Original Article

Effects of Age and Sex on Postprandial Glucose Metabolism

Differences in Glucose Turnover, Insulin Secretion, Insulin Action, and Hepatic Insulin Extraction

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To determine the effects of age and sex on the regulation of postprandial glucose metabolism, glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction were concurrently measured in 145 healthy elderly (aged 70 ± 1 years) and in 58 young (aged 28 ± 1 years) men and women before and after ingestion of a mixed meal containing [1-^{13}C]glucose. At the time of meal ingestion, [6-^{3}H]glucose and [6,6-$^{2}H_2$]glucose were infused intravenously to enable concurrent measurement of the rates of postprandial endogenous glucose production (EGP), meal appearance, and glucose disappearance. Fasting and postprandial glucose concentrations were higher ($P < 0.001$) in both elderly women and elderly men compared with young individuals of the same sex. The higher postprandial glucose concentrations in the elderly than young women were caused by higher rates of meal appearance ($P < 0.01$) and slightly lower ($P < 0.05$) rates of glucose disappearance immediately after eating. In contrast, higher glucose concentrations in the elderly than young men were solely due to decreased ($P < 0.001$) glucose disappearance. Although postprandial glucose concentrations did not differ in elderly women and elderly men, rates of meal appearance and glucose disappearance rates both were higher ($P < 0.001$) in the women. Fasting EGP was higher ($P < 0.05$) in elderly than young subjects of both sexes and in women than men regardless of age. On the other hand, postprandial suppression of EGP was rapid all groups. Insulin action and secretion were lower ($P < 0.001$) in the elderly than young men but did not differ in the elderly and young women. This resulted in lower ($P < 0.001$) meal disposition indexes in elderly than young men but no difference in elderly and young women. Total meal disposition indexes were lower ($P < 0.05$) in elderly men than elderly women, indicating impaired insulin secretion, whereas disposition indexes were higher ($P < 0.05$) in young men than young women. Hepatic insulin clearance was greater ($P < 0.001$) in the elderly than young subjects of both sexes but did not differ between men and women regardless of age. In contrast, the ability of glucose to facilitate its own uptake (glucose effectiveness) was higher ($P < 0.001$) in women than men but did not differ in elderly and young subjects. Thus, age and sex impact on insulin secretion, insulin action, hepatic insulin extraction, and glucose effectiveness, resulting in substantial differences in the regulation of postprandial glucose metabolism in men and women and in elderly and young subjects. *Diabetes* 55:2001–2014, 2006

It is well established that glucose tolerance decreases with age and that this decrease is commonly associated with impaired insulin secretion and action. However, most previous studies have measured insulin action during intravenous glucose or insulin administration, and many studies have measured plasma insulin concentrations rather than actual insulin secretion rates (1–16). Therefore, the contribution of these abnormalities to the alterations in glucose tolerance observed in elderly individuals under conditions of daily living remains uncertain. To our knowledge, only one study has attempted to assess the effects of age on postprandial glucose turnover. In that study, Jackson et al. (17) reported that higher glucose concentrations after glucose challenge in elderly men were caused by a combination of excessive endogenous glucose production (EGP) and decreased glucose disposal. However, only 10 elderly and 10 young men were studied, and the so-called "dual" tracer approach was used to assess postprandial glucose turnover; this method is now known to be inaccurate because of the marked changes in plasma tracee-to-tracer ratios that occur (18). We are unaware of any study that has specifically examined the mechanism of postprandial hyperglycemia in elderly women or that has determined whether the cause of postprandial hyperglycemia differs in elderly women and elderly men. We also are unaware of any study that has addressed the same question in young men and women. Of interest in this regard, epidemiologic studies have noted that impaired glucose tolerance (i.e., an elevated glucose concentration 2 h after glucose challenge) is more common in women than men (5–7,19,20).

We have previously reported that insulin secretion and action were lower and hepatic insulin clearance higher in

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EGP, endogenous glucose production.

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67 elderly subjects when compared with 23 younger subjects (1). Insulin secretion and action were measured in those studies using unlabeled oral and intravenous glucose and C-peptide models. However, because of the small sample size, we were unable to determine whether the defects observed in the elderly subjects were influenced by sex. In addition, because tracer data were not available at that time, we could not determine the relative contribution of alterations in the meal appearance, EGP, and glucose disposal to postprandial hyperglycemia. To address these questions, we have extended those studies to include 145 elderly and 58 young men and women. Rates of meal appearance, EGP, and glucose disposal were measured after ingestion of a mixed meal with a recently validated triple-tracer method that avoids marked postprandial changes in plasma tracer-to-tracee ratios (18). Net insulin action (S_I) and the effects of insulin on glucose disposal (S_I*), respectively, were measured with the unlabeled and labeled oral "minimal" models (1,21–25) and insulin secretion and clearance with the C-peptide minimal model (26–29). We report that age and sex impact on insulin secretion, insulin action, hepatic insulin extraction, and glucose effectiveness, resulting in substantial differences in the regulation of postprandial glucose metabolism in men and women and in elderly and young subjects.

RESEARCH DESIGN AND METHODS

After approval from the Mayo Institutional Review Board, 203 healthy subjects (86 elderly men, 59 elderly women, 30 young men, and 28 young women) gave informed written consent to participate in the study. All subjects were in good health and did not perform regular vigorous physical activity.

The experimental design has been previously described in detail (1). In brief, all subjects consumed a weight maintenance diet (55% carbohydrate, 15% protein, and 30% fat) provided by the General Clinical Research Center kitchen for 3 days preceding study. All subjects were admitted at 1600 on the afternoon before study and given a standard 10-kcal/kg meal (55% carbohydrate, 15% protein, and 30% fat), which was consumed between 1700 and 1730. No additional food was eaten until the next morning.

At ~0600 on the morning of study, an 18-gauge cannula was inserted in a retrograde fashion into a dorsal hand vein. The hand was then placed in a heated plexibox (~55°C) to obtain arterialized venous blood samples. Another 18-gauge cannula was inserted in the opposite forearm for infusion of tracers. A primed-continuous infusion of [6,6-$^2H_2$]glucose (11.84 mg/kg prime; 0.1184 mg · kg^{-1} · min^{-1} continuous; Mass-Trace, Woburn, MA) was started at 0700 and continued until the end of the study at 1600. [^{3}H]palmitate also was infused starting at 0800 to measure turnover as part of a separate protocol. At 0900 (0 time), a mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, and 40% fat) consisting of scrambled eggs, Canadian bacon, [1-^{13}C]glucose Jell-O (containing 1.2 g/kg body wt dextrose) was consumed within 15 min (18). An infusion of [6-^{3}H]glucose (1.2 μCi/ml; New England Nuclear, Boston, MA) was started at time 0, and the rate varied to mimic the anticipated rate of appearance of the [1-^{13}C]glucose contained within in the meal. At the same time, the rate of infusion of [6,6-$^2H_2$]glucose was altered to approximate the anticipated pattern of fall in EGP, thereby minimizing the change in plasma glucose enrichment. Blood was sampled from the arterialized venous site at −120, −30, −20, −10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, and 420 min. Intravenous lines were then removed, and the subject ate lunch immediately after completion of the study (~1600–1700) and a supper at ~2000–2030. An insulin-modified intravenous glucose tolerance test was also performed in these subjects; however, those data are not presented because of space limitations.

Analytical techniques. Plasma samples were placed on ice, centrifuged at 4°C, separated, and stored at −20°C until assay. Plasma glucose concentrations were measured using a glucose oxidase method (YSI, Yellow Springs, OH). Plasma insulin concentrations were measured using a chemiluminescence assay with reagents (Access Assay; Beckman, Chaska, MN). Plasma C-peptide concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO). Body composition was measured using dual-energy X-ray absorptiometry (DPX scanner; Lunar, Madison, WI). Visceral fat was measured by a single-slice computerized tomographic scan at the level of L2/L3 (30). Peak oxygen uptake ($V_{O_{2max}}$) was measured using a standard treadmill stress test (31). Knee extensor strength was measured by having each subject lift a progressively higher weight using a bilateral leg press machine (Cybex, Medway, MA) until the one-repetition maximum was reached. Consecutive attempts were separated by 1 min of rest (32). Subjects were familiarized with the equipment and test procedures before data collection.

Calculations. The "oral" glucose minimal model (22,25) was used to interpret plasma glucose and insulin concentrations measured during the meal test. The model assumes that insulin action on glucose production and disposal emanates from a compartment remote from plasma, which is usually identified with the interstitium. The most important parameters of the model, which are estimated from data, are S_I, which measures the overall effect of insulin to stimulate glucose disposal and inhibit glucose production, and net glucose effectiveness (GE), which measures the ability of glucose per se to promote glucose disposal and inhibit glucose production. Similarly, the labeled oral glucose minimal model (23) was used to interpret glucose tracer and insulin concentrations. The most important parameters of the model are the selective effect of glucose on glucose disposal (GE*) and S_I*.

