

Skeletal Muscle Insulin Resistance Promotes Increased Hepatic De Novo Lipogenesis, Hyperlipidemia, and Hepatic Steatosis in the Elderly

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Aging is closely associated with muscle insulin resistance, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes. We examined the hypothesis that muscle insulin resistance in healthy aging promotes increased hepatic de novo lipogenesis (DNL) and hyperlipidemia by altering the distribution pattern of postprandial energy storage. Healthy, normal weight, sedentary elderly subjects pair-matched to young subjects were given two high-carbohydrate meals followed by ¹³C/¹H magnetic resonance spectroscopy measurements of postprandial changes in muscle and liver glycogen and lipid content, and assessment of DNL using ²H₂O. Net muscle glycogen synthesis was reduced by 45% ($P < 0.007$) in the elderly subjects compared with the young, reflecting severe muscle insulin resistance. Net liver glycogen synthesis was similar between groups (elderly, 143 ± 23 mmol/L vs. young, 138 ± 13 mmol/L; $P = \text{NS}$). Hepatic DNL was more than twofold higher in the elderly than in the young subjects (elderly, $14.5 \pm 1.4\%$ vs. young, $6.9 \pm 0.7\%$; $P = 0.00015$) and was associated with approximately threefold higher postprandial hepatic triglyceride (TG) content ($P < 0.005$) and increased fasting plasma TGs (elderly, 1.19 ± 0.18 mmol/L vs. young, 0.74 ± 0.11 mmol/L; $P = 0.02$). These results strongly support the hypothesis that muscle insulin resistance in aging promotes hyperlipidemia and NAFLD by altering the pattern of postprandial carbohydrate storage away from muscle glycogen and into hepatic DNL. *Diabetes* 61:2711–2717, 2012

The prevalence of hyperlipidemia and nonalcoholic fatty liver disease (NAFLD), as part of the metabolic syndrome, increases significantly with age (1,2). However, age is also generally associated with increased weight and a sedentary lifestyle, so it is unclear whether the higher prevalence of hyperlipidemia and NAFLD in older people is a function of age per se, excess weight, and/or inactivity. In young, normal weight, healthy individuals, muscle insulin resistance has been proposed to be an important predisposing factor for atherogenic dyslipidemia and NAFLD by changing the pattern of energy storage from ingested carbohydrate away from skeletal muscle glycogen synthesis into hepatic de novo lipogenesis (DNL), resulting in an increase in plasma triglyceride (TG) concentrations and increased hepatic TG synthesis (3). This hypothesis was further supported by

a recent study demonstrating a marked improvement in postprandial muscle glycogen synthesis and a decrease in hepatic DNL after reversal of muscle insulin resistance with a single bout of exercise in young, insulin-resistant individuals (4).

We have previously shown that even healthy, normal weight, older individuals (65–80 years) have severe muscle insulin resistance, which is associated with increased intramyocellular lipid (IMCL) content and reduced basal rates of mitochondrial activity in muscle and brain (5). We therefore examined the hypothesis that aging-related hyperlipidemia and hepatic steatosis result from skeletal muscle insulin resistance, causing a redistribution of ingested carbohydrate away from muscle glycogen synthesis to the liver, resulting in increased hepatic DNL. In order to examine this hypothesis, we measured muscle and liver glycogen synthesis by ¹³C magnetic resonance spectroscopy (MRS) (3) and muscle and liver lipid synthesis by ¹H MRS (3) along with hepatic DNL measuring deuterium-labeled water (²H₂O) incorporation into plasma VLDL (6,7) in elderly and young volunteers following ingestion of two high-carbohydrate meals. Healthy, normal weight, sedentary elderly subjects were pair-matched by sex, body weight, height, BMI, lean body mass, fat mass, and physical activity with healthy, young subjects in order to determine the effect of age-related primary muscle insulin resistance on postprandial energy distribution, independent of these potentially confounding factors.

RESEARCH DESIGN AND METHODS

Healthy, normal weight, nonsmoking subjects age 73 ± 2 years were invited to participate after a test for glucose tolerance and activity monitoring. A group of young subjects with normal insulin sensitivity, age 26 ± 2 years, were pair-matched to the elderly subjects for sex, body weight, height, BMI, body composition, physical activity, and nonsmoking status (Table 1).

All subjects had normal glucose tolerance as verified by a 3-h 75-g oral glucose tolerance test (OGTT) and a sedentary lifestyle with no regular exercise regimens as confirmed by a questionnaire (8) and by 3 consecutive days of activity monitoring using pedometers (GO-Walking; Sportline, Hazelton, PA). Insulin sensitivity was initially assessed from the OGTT using the insulin sensitivity index (ISI) (9). Body composition was measured by bioelectrical impedance (Tanita BC-418; Tanita, Arlington Heights, IL).

For 3 days before the study, the subjects were given a eucaloric diet (elderly, 20 kcal/kg; young, 35 kcal/kg, containing 55% carbohydrate, 10% protein, and 35% fat) consisting of three regular meals and snacks prepared by the Metabolic Kitchen of the Yale University Hospital Research Unit (HRU).

