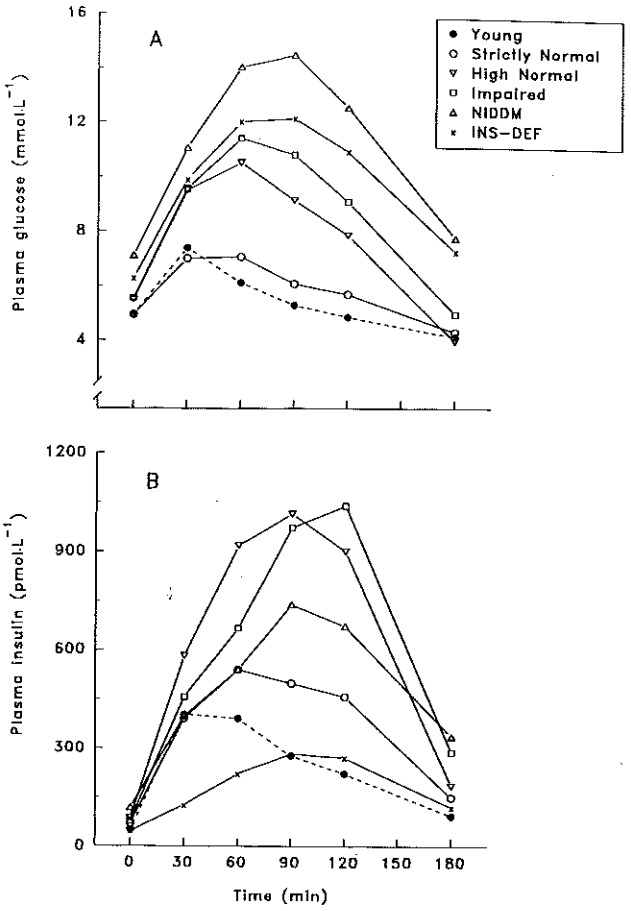

FIG. 1. Plasma glucose (*A*) and insulin (*B*) concentrations during an OGTT in young subjects and older subjects with strictly normal, high normal, impaired, or NIDDM glucose tolerance, and in older subjects with abnormal glucose tolerance as a result of insulin deficiency (*INS-DEF*).

Body composition. Body fat content was greater in all groups of older subjects than in the young subjects and tended to be highest in the men and women with NIDDM, as did body weight (Table 1). In terms of skin-fold thickness and circumference measures, which were used as indexes of body fat distribution, only a few significant differences occurred between the groups at peripheral sites, but the subjects with high normal, impaired, and NIDDM glucose tolerance tended to have larger skin-fold thicknesses and girths at central body sites than did subjects in the young, strictly normal, and insulin-deficient groups (data not shown). The lack of statistical significance of differences at some sites likely was attributable to the small number of subjects in each group.

Because both insulin sensitivity and measures of fat distribution were similar in the strictly normal and insulin-deficient older groups, these groups were combined (insulin-sensitive) and compared with the group (insulin-resistant) that included subjects with high normal, im-

TABLE 1
Physical characteristics of young men and women; older men and women with strictly normal, high normal, impaired, or NIDDM glucose tolerance; and older men and women with abnormal glucose tolerance combined with insulin deficiency

		Older				
	Young	Strictly normal	High normal	Impaired	NIDDM	Insulin deficient
Men						
n	11	4	5	7	10	8
Weight (kg)	76.6 ± 3.1	77.0 ± 3.3	85.3 ± 7.7	75.9 ± 3.8	94.0 ± 3.1*	75.3 ± 3.1
Height (cm)	179.6 ± 1.5	177.9 ± 3.2	175.4 ± 2.5	174.2 ± 3.8	176.8 ± 2.9	176.5 ± 2.0
Body fat (%)	15.8 ± 1.6†	23.8 ± 1.9	27.2 ± 2.2	28.4 ± 1.5	31.9 ± 1.4‡	24.6 ± 1.8
VO_{2max} ($ml \cdot min^{-1} \cdot kg^{-1}$)	49.0 ± 1.5†	31.0 ± 2.6	26.2 ± 2.3	26.0 ± 0.9	22.6 ± 0.5§	26.9 ± 0.5
Women						
n	6	9	7	9	5	3
Weight (kg)	67.8 ± 4.0	65.9 ± 3.1	71.7 ± 5.3	74.4 ± 4.6	82.3 ± 5.3	56.2 ± 3.5‖
Height (cm)	170.4 ± 3.8	164.9 ± 2.7	163.4 ± 2.3	162.4 ± 1.7	159.3 ± 1.1	158.1 ± 6.3
Body fat (%)	26.2 ± 1.9†	40.1 ± 0.9	40.2 ± 1.7	37.9 ± 1.4	40.8 ± 3.1	36.7 ± 0.8
VO_{2max} ($ml \cdot min^{-1} \cdot kg^{-1}$)	35.2 ± 2.5†	21.3 ± 0.6	20.0 ± 1.1	20.1 ± 0.8	19.6 ± 1.3	21.4 ± 0.8