The oral C-peptide minimal model (26), incorporating age-associated changes in C-peptide kinetics as measured by Van Cauter et al. (33), was used to interpret plasma glucose and C-peptide concentrations measured during the test. The model assumes that insulin secretion is made up of two components. The dynamic component is likely to represent secretion of promptly releasable insulin and is proportional to the rate of increase of glucose concentration through a parameter, Phi, which defines the response to a given increment in glucose. The static component is believed to represent the provision of new insulin into a releasable pool and is characterized by a static index, Phi_{static}, and by a delay time constant, T Phi_{static}, the response to an increment in glucose above basal that tends with time as constant T toward a steady state. The overall β-cell response to glucose (Phi_{total}) is a composite of $Phi_{dynamic}$ and Phi_{static}. As previously suggested (1,34,35), the appropriateness of insulin secretion for the prevailing level of insulin resistance can be determined by calculating disposition indexes $Di_{dynamic}$, Di_{static}, and Di_{total} by multiplying $Phi_{dynamic}$, Phi_{static}, and Phi_{total}, respectively, by S_I. Hepatic insulin extraction in the basal state and during the meal was determined by calculating insulin secretion using plasma C-peptide concentrations and the C-peptide minimal model and by calculating posthepatic delivery using plasma insulin concentrations and the insulin minimal model (28,29).

The systemic rates of meal appearance (Ra_{meal}), EGP, and glucose disappearance were calculated using Radzuik's two-compartment model (36) by using the triple-tracer approach (18). In brief, Ra_{meal} was calculated by multiplying rate of appearance of [1-^{13}C]glucose (obtained form the infusion rate of [6-^{3}H]glucose and the clamped plasma ratio of [6-^{3}H]glucose and [1-^{13}C]glucose) by the meal enrichment (i.e., the ratio of total glucose to tracer in the meal). EGP was calculated from the infusion rate of [6,6-$^2H_2$]glucose and the clamped plasma ratio of [6,6-$^2H_2$]glucose to endogenous glucose concentration. Glucose disappearance was calculated by subtracting the change in glucose mass from the overall rate of glucose appearance (i.e., Ra_{meal} + EGP). As previously discussed in detail (18), this approach is virtually model independent, yielding essentially the same results when interpreted using steady-state or non–steady-state assumptions and either a one-compartment or a two-compartment model.

Values from −30 to 0 min were averaged and considered as basal. Area above basal was calculated using the trapezoidal rule. Parameters of all models were estimated by using the SAAMII software (37). Measurement errors have been assumed to be independent and Gaussian, with zero mean and variance for glucose and tracer glucose as described by Dalla et al. (38) and for C-peptide as described previously (29).

Statistical analysis. Data are presented as means ± SE. Two sample comparisons between the elderly and young subjects and between men and women were made using t tests or rank-sum tests for data that were not normally distributed. Pearson's or Spearman's r was used to evaluate univariate correlations. All predictors were considered in a forward stepwise model selection process using multiple linear regression to determine significant multivariate predictors. Age was used as an indicator of elder or young status. A P value of <0.05 was considered to be statistically significant.

RESULTS

As expected, both percent body fat and visceral fat were greater ($P < 0.001$) in elderly than young women and in elderly than young men. Lean body mass was lower ($P < 0.05$) in elderly than young women but did not differ in elderly and young men. Peak oxygen consumption, one-time bench press, double knee extension, and isometric knee extension all were lower ($P < 0.001$) in elderly than young women and in elderly than young men (Table 1).

TABLE 1
Volunteer characteristics

	Elderly men	Young men	Elderly women	Young women
Subjects (n)	86	30	59	28
Age (years)	68.6 ± 0.6	23.5 ± 0.6	70.3 ± 0.8	22.3 ± 0.6
BMI (kg/m^2)	27.6 ± 0.3	25.1 ± 0.5	27.3 ± 0.5	24.0 ± 0.5
Percent body fat	27.0 ± 0.6	20.8 ± 1.3	41.8 ± 0.8	31.9 ± 1.3
Lean body mass (kg)	57.4 ± 0.6	59.3 ± 0.9	37.3 ± 0.5	39.4 ± 0.6
Visceral fat (cm^2)	208 ± 10	74 ± 8	117 ± 7.0	37 ± 4
Vo_{2max} (ml · kg^{-1} · min^{-1})	27.1 ± 0.6	42.9 ± 1.2	20.0 ± 0.6	34.6 ± 1.1
Double knee extension (lb)	102 ± 3	166 ± 6	70 ± 3	97 ± 4
Isometric knee extension (lb)	98 ± 2	133 ± 5	59 ± 2	84 ± 4
Seated chest press (lb)	119 ± 2	178 ± 6	69 ± 2	88 ± 3

Data are means ± SE.

Percent body fat was greater ($P < 0.0001$), whereas visceral fat and lean body mass were lower ($P < 0.001$) in elderly women than elderly men and in young women than young men. Peak oxygen consumption, one-time bench press, double knee extension, and isometric knee extension all were lower ($P < 0.001$) in elderly women than in elderly men and in young women than in young men.

Effects of age

Effects of age on plasma glucose, insulin, and C-peptide concentrations. To determine the effects of age independent of sex on postprandial glucose metabolism, results observed in the elderly women were compared with those observed in the young women, and those observed in the elderly men were compared with those observed in young men (Fig. 1 and Table 2). Fasting plasma glucose concentrations were higher ($P < 0.001$) in elderly than young women and in elderly than young men. Meal ingestion resulted in a greater postprandial glycemic excursion (i.e., area above basal) in elderly women than young women ($P < 0.05$) and in elderly than young men ($P < 0.001$).

Neither fasting insulin nor peak insulin concentrations differed in the elderly and young women or in the elderly and young men. Total insulin area above basal did not differ in the elderly and young women but was higher ($P < 0.05$) in the elderly than young men. On the other hand, the area above basal of plasma insulin during the 1st h after food ingestion (i.e., when glucose concentrations were diverging between groups) tended to be lower in elderly than young women ($P = 0.06$) and was significantly lower in elderly than young men ($P < 0.001$).

Fasting C-peptide concentrations were higher in elderly than young women ($P < 0.01$) and in elderly than young men ($P < 0.001$). The C-peptide area above basal was greater in elderly than young women ($P < 0.001$) and in elderly than young men ($P < 0.001$). C-peptide area above basal during the 1st h after meal ingestion tended to be lower in elderly than young women ($P = 0.05$) and was lower in the elderly than young men ($P < 0.001$).

Effects of age on meal appearance, EGP, and glucose disappearance. Meal appearance peaked at ~30 min and then fell thereafter to rates that approximated basal by the end of the 7 h of study. Whereas the total meal appearance was greater ($P < 0.01$) in elderly than young women, it did not differ in the elderly and young men (Fig. 2 and Table 2).

Fasting EGP was higher in elderly than young women ($P < 0.05$) and in elderly than young men ($P < 0.01$). After meal ingestion, EGP promptly decreased in all groups with the degree of suppression (i.e., area below basal) being greater in elderly women than young women ($P < 0.01$) and in the elderly than young men ($P < 0.001$).

The area above basal of glucose disappearance did not differ in elderly and young women or in elderly and young men. However, glucose disappearance was slightly but significantly lower ($P < 0.05$) in the elderly than young women during the 1st h after meal ingestion when postprandial glucose concentrations were diverging between groups. Glucose disappearance during the 1st h after meal ingestion was markedly lower ($P < 0.001$) in elderly than young men.

Effects of age on insulin action and glucose effectiveness. Both S_I and S_I* were lower ($P < 0.001$) in the elderly than young men. In contrast, neither S_I or S_I* differed in the elderly and young women. GE did not differ in any of the groups. The GE* also did not differ in the elderly and young women or in the elderly and young men (Fig. 3).

Effects of age on insulin secretion, hepatic insulin extraction, and disposition indexes. Phi_{total} was lower ($P < 0.001$) in the elderly than young men because of a decrease ($P < 0.001$) in the dynamic response to glucose ($Phi_{dynamic}$), indicating a decreased ability to secrete insulin in response to a change in glucose concentration (Figs. 4–6). On the other hand, the response to a given increment in glucose above basal concentration (Phi_{static}) did not differ between the elderly and young men. Phi_{total}, $Phi_{dynamic}$, and Phi_{static} did not differ in the elderly and young women. Disposition indexes were calculated to determine whether insulin secretion was appropriate for the prevailing level of insulin action. As is evident in Fig. 6, the relationship between insulin action and insulin secretion was shifted to the left in the elderly compared with the young men. This resulted in lower ($P < 0.001$) mean Di_{total}, $Di_{dynamic}$, and Di_{static} in elderly than young men (690 ± 43 vs. 1,536 ± 149; 8,235 ± 592 vs. 20,332 ± 2,042; and 621 ± 38 vs. 1,192 ± 110; 10^{-14} dl/kg/min^2 per pmol/l for Di_{total} and Di_{static} and 10^{-14} dl/kg/min per pmol/l for $Di_{dynamic}$), indicating that insulin secretion was not appropriate for the prevailing level of insulin action in elderly men. In contrast, the relationship between insulin action and insulin secretion was the same in the elderly and young women, resulting in no difference in mean Di_{total}, $Di_{dynamic}$, or Di_{static} (730 ± 58 vs. 931 ± 96; 9,272 ± 1,033 vs. 11,954 ± 1,555; and 645 ± 49 vs. 799 ± 79; 10^{-14} dl/kg/min^2 per pmol/l for Di_{total} and Di_{static} and 10^{-14} dl/kg/min per pmol/l for $Di_{dynamic}$). Hepatic insulin extraction was higher in elderly than young women ($P < 0.002$) and in elderly than young men ($P < 0.02$) both before and after meal ingestion (Fig. 5).

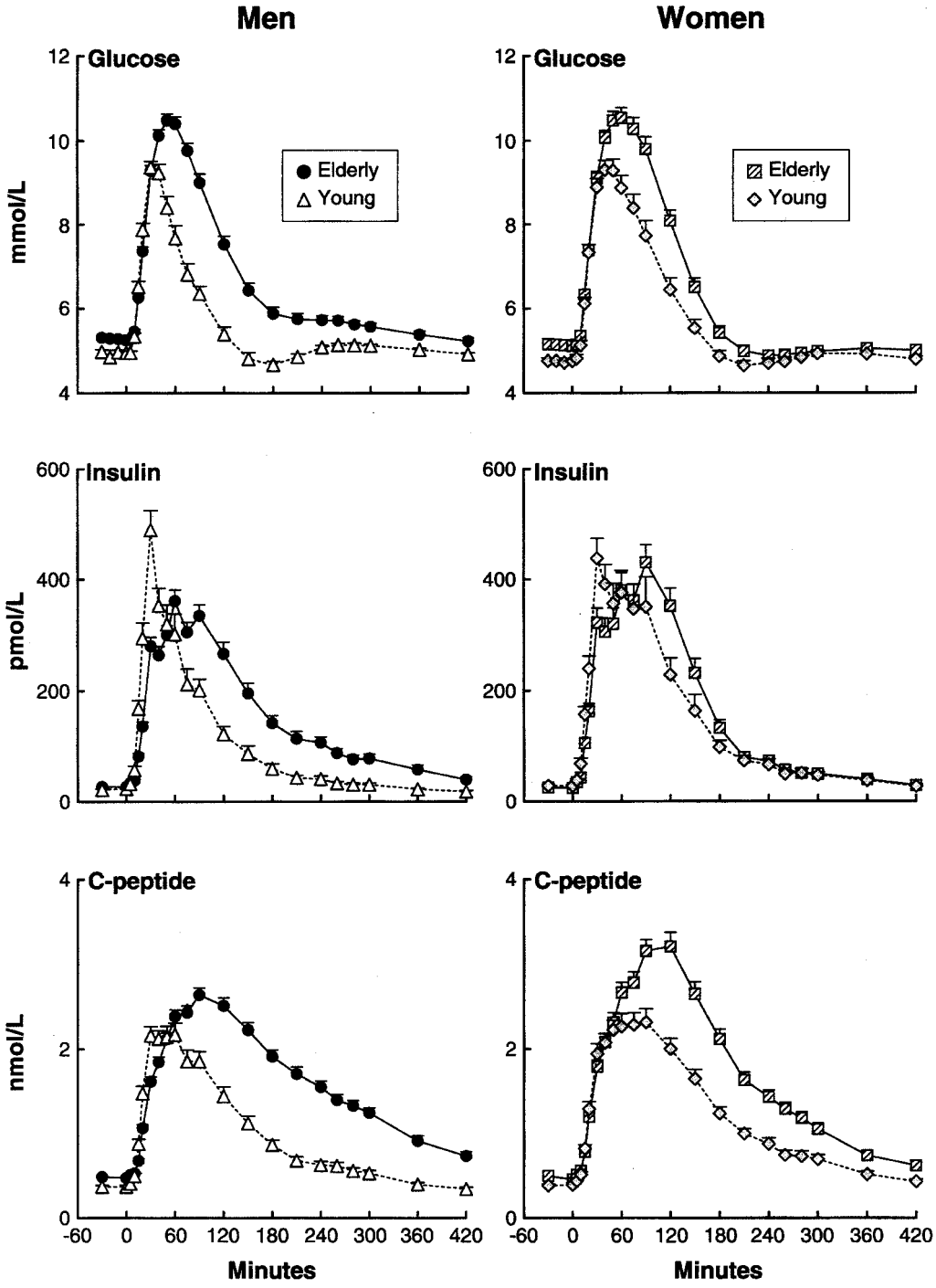

FIG. 1. Plasma glucose, insulin, and C-peptide concentrations observed in elderly and young men (*left*) and elderly and young women (*right*) before and after ingestion of a mixed meal at time 0.

Effects of sex

Effects of sex on glucose, insulin, and C-peptide concentrations. To determine the effects of sex independent of age on postprandial glucose metabolism, results observed in the elderly women were compared with those observed in the elderly men, and those observed in the young women were compared with those observed in young men (Fig. 6 and Table 2). Fasting plasma glucose concentrations were lower ($P < 0.05$) in elderly women than elderly men and in young women than young men. Whereas the postprandial glycemic area above basal did not differ in elderly men and women, it was greater ($P < 0.001$) in young women than young men. Fasting and postprandial area above basal plasma insulin and C-peptide concentrations did not differ in the elderly women and men. Peak postprandial insulin ($P < 0.02$) and C-peptide ($P < 0.001$) concentrations were higher in the elderly women than elderly men. Fasting insulin concentrations did not differ in the young women and young men; however, postprandial insulin concentrations were higher in the women ($P < 0.01$). C-peptide area above basal also was higher ($P < 0.002$) in the young women than young men.

Effects of sex on meal appearance, EGP, and glucose disappearance. Fasting EGP was higher ($P < 0.001$) in elderly women than elderly men and in young women than young men. EGP rapidly suppressed to comparable rates in both women and men after meal ingestion. Meal appear-

TABLE 2
Hormone concentrations and glucose turnover before and after mixed meal ingestion

	Elderly men	Elderly women	Young men	Young women
Glucose (mmol/l)				
Fasting	5.3 ± 0.1	5.1 ± 0.1	4.9 ± 0.1	4.7 ± 0.1
Area 0–60 min	188 ± 5	193 ± 6	168 ± 7	181 ± 9
Area 0–420 min	550 ± 25	519 ± 24	272 ± 24	420 ± 32
Insulin (nmol/l)				
Fasting	0.03 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.03 ± 0.00
Area 0–60 min	10.5 ± 0.6	12.0 ± 0.9	15.2 ± 1.2	15.1 ± 1.3
Area 0–420 min	51.0 ± 3.3	54.2 ± 4.1	31.8 ± 2.9	46.2 ± 5.0
C-peptide (nmol/l)				
Fasting	0.5 ± 0.0	0.5 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
Area 0–60 min	56 ± 2	65 ± 3	73 ± 4	69 ± 4
Area 0–420 min	467 ± 18	502 ± 25	244 ± 15	329 ± 21
Meal appearance (μmol · kg^{-1} · min^{-1})				
Total area 0–60 min	2,135 ± 81	2,990 ± 104	2,774 ± 106	2,773 ± 99
Total area 0–420 min	9,029 ± 228	11,666 ± 353	8,929 ± 336	10,073 ± 331
Glucose production (μmol · kg^{-1} · min^{-1})				
Fasting	15.2 ± 0.4	18.6 ± 0.6	13.4 ± 0.3	16.4 ± 0.3
Area 0–60 min	−429 ± 31	−621 ± 42	−522 ± 41	−553 ± 55
Area 0–420 min	−3,910 ± 185	−4,305 ± 189	−2,306 ± 179	−3,298 ± 222
Glucose disappearance (μmol · kg^{-1} · min^{-1})				
Fasting	15.9 ± 0.4	19.3 ± 0.7	14.6 ± 0.3	17.2 ± 0.3
Area 0–60 min	631 ± 63	898 ± 98	1,672 ± 97	1,229 ± 80
Area 0–420 min	5,497 ± 246	7,849 ± 309	6,775 ± 277	7,096 ± 294

Data are means ± SE. Area denotes above or below basal.

ance was higher in elderly women than elderly men ($P < 0.001$) and in young women than young men ($P < 0.05$). Both total area above basal of glucose disappearance ($P < 0.001$) and the area above basal during the 1st h after meal ingestion ($P < 0.05$) were lower in elderly men than women. On the other hand, whereas the area above basal of glucose disappearance was lower ($P < 0.002$) in young women than young men during the 1st h after eating, the total area above basal did not differ between groups (Fig. 7 and Table 2).