Data are means ± SE.
*$P < 0.05$, different from young, normal, insulin-deficient, and impaired.
†$P < 0.05$, different from all other groups.
‡$P < 0.05$, different from young, normal, and insulin-deficient.
§$P < 0.05$, different from normal.
‖$P < 0.05$, different from NIDDM.

paired, and diabetic glucose tolerance (Tables 2 and 3). These analyses indicated that, compared with young and insulin-sensitive older subjects, the insulin-resistant men and women weighed more and had larger skin-fold thicknesses and girths at most of the sites measured, particularly central body sites. The insulin-resistant men also had a higher body fat content.

Maximal oxygen consumption. $\dot{V}O_{2max}$ was significantly higher in the young than the older subjects (Table 1). Among the older men, those in the NIDDM group had a lower $\dot{V}O_{2max}$ than those in the strictly normal group, even when $\dot{V}O_2$ was expressed relative to FFM. No significant differences in $\dot{V}O_{2max}$ occurred among the groups of older women.

Insulin action. FPG was elevated in the subjects with NIDDM and was higher ($P < 0.05$) in the group with insulin deficiency and abnormal glucose tolerance than in the young and strictly normal older subjects, but was

TABLE 2
Body composition of men

		Older	
	Young	Insulin sensitive	Insulin resistant
n	11	12	22
Weight (kg)	76.6 ± 3.1	75.8 ± 2.5	86.2 ± 3.0*
Height (cm)	179.6 ± 1.5	177.0 ± 1.6	175.6 ± 1.8
Body fat (%)	15.8 ± 1.6	24.3 ± 1.3†	29.7 ± 1.0‡
Skin folds (mm)			
Triceps	12 ± 2	11 ± 1	17 ± 1‡
Subscapula	16 ± 2	17 ± 2	28 ± 2‡
Pectoralis	13 ± 2	20 ± 2	28 ± 2‡
Suprailiac	12 ± 2	16 ± 2	22 ± 2*
Umbilicus	24 ± 3	24 ± 3	37 ± 3‡
Thigh	15 ± 2	15 ± 1	19 ± 2
Girths (cm)			
Arm	30 ± 1	30 ± 1	32 ± 2
Chest	95 ± 1	99 ± 2	107 ± 2‡
Waist	84 ± 2	91 ± 2	101 ± 2‡
Abdomen	87 ± 2	93 ± 2	105 ± 2‡
Hips	94 ± 2	98 ± 2	105 ± 2*
Thigh	57 ± 1	55 ± 1	56 ± 1
WHR	0.90 ± 0.02	0.92 ± 0.01	0.96 ± 0.01*

Data are means ± SE.
*$P < 0.05$, different from young and insulin-sensitive older.
†$P < 0.01$, different from young.
‡$P < 0.01$, different from young and insulin-sensitive older.

TABLE 3
Body composition of women

	Young	Older	
		Insulin sensitive	Insulin resistant
n	5	12	21
Weight (kg)	66.8 ± 4.7	63.5 ± 2.6	75.4 ± 2.9*
Height (cm)	170.9 ± 4.6	163.2 ± 2.6	162.0 ± 1.1†
Body fat (%)	25.1 ± 1.9	39.2 ± 0.8‡	39.4 ± 1.1‡
Skin folds (mm)			
Triceps	19 ± 2	25 ± 2	27 ± 2
Subscapula	17 ± 3	21 ± 2	30 ± 2§
Pectoralis	26 ± 2	28 ± 2	35 ± 2§
Suprailiac	14 ± 2	20 ± 2	28 ± 2*
Umbilicus	21 ± 3	31 ± 3	41 ± 3*
Thigh	29 ± 4	37 ± 3	40 ± 3
Girths (cm)			
Arm	27 ± 1	31 ± 1†	31 ± 1†
Chest	88 ± 3	90 ± 2	97 ± 2*
Waist	76 ± 4	81 ± 1	93 ± 3§
Abdomen	82 ± 4	95 ± 2†	106 ± 3§
Hips	99 ± 4	100 ± 2	109 ± 3*
Thigh	59 ± 2	58 ± 1	60 ± 1
WHR	0.75 ± 0.02	0.81 ± 0.02†	0.85 ± 0.01*