Effects of sex on insulin action and glucose effectiveness. Although S_I was numerically lower in elderly men than elderly women and in young women than young men, the differences were not statistically significant (Fig. 3). On the other hand, the S_I* was lower ($P < 0.005$) in young women than young men but did not significantly differ in elderly women and elderly men.

GE did not differ in elderly women and elderly men or in young women and young men. On the other hand, GE* was greater in elderly women than elderly men ($P < 0.001$) and in young women than young men ($P < 0.001$).

Effects of sex on insulin secretion. Indexes of insulin secretion did not differ in elderly women and elderly men or in young women and young men (Figs. 4 and 5). However, as is evident in Fig. 5, the relationship between insulin action and insulin secretion was shifted to the left in elderly men compared with elderly women, resulting in a lower ($P < 0.01$) mean Di_{total}, Di_{static}, and $Di_{dynamic}$ in the elderly men. In contrast, mean Di_{total} and $Di_{dynamic}$ were lower ($P < 0.05$) in young women than young men, whereas Di_{static} did not differ between groups. Hepatic insulin extraction was higher ($P < 0.01$) in elderly women than elderly men before meal ingestion but did not differ after meal ingestion. Hepatic insulin extraction did not differ in young women and young men after meal ingestion.

Correlations. To determine whether differences (or lack thereof) in insulin action were influenced by other variables, multivariate analyses were performed. Visceral fat was an independent predictor of both S_I ($P < 0.002$) and S_I* ($P < 0.001$), whereas age, sex, fasting glucose, peak oxygen consumption, postprandial plasma free fatty acids, and double knee and isometric knee extension were not.

DISCUSSION

The present study provides new insight regarding the independent effects of age and sex on the regulation of postprandial glucose metabolism. First, higher postprandial glucose concentrations in the elderly than young men result from lower rates of glucose disappearance because postprandial suppression of EGP and systemic appearance of ingested glucose do not differ between groups. In contrast, higher postprandial glucose concentrations in elderly than young women are due to greater meal appearance combined with a slight decrease in early postprandial glucose disappearance. Second, although both S_I and S_I* are lower in elderly than young men, these differences are accounted for by greater visceral obesity in the elderly men rather than age per se. Third, the ability of insulin to stimulate glucose disposal is lower in young women than young men despite lower visceral obesity in the former, indicating that other factors also modulate insulin action.

Fourth, when considered in light of the prevailing degree of insulin action, all aspects of insulin secretion (i.e., the total, dynamic, and static responses to glucose) are lower in elderly than young men. In contrast, postprandial insulin secretion and action do not differ in elderly and young women. Fifth, despite equivalent postprandial glucose concentrations, meal appearance and postprandial glucose disappearance are higher in elderly women than elderly men. Sixth, the ability of glucose to stimulate its own uptake is greater in women than men regardless of age, implying a more important role of glucose effectiveness in the regulation of postprandial glucose concentra-

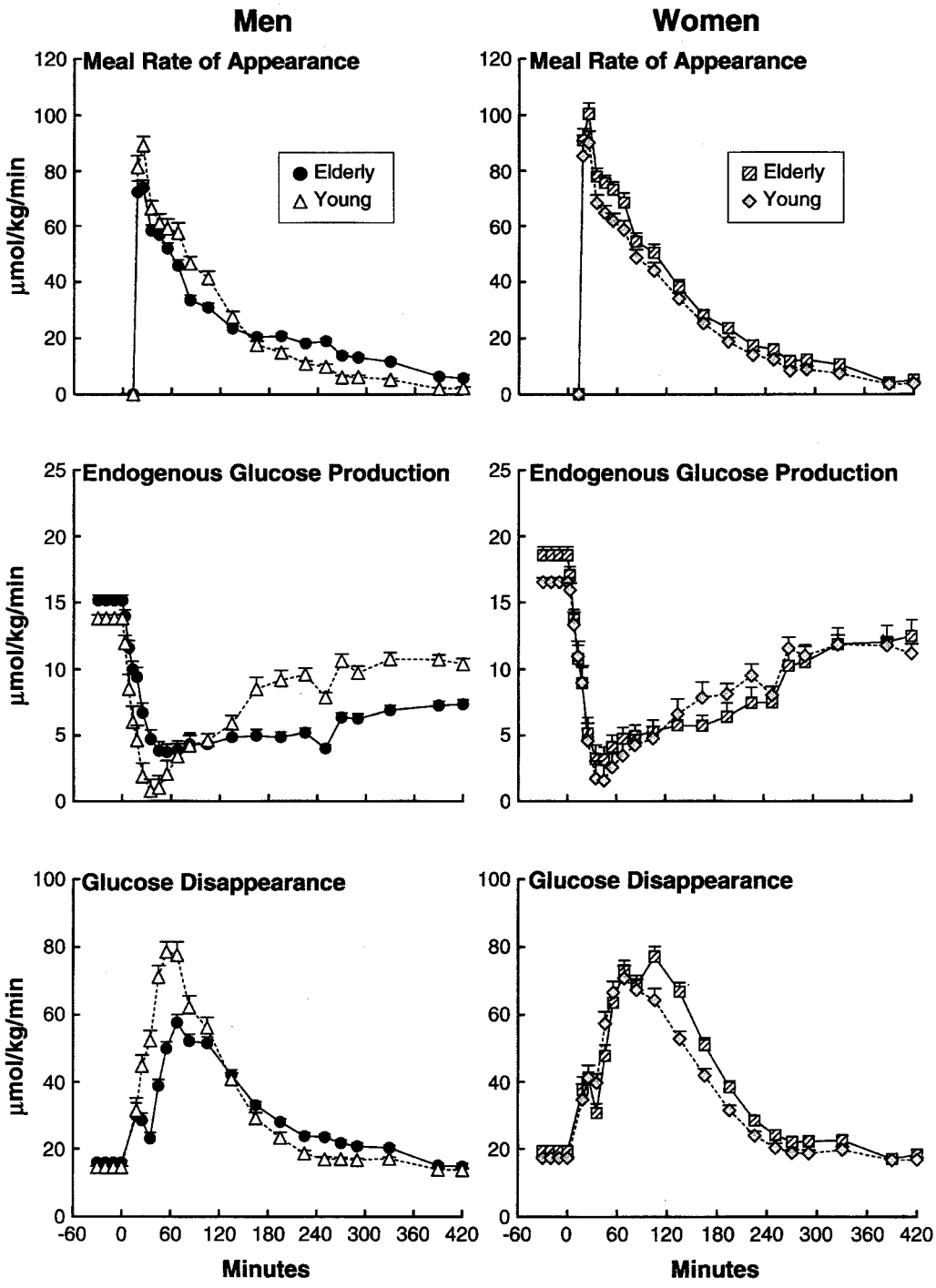

FIG. 2. Meal rate of appearance, EGP, and glucose disappearance observed in elderly and young men (*left*) and elderly and young women (*right*) before and after ingestion of a mixed meal at time 0.

tions in women. Finally, the greater hepatic insulin extraction in elderly than young subjects reduces the amount as well as the rate at which insulin reaches the systemic circulation, thereby exacerbating other age-related defects in postprandial glucose metabolism.

Effects of age on glucose metabolism

Differences in the regulation of glucose metabolism in elderly and young men. Fasting rates of EGP were higher in the elderly than young men despite higher fasting C-peptide concentrations and therefore presumably higher portal insulin concentrations. This implies that hepatic insulin resistance contributes to fasting hyperglycemia in the elderly men. On the other hand, suppression of endogenous glucose in response to the concurrent rise in glucose and insulin after meal ingestion, if anything, was greater in the elderly than young men. This conclusion contradicts that of Jackson et al. (17), who reported that suppression of glucose production after drinking 100 g glucose was lower in elderly than young men. However, only 10 elderly and young men were studied, and the dual-tracer method was used to measure postprandial glucose turnover precluding accurate measurement of EGP due to the marked tracer-to-tracee non–steady state that occurs after meal ingestion (18).

Meal appearance also did not differ in the elderly and young men in the present studies. Because overall glucose disposal is the sum of hepatic and extrahepatic glucose uptake, the absence of a change in meal appearance

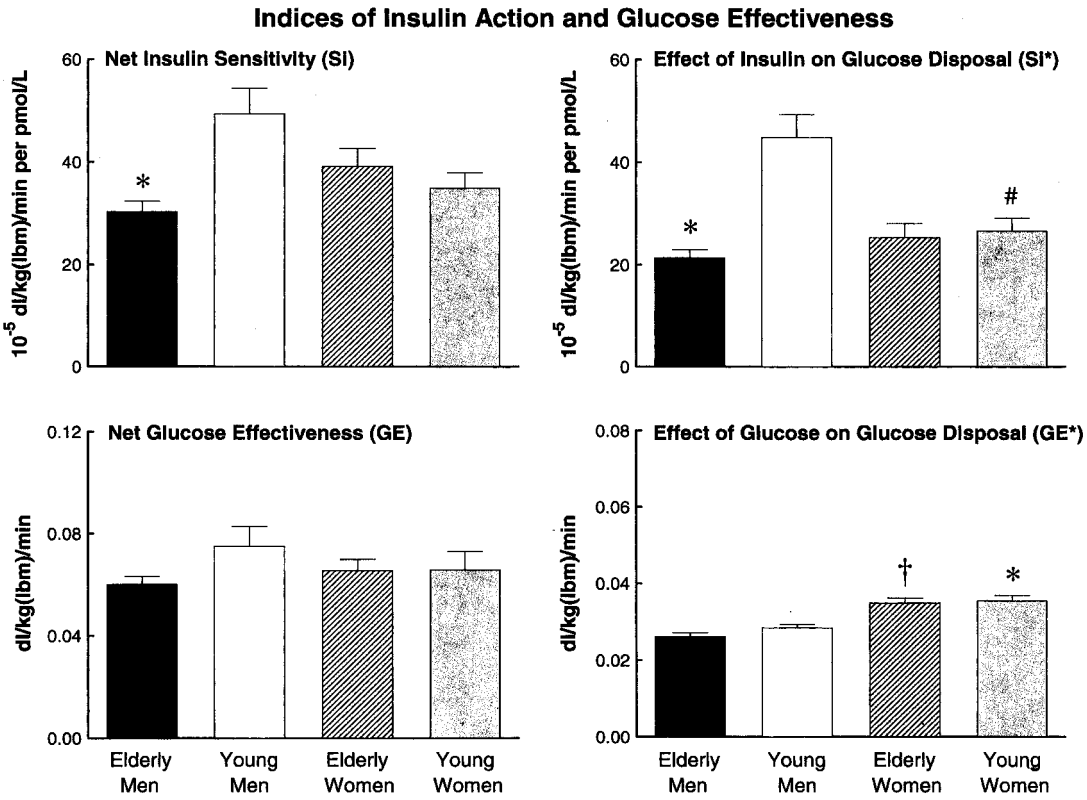

FIG. 3. Indexes of insulin action and glucose effectiveness observed in elderly and young men and elderly and young men women after ingestion of a mixed meal. #P < 0.01 vs. young men; *P < 0.001 vs. young men; †P < 0.001 vs. elderly men.

strongly suggests that the lower rates of glucose disposal in the elderly men were due to reduced uptake by peripheral tissue (e.g., muscle). Meal appearance also did not contribute to the higher postprandial glucose concentrations in the elderly than young men because it did not differ between groups. Taken together, these data indicate that decreased glucose disposal by peripheral tissues was the sole cause of the higher postprandial glucose concentrations in the elderly men.

Defects in insulin action, insulin secretion, and hepatic insulin extraction alone or in combination can cause lower rates of glucose disposal. Insulin action was measured in the current experiments with both the labeled and unlabeled minimal models (1,22–25). This enabled determination that the reduction of S_I in elderly subjects previously reported after food ingestion (1) or glucose infusion (1,2,4,8–12) primarily is due to a decrease in S_I* in elderly men. In addition, as previously reported for S_I (1,4,8,9,12), the S_I* no longer differed in the elderly and young men after adjusting for differences in visceral fat between groups. These data further support the conclusion that the degree of adiposity rather than age per se is the primary cause of peripheral insulin resistance in elderly men.

Insulin secretion involves multiple intracellular processes. When considered in light of the prevailing degree of insulin resistance by calculation of disposition indexes, the present data strongly suggest that many, if not all, of these steps are impaired in elderly men. Consistent with previous investigations that studied elderly subjects of both sexes (1,8,14), the acute response to intravenous glucose, whether measured as the acute insulin response or as Phi_1, was lower in the elderly than young men, implying decreased release of insulin from the readily releasable pool (data not shown). Meal $Phi_{dynamic}$ also was lower. Because this parameter assesses insulin secretion in response to the increase in glucose that occurs during the 45–60 min after meal ingestion, this index reflects multiple distal steps in the insulin secretory pathway (e.g., rate of granule docking, priming, and exocytosis). In addition, steps earlier in the insulin secretory pathway (e.g., synthesis, processing and granule maturation) also were likely involved because both intravenous Phi_2 (data not shown) and meal Phi_{static} were decreased as well. Thus insulin secretion was markedly abnormal in the elderly men regardless of whether the stimulus was glucose alone or glucose in the presence of incretins and other nutrients.

Hepatic insulin extraction was greater in the elderly than young men further reducing the amount of insulin that reached the peripheral circulation. Increased hepatic insulin extraction has previously been reported in a mixed cohort of elderly men and women (1,39). Increased hepatic insulin extraction in the elderly men, combined with impaired insulin secretion and peripheral insulin resistance, presumably resulted in a substantial reduction in peripheral glucose disposal. On the other hand, the liver was exposed to a relatively greater amount of insulin. This combined with the ability of hyperglycemia per se to inhibit hepatic glucose release (40) presumably resulted in normal postprandial suppression of EGP in the elderly men. Taken together, these data indicate that the greater postprandial rise in glucose concentrations in the elderly compared with young men was caused by lower rates of glucose disposal due to insulin resistance, impaired insulin secretion, and increased hepatic insulin extraction.

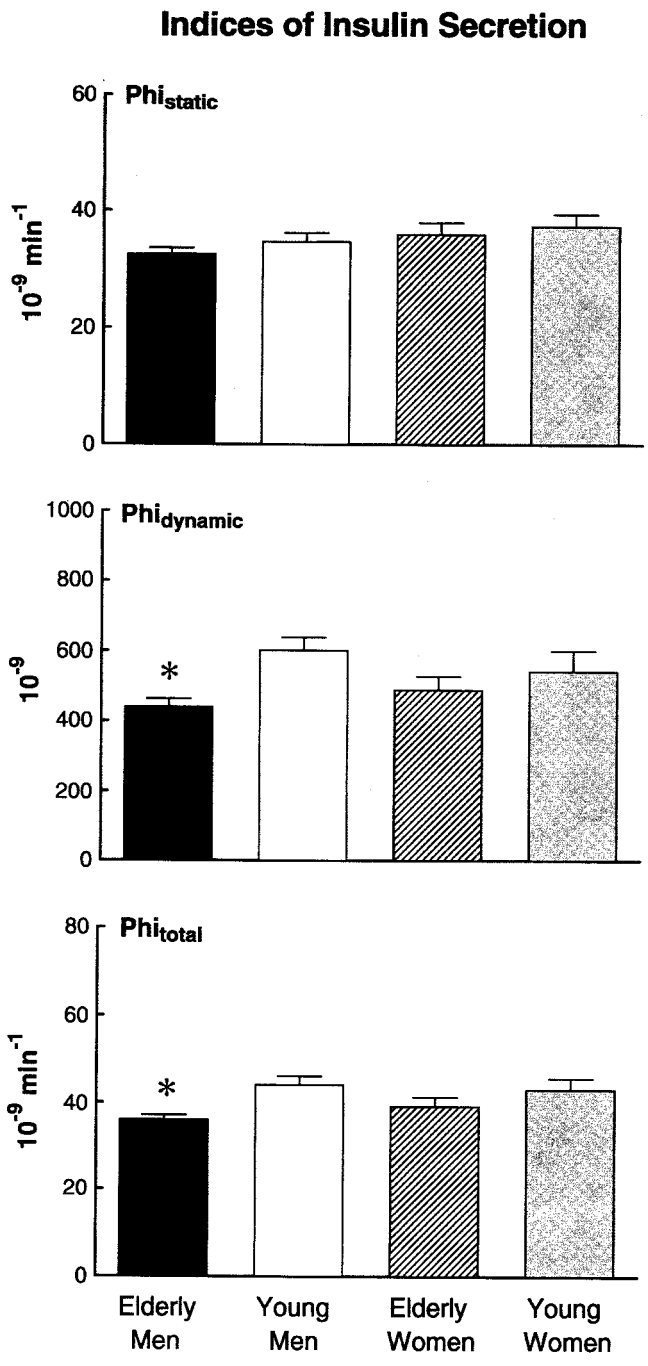

FIG. 4. Insulin secretion indexes observed in elderly and young men and elderly and young women after ingestion of a mixed meal. *P < 0.001 vs. young men; §P < 0.001 vs. young women.