Data are means ± SE.
*$P < 0.05$, different from young and insulin-sensitive older.
†$P < 0.05$, different from young.
‡$P < 0.01$, different from young.
§$P < 0.01$, different from young and insulin-sensitive older.

not significantly different among the other groups (Table 4). Fasting plasma insulin concentration was significantly higher in the NIDDM group than in the young, strictly normal, and insulin-deficient subjects ($P < 0.05$). The basal rate of HGP did not differ significantly among the groups of older subjects with various levels of glucose tolerance.

During the final 30 min of the first stage of insulin infusion, plasma glucose and insulin concentrations did not differ significantly among the groups. Mean HGP in the older subjects ranged from 0 to 2.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and was not significantly different among the groups. GDR ($\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$) in the older subjects with strictly normal glucose tolerance and in those with insulin deficiency was similar to that of the young group, but was reduced by 30–40% in the groups with

TABLE 4
Hyperinsulinemic euglycemic clamp data

	Young	Older				
		Strictly normal	High normal	Impaired	NIDDM	Insulin-deficient
n	17	13	12	16	15	11
Basal						
Plasma glucose (mM)	4.94 ± 0.11	4.94 ± 0.11	5.50 ± 0.11	5.55 ± 0.11	7.27 ± 0.44*	6.00 ± 0.28†
Plasma insulin (pM)	51 ± 12	71 ± 11	87 ± 9	79 ± 10	115 ± 13‡	44 ± 5
R_a ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)		11.7 ± 0.6	11.7 ± 1.1	12.8 ± 1.1	11.1 ± 1.1	12.8 ± 0.6
First stage						
Plasma glucose (mM)	5.00 ± 0.06	4.88 ± 0.06	4.88 ± 0.06	4.94 ± 0.06	5.11 ± 0.17	5.00 ± 0.06
CV (%)	3.8 ± 0.6	2.5 ± 0.2	3.2 ± 0.4	2.9 ± 0.4	3.2 ± 0.5	2.5 ± 0.2
Plasma insulin (pM)	414 ± 30	384 ± 24	486 ± 42	438 ± 30	492 ± 42	474 ± 30
GDR ($\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$)	45.6 ± 3.3	48.3 ± 4.4	31.3 ± 2.2‡	28.3 ± 1.7‡	17.2 ± 1.1*	42.2 ± 3.9
Second stage						
Plasma glucose (mM)	5.05 ± 0.06	5.00 ± 0.06	5.00 ± 0.06	5.00 ± 0.06	4.94 ± 0.06	5.05 ± 0.06
CV (%)	3.9 ± 0.5	4.5 ± 1.0	3.0 ± 0.3	3.2 ± 0.2	4.0 ± 0.5	3.8 ± 0.8
Plasma insulin (pM)	11850 ± 2772	29400 ± 4218	28140 ± 5502	24198 ± 3612	24810 ± 5376	25422 ± 4494
GDR ($\mu mol \cdot kg\ FFM^{-1} \cdot min^{-1}$)	92.2 ± 3.3	101.1 ± 4.4	81.7 ± 3.3	80.0 ± 3.3	65.0 ± 5.6*	87.8 ± 6.1

Data are means ± SE.
*$P < 0.05$, different from all other groups.
†$P < 0.05$, different from young and normal.
‡$P < 0.05$, different from young, normal, and insulin-deficient.