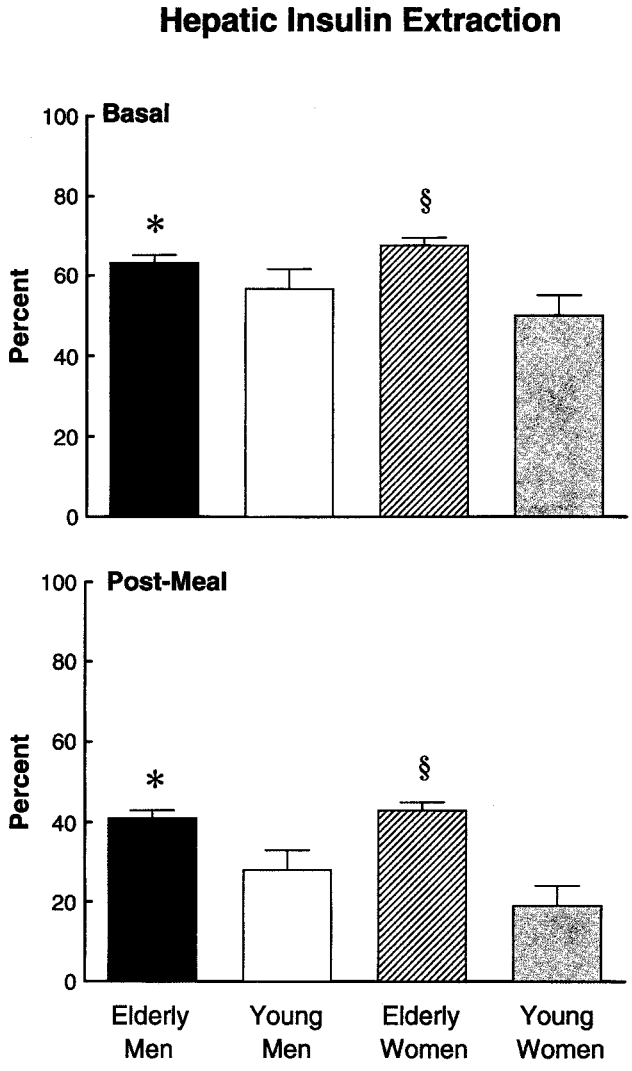

FIG. 5. Hepatic insulin extraction observed in elderly and young men and elderly and young women before and after ingestion of a mixed meal. *P < 0.001 vs. young men; §P < 0.001 vs. young women.

Differences in regulation of glucose metabolism in elderly and young women. As with the men, fasting glucose and C-peptide concentrations and rates of EGP were higher in the elderly than young women, implying that hepatic insulin resistance contributed to the elevated fasting glucose concentrations. EGP also promptly suppressed after meal ingestion in both the elderly and young women. However, in contradiction to what was observed in the elderly men, meal appearance was higher in the elderly than young women. Glucose disappearance was slightly but significantly lower in the elderly than young women during the 1st h after meal ingestion when glucose concentrations were diverging between groups. Therefore, the higher postprandial glucose concentrations in the elderly women were caused by a combination of higher meal appearance and lower glucose disposal. The slightly slower increase in glucose disposal during the 1st h after meal ingestion appeared to be caused by a decrease in posthepatic insulin delivery due to increased hepatic insulin extraction because insulin secretion and insulin action did not differ in the elderly and young women. In addition, the higher glucose concentrations from 60 min onward resulted in a compensatory increase in plasma insulin concentrations that was sufficient to restore glucose concentrations to preprandial levels over the next several hours. Thus, increased meal appearance in the elderly women resulted in the need to dispose of more glucose; this was accomplished by an appropriate increase in insulin secretion in response to the associated higher postprandial glucose concentrations.

The higher rates of meal appearance in the elderly than young women are intriguing. Although this could be due to more rapid absorption in the elderly women, we are unaware of any data indicating that the rate of carbohydrate absorption increases with age. On the other hand, the elderly women ingested slightly more glucose than did

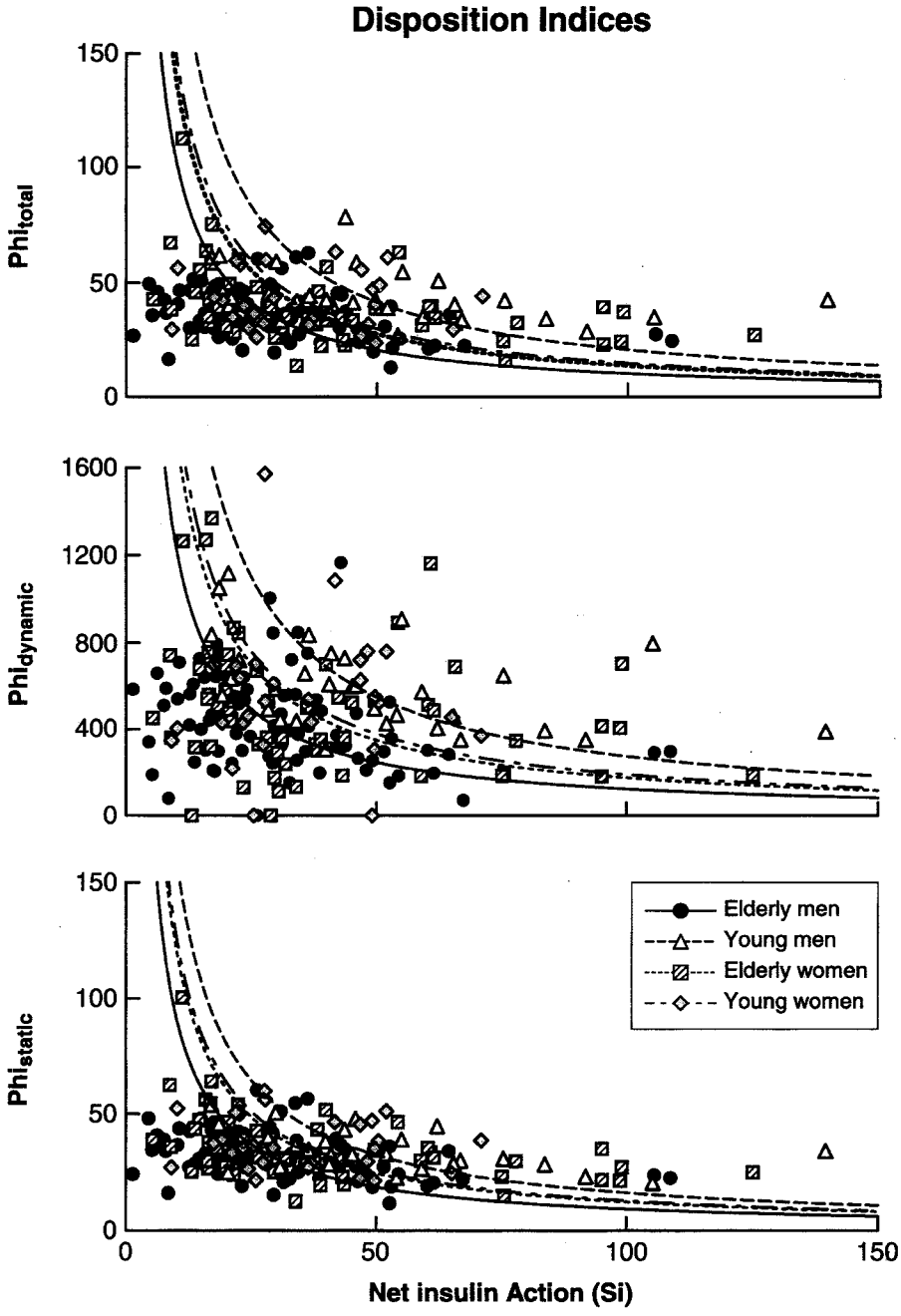

FIG. 6. The relationship between insulin secretion (*x*-axis) and insulin action (*y*-axis) observed in elderly and young men and women after ingestion of a mixed meal.

the young women because their weight also was slightly greater. However, we doubt if this is the explanation because the rate of meal appearance also was greater in elderly women than elderly men (Fig. 8) despite ingesting considerably less glucose (~83 vs. ~105 g). Of interest, in each instance, the elderly women ingested more glucose per lean body weight than did the comparison group. Because lean body mass reflects muscle mass and because muscle is believed to be the primary site of glucose disposal after food ingestion (41), this means that muscle would need to dispose of more glucose per gram of tissue in the elderly women. If this explanation is correct, this potentially has important implications, because 75 g glucose is given during a standard OGTT, which means that women are likely to ingest more glucose per lean body mass than men. This, rather than a greater defect in either insulin secretion or action, may account for the observation that impaired glucose tolerance (i.e., a 2-h glucose concentration over 140 mg/dl) is more common in women than men (5–7,19,20). If so, studies examining the pathogenesis of impaired glucose tolerance may need to reconsider the use of a standard 75-g glucose challenge in individuals whose body weight and composition widely varies.

First-phase insulin secretion was lower in the elderly than young women after intravenous glucose injection (data not shown), implying a decrease in exocytosis from primed insulin granules (42,43). This finding is consistent with previous reports of studies in which sex was mixed (8,39). On the other hand, insulin secretion after meal ingestion, whether measured as change in plasma C-peptide concentration or indexes of insulin secretion derived from the meal C-peptide model, did not differ in the elderly and young women. To our knowledge, this is

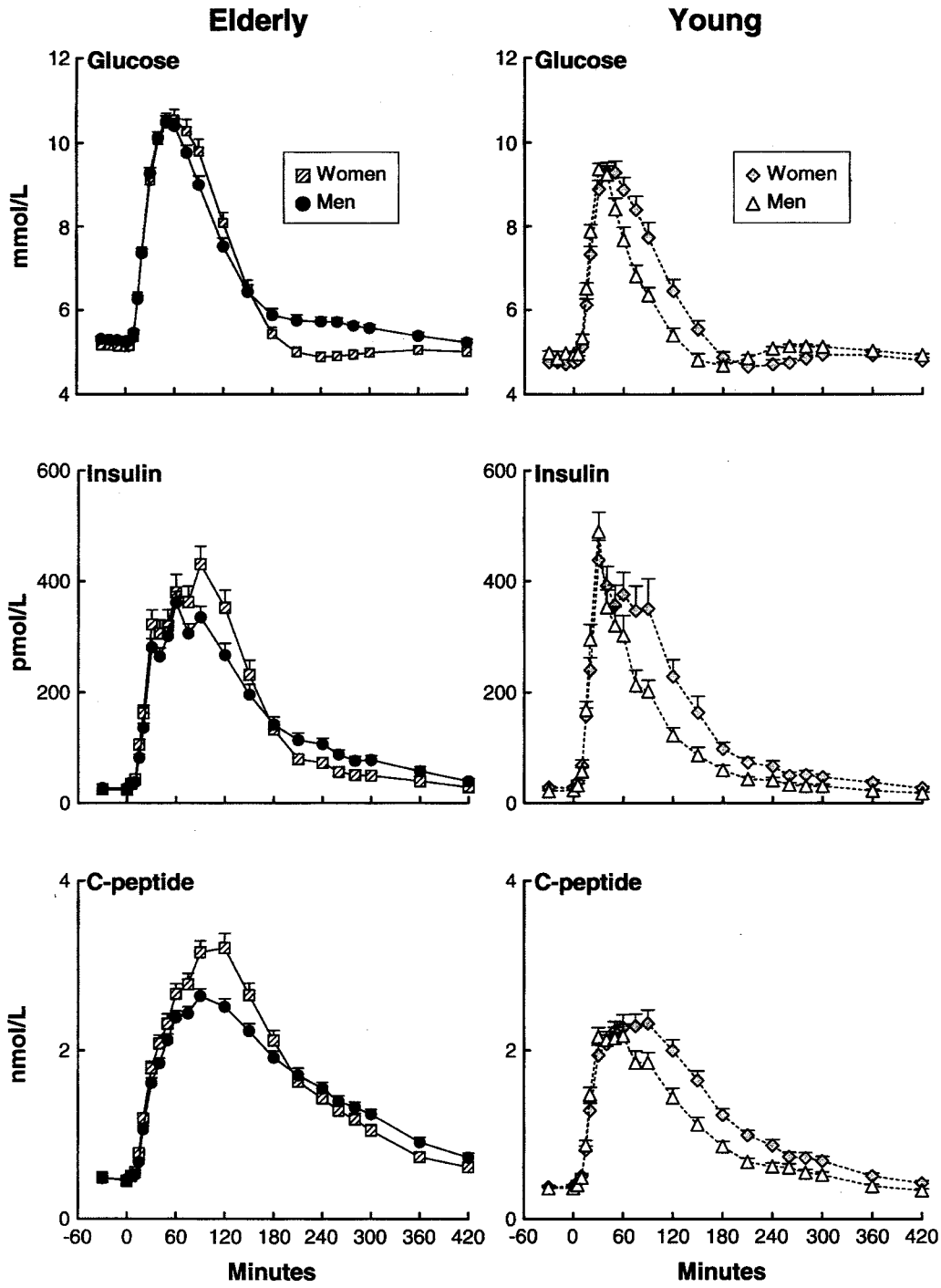

FIG. 7. Plasma glucose, insulin, and C-peptide concentrations observed in elderly (*left*) and young (*right*) men and women before and after ingestion of a mixed meal at time 0 min.

the first time such a discordance between insulin secretion measured after glucose injection and meal ingestion has been observed. As discussed above, insulin secretion after a mixed meal is complex, presumably involving insulin processing, granule docking and priming, and exocytosis. Therefore, the lack of difference in insulin secretion or in any of the meal disposition indexes (Fig. 5) in the elderly and young women after ingestion of a mixed meal implies that the presence of incretins and other nutrients compensates for a defect in insulin exocytosis by stimulating one or more of these processes. These data are particularly interesting because they suggest that intravenous glucose injection may be a more sensitive way of detecting subtle defects in insulin secretion. On the other hand, they also show that a decrease in first-phase insulin secretion after intravenous injection of glucose does not necessarily mean that postprandial hyperglycemia can be attributed to impaired insulin secretion under conditions of daily living.

Insulin action did not differ in the elderly and young women after meal ingestion. The lack of difference in insulin action is noteworthy because despite efforts to match the groups, attributes normally associated with insulin resistance (e.g., higher percent body fat and visceral fat; lower $V\text{O}_{2\text{max}}$ and strength) were more common in the elderly than young women. The lack of difference in insulin action in the elderly and young women but lower insulin action in the elderly than young men primarily occurred because insulin action tended to be lower in the