TABLE 5
Zero-order correlations of age, VO_{2max}, body fat content, and measures of body fat distribution with GDR during the first stage of the euglycemic clamp

	GDR (μmol · kg FFM^{-1} · min^{-1})	
	Men	Women
Age	−0.33*	−0.44†
Body fat (%)	−0.58‡	−0.45†
VO_{2max} (ml · min^{-1} · kg FFM^{-1})	0.42*	0.50†
Skin folds (mm)		
Triceps	−0.50†	−0.32*
Subscapula	−0.57‡	−0.63‡
Pectoralis	−0.38*	−0.47†
Umbilicus	−0.53‡	−0.62‡
Suprailiac	−0.57‡	−0.64‡
Thigh	−0.31	−0.13
Girths (cm)		
Arm	−0.55‡	−0.41*
Chest	−0.68‡	−0.64‡
Waist	−0.66‡	−0.71‡
Abdomen	−0.64‡	−0.67‡
Hip	−0.57‡	−0.39*
Thigh	−0.27	−0.12
WHR	−0.50‡	−0.70‡

*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

high normal and impaired glucose tolerance, and by ~60% in the NIDDM group.

The plasma glucose concentrations were similar in all of the groups during the final 30 min of the second stage of the euglycemic clamp. The maximal GDR (mg · kg FFM^{-1} · min^{-1}) was ~30% lower in the NIDDM group than in the insulin-sensitive groups ($P < 0.05$).

Associations of age, VO_{2max}, and body composition with insulin sensitivity and glucose tolerance. The GDR during the first stage of the euglycemic clamp (plasma insulin concentration ~450 pM), which is an index of insulin sensitivity, was significantly associated with age, VO_{2max} (ml · min^{-1} · kg FFM^{-1}), body fat content, and a number of anthropometric markers of central obesity in both men and women (Table 5). Insulin action was more strongly associated with skin-fold and girth measures at central body sites than with measures at peripheral sites. In general, the strength of these relationships was lower when GDR at the high insulin concentration (insulin responsiveness) was used (data not shown). Because insulin responsiveness was similar among all groups except the NIDDM group, further analyses of the relationships among age, VO_{2max}, body composition, and insulin action were performed using only the GDR at the lower insulin concentration.

Stepwise multivariate regression analyses were used to determine the independent effects of age, VO_{2max}, total adiposity, and fat distribution (waist circumference and WHR) on insulin action (Table 6). Waist circumference was selected because it was one of the strongest single predictors of insulin sensitivity in men and women (Table 5, Fig. 2). The WHR was included in the model because it is a common index of abdominal obesity. In men, waist circumference accounted for 43% of the variance in GDR at the low insulin concentration, and the remaining independent contributions of age, VO_{2max}, total adiposity, and the WHR were not significant. In women, waist circumference alone accounted for 50% of the variance in insulin action, and this increased to 60% when the WHR was added. The remaining partial correlations of age, VO_{2max}, and body fat percentage were not significant.

DISCUSSION

The major finding of this study was that insulin resistance, quantified as the GDR at a physiological concentration of insulin that induced a rate of glucose disposal that was ~50% of maximal in insulin-sensitive subjects, was more closely related to measures of regional adiposity than its age. Waist circumference alone accounted for >40% of the variance in GDR among the 84 young and older men and women studied, whereas age explained only 10–20% of the total variance and <2% of the variance when the effects of waist circumference were statistically controlled.

Our findings are in keeping with those of previous studies, which suggested that an age-related increase in insulin resistance occurs independently of changes in total adiposity (8–10). This was most evident among the

TABLE 6
Multivariate regression analysis of the effects of age, VO_{2max} (ml · min^{-1} · kg FFM^{-1}), body fat content, waist circumference, and WHR on GDR (μmol · kg FFM^{-1} · min^{-1}) during the first stage of the euglycemic clamp

Step	Variable entered	Multiple r^2	Adjusted* r^2	Partial correlations†				
				Age	VO_{2max}	Body fat content (%)	Waist	WHR
Men								
0				−0.33	0.42	−0.58	−0.66	−0.50
1	Waist	0.43	0.42	−0.02	0.07	−0.07		0.01
Women								
0				−0.44	0.50	−0.45	−0.71	−0.70
1	Waist	0.50	0.48	−0.27	0.29	0.04		−0.45
2	W/H	0.60	0.58	−0.14	0.24	0.02		

*Multiple correlation coefficient adjusted for sample size and the number of predictor variables.
†The association with the dependent variable independent of the variance accounted for by predictor variables already entered into the regression model.