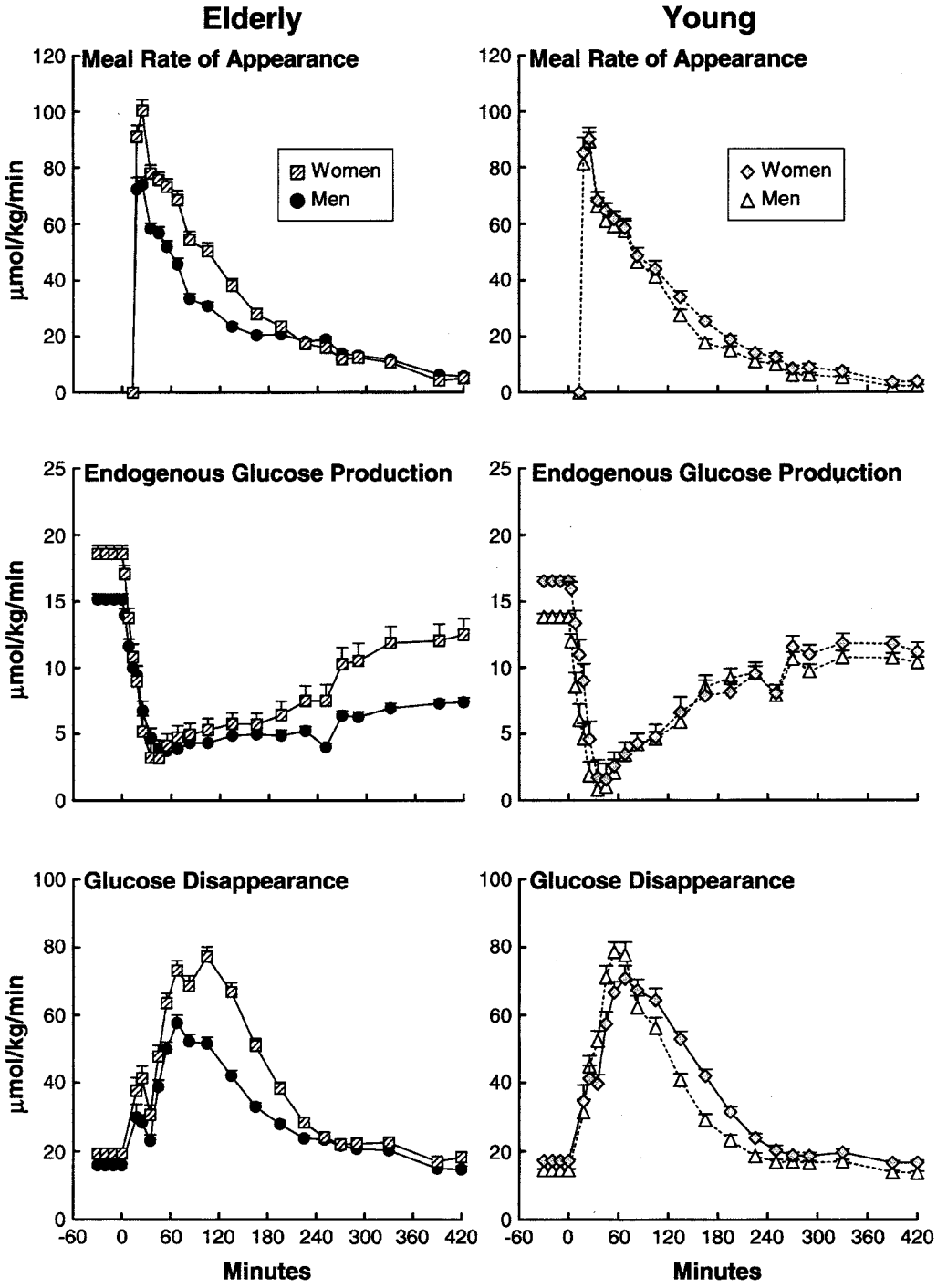

FIG. 8. Meal rate of appearance, EGP, and glucose disappearance observed in elderly (*left*) and young (*right*) men and women before and after ingestion of a mixed meal ingestion at time 0.

young women than young men (see below). Because the lack of difference in insulin action in the elderly and young women is somewhat surprising, it should be emphasized that insulin action was separately assessed using the unlabeled (S_I) and the labeled (S_I*) "minimal" models. In addition, results from the unlabeled and labeled meals and intravenous glucose minimal models (data not shown) were entirely concordant. Because these tests were performed on separate days, they provided two independent measures of insulin action in all subjects. Therefore, although it is possible that a decrease in insulin action in the elderly men but not women when compared with younger individuals of the same sex could have occurred by chance alone, we believe this to be improbable.

As with the elderly men, hepatic insulin extraction was greater in the elderly than young women. Although the cause of the increase in hepatic insulin extraction is not known, the increase in hepatic insulin extraction appeared to have physiologic consequents in the elderly women because it slowed the initial rise in peripheral insulin concentrations, thereby likely contributing to the slightly slower rate of increase in postprandial glucose disposal. If so, therapies that restore hepatic insulin extraction to normal may improve glucose tolerance in elderly individuals.

Effects of sex on glucose metabolism

Regulation of postprandial glucose metabolism in elderly women and elderly men. Because the elderly women and elderly men were matched for age, the present

TABLE 3
Effects of age and sex on postprandial glucose metabolism

	Meal appearance	Glucose production	Glucose disappearance	Insulin action	Insulin secretion*	Glucose effectiveness	Hepatic insulin extraction
Effects of age							
Elderly men vs. young men	↔	↓	↓	↓	↓	↔	↑
Elderly women vs. young women	↑	↓	↔	↔	↔	↔	↑
Effects of sex							
Elderly women vs. elderly men	↑	↔	↑	↔	↔	↑†	↔
Young women vs. young men	↑	↔	↔	↓†	↔	↑†	↔

As per disposition indexes. †S_I lower; GE* higher.

studies also provided insight regarding the effects of sex independent of age on the regulation of glucose metabolism. Fasting glucose concentrations were higher in the elderly women than in the elderly men. On the other hand, fasting EGP was lower in the elderly women, indicating that elevated fasting glucose concentrations are not invariably caused by increased rates of glucose production. Although hepatic insulin action was not directly measured in the current studies, lower rates of EGP in presence of the equal insulin and C-peptide concentrations imply that hepatic insulin and/or glucose sensitivity was greater in the elderly women than elderly men.

Glucose concentrations did not differ in the elderly women and men after meal ingestion. In contrast, postprandial glucose turnover differed dramatically. Meal appearance and postprandial glucose disposal both were substantially higher in the elderly women than elderly men. On the other hand, postprandial suppression of EGP did not differ between groups. Because lean body mass was lower in the elderly women, this meant greater uptake of glucose per kilogram lean body mass. Other components of lean body mass (e.g., bone mass) differed minimally between groups; this implies greater glucose uptake per kilogram of muscle in the elderly women. If so, then changes in muscle glucose metabolism are likely to have a greater impact on glucose tolerance in elderly women than in elderly men. Of note, both S_I* and S_I are expressed per kilogram of lean body mass in the present studies. If S_I were not normalized for lean body mass, it would have been erroneously concluded that insulin action was lower in the elderly women than men because of the fact that the amount of tissue capable of responding to insulin (i.e., muscle) was lower in women rather than to a decreased response per kilogram of insulin-sensitive tissue to insulin. The same situation applies whenever lean body mass differs between groups (e.g., women versus men; elderly versus young). Although insulin action did not differ, the ability of glucose to enhance its own disposal was greater in the elderly women than men. In addition, the Di_{total} was higher in elderly women than the elderly men, reflecting greater insulin secretion for a given level of insulin action. Together, these processes may enhance postprandial glucose disposal and thereby enable elderly women to better compensate for proportionately higher rates of meal appearance.

Regulation of postprandial glucose metabolism in young women and young men. Despite ingesting less glucose (i.e., ~72 vs. ~92 g), the glycemic area above basal was greater in young women than young men. Consistent with the pattern observed in the elderly subjects, meal appearance was greater and lean body mass was lower in the young women than young men. However, in contrast to the elderly subjects, there was not a compensatory increase in postprandial glucose disposal in the young women. In addition, the S_I* was lower in the young women than young men. This observation is consistent with some (44) but not all (45) previous studies that have compared insulin action in young women and men. It is not explained by differences in visceral fat, which was lower in the women than men. In contrast, all measures of fitness and strength (e.g., Vo_{2max}, seated chest press, and double knee extension) were lower in the young women. Therefore, lower fitness may account for the lower insulin action in the young women. If so, then exercise training may improve insulin action in the young women and thereby narrow the difference between groups. On the other hand, as with the elderly women, the ability of glucose to enhance its own uptake (GE*) was greater in the young women than young men, thereby potentially mitigating adverse effects resulting from lower insulin action. We are unaware of any previous study that has compared GE* in young women and men. However, because insulin action and glucose effectiveness interact to determine rates of glucose disposal, this area warrants further investigation.

Limitations

As discussed above, the elderly subjects were less fit, weaker, and more obese than their young counterparts. In addition, they were selected to have low normal dehydroepiandrosterone (in the men and women) and low normal testosterone (in the men). Therefore, the extent and mechanism by which interventions such as exercise, weight reduction, and hormone replacement improve postprandial glucose metabolism in elderly women and men remains to be determined. Comorbid conditions precluded eligibility. Therefore, participants in the study likely are healthier than nonparticipants of the same age. Hepatic insulin action and the ability of glucose to suppress glucose production were not directly measured. Because EGP was higher in the elderly than young subjects of both sexes despite higher fasting glucose and insulin concentrations, future studies examining the effects of age on hepatic insulin action and hepatic glucose effectiveness would be of interest.

Summary

Increasing data indicate that regulation of glucose postprandial glucose metabolism differs in men and women and that multiple factors contribute to the deterioration of glucose tolerance that occurs with age (Table 3). Relative to young subjects of the same sex, fasting glucose concentrations were higher and the glycemic excursion after meal ingestion was greater in both elderly women and elderly men than young individuals of the same sex. Postprandial hyperglycemia in the elderly men was caused by lower rates of glucose disposal due to defects in insulin secretion

and action that were further exacerbated by increased hepatic insulin extraction. In contrast, postprandial hyperglycemia in the elderly women was caused by increased rates of meal appearance perhaps due to the fact that the elderly women ingested more glucose per lean body mass than did the young women. Insulin secretion and action did not differ in the elderly and young women after meal ingestion, indicating that age per se does not invariably lead to β-cell failure or insulin resistance in women.

Fasting glucose concentrations were lower but EGP was higher in women than men regardless of age. In addition, despite comparable postprandial glucose concentrations, both meal appearance and postprandial rates of glucose disappearance were substantially higher in elderly women than elderly men, suggesting that a process that causes comparable impairment in glucose uptake will result in a more marked deterioration of glucose tolerance in elderly women. Regulation of postprandial glucose metabolism also differed in young women and young men with the former having higher rates of meal appearance and a greater ability of glucose but a reduced ability of insulin to stimulate glucose disposal. Therefore, depending on their mode of action, the effectiveness of therapies aimed at reducing postprandial glucose concentrations may differ in the elderly and young and in men and women.

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