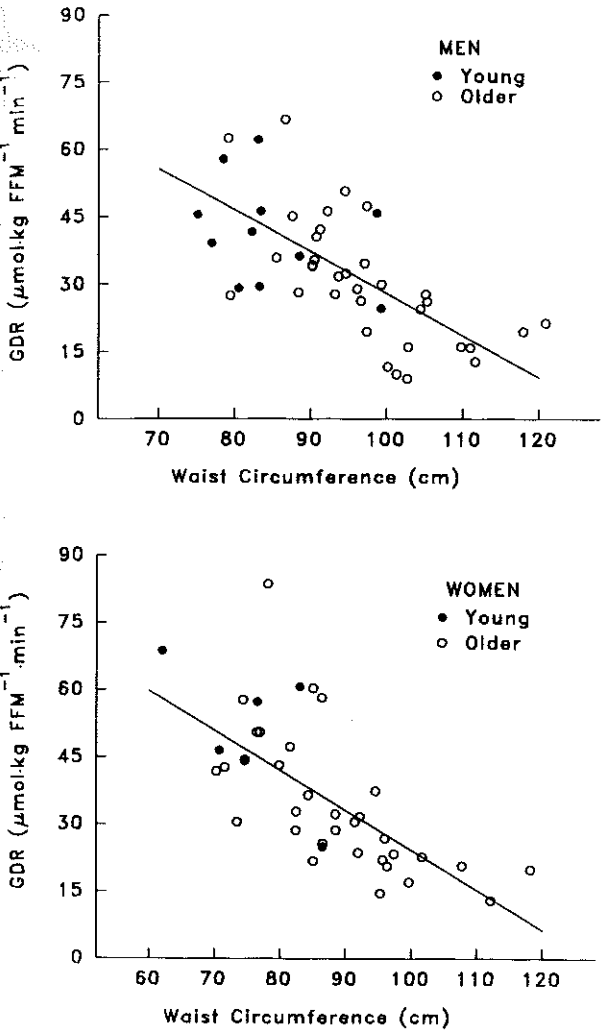

FIG. 2. Relationship between GDR at a physiological insulin concentration (~450 pM) and waist circumference in men ($r = -0.65$, $P < 0.01$) and women ($r = -0.71$, $P < 0.01$).

groups of older women in this study, as GDRs during the submaximal insulin infusion varied markedly despite no difference in body fat percentage. Although we did find significant zero-order correlations between insulin sensitivity and body fat percentage in both men and women, these relationships were not independent of the effects attributable to abdominal obesity (Table 6).

The significant positive correlation between $\dot{V}O_{2max}$ and insulin action we found has also been reported by others (28,29). This does not appear to be a causative relationship, however, because insulin action in older men and women with strictly normal glucose tolerance was the same as in young subjects despite the fact that $\dot{V}O_{2max}$ values were 35–40% lower. That $\dot{V}O_{2max}$ was not an independent predictor of insulin sensitivity was confirmed in the multivariate regression analyses.

Our data indicate, therefore, that insulin action was significantly related to age and $\dot{V}O_{2max}$ and to both total and regional adiposity. However, when variance attributable to regional adiposity was statistically controlled, the remaining independent effects of age, $\dot{V}O_{2max}$, and total adiposity were no longer significant. This finding is consistent with the results of a recent hyperinsulinemic euglycemic clamp study by Broughton et al. (30), who found that insulin action in a group of lean older men was similar to that of young men. Research also has shown fasting and glucose-stimulated plasma insulin levels are more closely related to regional adiposity than to age in men aged 46–73 yr (31).

In our study, the insulin-sensitive older subjects with strictly normal glucose tolerance or insulin deficiency had less central obesity than those with mild or more severe glucose intolerance, and were as insulin sensitive as the young subjects. Collectively, our results and those of Broughton et al. (30) and Coon et al. (31) suggest that insulin resistance is an avoidable consequence of abdominal fat accumulation with advancing age.

Intra-abdominal fat accumulation may be associated with the development of insulin resistance, although mechanisms have not been fully elucidated (11,32–34). Adipose tissue in the visceral region is highly sensitive to lipolytic stimuli, particularly in those regions drained by the portal circulation (35). As a consequence, an increased flux of free fatty acids to the liver may, by stimulating gluconeogenesis (36) and inhibiting hepatic insulin clearance (37,38), lead to hyperinsulinemia and, consequently, insulin resistance (39). These mechanisms have not been directly studied in humans because of the difficulty of measuring portal FFA concentration. However, some studies have shown that an acute elevation in FFA concentration results in increased HGO (40), and that hepatic clearance of insulin is reduced in people with abdominal obesity (41).

A marked reduction in insulin sensitivity apparently can occur despite only a mild deterioration in oral glucose tolerance. The GDR at a physiological concentration of insulin was 35% lower in those older subjects with high normal glucose tolerance than in those with strictly normal glucose tolerance. Although insulin responsiveness also tended to decline as the degree of glucose intolerance worsened, the GDR at a maximally effective insulin concentration was significantly blunted only in those subjects with NIDDM. These findings concur with those of Kolterman et al. (42) and suggest that the insulin-resistant state is a continuum, ranging from reduced insulin sensitivity and mild glucose intolerance in the least severe form, to reduced insulin sensitivity and responsiveness and NIDDM in the most severe form.

It is well established that the majority of older people with glucose intolerance are insulin resistant (4–10). This is not surprising in view of the high prevalence of obesity (14) and increased intra-abdominal fat (16,17) in older people in our society and the association between these factors and insulin resistance (Fig. 2) (11,32–34). As shown in this study, however, a subgroup of insulin-sensitive older men and women have abnormal glucose tolerance solely because of an inadequate glucose-stimulated insulin response. Inclusion of this subgroup was not envisioned a priori, but during the course of the study we discovered that some lean older subjects with normal insulin sensitivity had impaired glucose tolerance

or mild NIDDM because of a deficient insulin response to glucose. This observation is not consistent with the work of DeFronzo (39), who found that normal-weight individuals with NIDDM are typically insulin resistant and tend to have insulinopenia only when FPG levels are >8.88 mM. Our findings confirm those of Arner et al. (43), who also described a subgroup of older men with NIDDM but normal insulin sensitivity. As in our study, subjects in the insulin-sensitive NIDDM group studied by Arner differed from those in the insulin-resistant NIDDM group in that they were leaner, had a lower WHR, and had a markedly blunted insulin response to intravenous glucose. We do not have data on a sufficiently large population to estimate the incidence of this abnormality. In the recruitment process for the research of which this study was a component, we used a 75-g OGTT to screen a total of 284 subjects in the 60–72–yr age range with no known history of impaired or diabetic glucose tolerance. Of these 284 subjects, 56 had impaired or mildly diabetic glucose tolerance. In 17 of those 56 subjects, the area under the OGTT insulin curve was within the range described in this study for the insulin-deficient, insulin-sensitive subjects (~30%).

In those older subjects whose glucose tolerance was strictly normal, exogenous insulin action was similar to that found in the young subjects. Note, however, that despite similar glucose concentrations in these two groups during the OGTT, insulin concentrations tended to be higher ($P < 0.1$) in the older subjects, suggesting mild insulin resistance. We have no data to explain the apparent discrepancy between our OGTT and euglycemic clamp results. Other research, however, has reported an age-related increase in the glucose-stimulated plasma proinsulin/insulin ratio (44). Because we measured total immunoreactive insulin, this might explain what appears as a reduced action of endogenous insulin (OGTT) relative to that of exogenous insulin (euglycemic clamp) in the older subjects.

In summary, we found that insulin sensitivity and responsiveness were normal (i.e., similar to that of young, lean subjects) in 24 of the 67 older men and women studied. These older subjects with normal insulin sensitivity had either strictly normal glucose tolerance or glucose intolerance as a result of an insulin deficiency. Few significant differences were evident in regional adiposity between the young and older insulin-sensitive subjects. In contrast, the insulin-resistant older subjects, whose glucose tolerance ranged from high normal to mild diabetic, had larger skin-fold thicknesses and circumferences than the young and older insulin-sensitive subjects, particularly in the central regions of the body. Waist cicumference explained >40% of the variance in insulin sensitivity among young and older men and women. Age, on the other hand, accounted for only 10–20% of the total variance in insulin action, and <2% of the variance independent of that explained by waist circumference. Our data suggest, therefore, that regional adiposity, rather than age, is the more important determinant of insulin resistance and the associated glucose intolerance.

ACKNOWLEDGMENTS

This research was supported by NIH Program Project Award AG-05562, General Clinical Research Grant 5-MOIRR-00036, and Diabetes Research and Training Center Grant AM-20579. W.M.K. was supported by NIH Institutional National Research Service Award HL-07456. J.P.K., R.E.B., and D.S.K. were supported by NIH Institutional National Research Service Award and AG-00078. Computing facilities were provided by the General Clinical Research Center.

The authors gratefully acknowledge the excellent technical assistance of Robert Hickner, Charles Lambert, David Van Houten, and the nursing staff of the General Clinical Research Center.

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