On study day 1, the subjects were admitted to the HRU at 5 P.M., served dinner at 6 P.M. (33% of their daily caloric intake), and remained fasting until the first study meal the following day (day 2). In the morning of day 2, the subjects were transported in a wheelchair to the Yale Magnetic Resonance Research Center (MRRC) for measurement of baseline muscle and liver lipid and glycogen content using ¹H/¹³C MRS. At 9:30 A.M., the subjects were then returned to the HRU, where an intravenous line was inserted into an antecubital vein, and baseline blood samples were collected. The liquid high-carbohydrate meals were of equal size and served at 10 A.M. and 1 P.M. The meals were prepared by the HRU Metabolic Kitchen and contained all of the required daily

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TABLE 1
Baseline subject characteristics

	Young	Elderly	<i>P</i> value
Women/men	6/6	6/6	
Age (years)	26 ± 2	73 ± 2	<0.0001
BMI (kg/m ²)	23.0 ± 0.6	23.9 ± 0.7	NS
Body fat (%)	23.0 ± 1.5	25.9 ± 2.0	NS
Systolic blood pressure (mmHg)	111 ± 2	129 ± 4	0.003
HbA _{1c} (%)	5.4 ± 0.1	5.6 ± 0.1	NS
Plasma glucose (mmol/L)	5.02 ± 0.10	5.43 ± 0.12	0.0142
Plasma insulin (pmol/L)	58.5 ± 6.4	68.9 ± 11.2	NS
Plasma total cholesterol (mmol/L)	3.81 ± 0.21	4.57 ± 0.22	0.02
Plasma TGs (mmol/L)	0.74 ± 0.11	1.19 ± 0.18	0.02
Plasma HDL (mmol/L)	1.20 ± 0.09	1.48 ± 0.09	0.04
Plasma LDL (mmol/L)	0.92 ± 0.07	1.06 ± 0.09	NS
Plasma uric acid (μmol/L)	292 ± 24	306 ± 20	NS
ISI (dL/min per μU/mL)	6.7 ± 0.5	4.2 ± 0.4*	0.002
Physical activity (miles/day)	3.28 ± 0.46	3.70 ± 0.46	NS

**N* = 11.

energy (30 kcal/kg of body weight; 55% carbohydrate, 10% protein, and 35% fat) with an additional 25% of the daily energy requirements added in the form of sucrose (3). The total amount of energy in these two meals was similar between the elderly (2,553 ± 143 kcal) and young (2,490 ± 128 kcal). At 11 A.M. and 11:30 A.M., loading doses of ²H₂O were given orally (3 mL ²H₂O/kg of body water; 99.8%, Cambridge Isotopes, Cambridge, MA). Plasma deuterium enrichment was maintained by providing the subjects with deuterium-labeled water (0.45% ²H₂O) for ad libitum drinking during the remaining part of the study (3,4).

Indirect calorimetry (Deltatrac; Datex-Ohmeda, Madison, WI) was performed on day 2 in the fasted state at 6 A.M. and in the postprandial state at 2 P.M. The subjects stayed in bed throughout the study (except for bathroom breaks) and were transported in wheelchair to and from the MRRC.

At 4:30 P.M. on day 2, the subjects were returned to the MRRC for postprandial ¹H/¹³C MRS measurements of muscle and liver lipid and glycogen contents. After completion, the subjects were returned to the HRU, where they remained in bed until the end of the study at 6 A.M. on day 3. Blood samples were collected hourly throughout the study except during the second ¹H/¹³C MRS measurements on day 2.

The Yale University Human Investigation Committee approved the protocol, and written consent was obtained from each subject after the purpose, nature, and potential complications of the studies were explained.

Hepatic DNL. The incorporation of deuterium for ²H₂O into plasma VLDL during administration of ²H₂O was used to determine the fractional synthetic rate of fatty acids (FAs) as described previously (6,7). Blood was collected and processed to calculate DNL before the first dose of ²H₂O and hourly until 6 A.M. on day 3 as previously described (3,4). Deuterium enrichment in palmitate isolated from plasma VLDL and plasma water was measured by gas chromatography-mass spectrometry (5971A Mass Selective Detector; Hewlett-Packard, Wilmington, DE), and fractional rates of hepatic DNL were calculated as previously described (3,4).

¹H/¹³C MRS measurements of liver and muscle lipid and glycogen content. All MRS measurements were performed on a whole-body, 4.0-T magnet interfaced to a Bruker AVANCE spectrometer (Bruker, Billerica, MA). Muscle glycogen and lipid content were measured in the calf muscles by using an 8.5-cm diameter, circular ¹³C surface coil with twin, orthogonal circular 13-cm ¹H quadrature coils. The probe was tuned and matched, and scout images of the lower leg were obtained to ensure correct positioning of the subject and to define an adequate volume for localized shimming using the FASTMAP procedure (10). ¹³C nuclear magnetic resonance spectra were acquired in a 60 × 30 × 60-mm³ volume placed within the gastrocnemius/soleus muscles to measure glycogen content with the following parameters: 2-ms adiabatic half passage pulse, transverse relaxation 400 ms, and 512 points over 10,000 Hz. Protons were decoupled during the 25-ms acquisition time with a WALTZ-4, and localization of the volume was performed with a three-dimensional adiabatic outer-volume suppression. Glycogen content was calculated by comparing the spectra obtained from the subjects to a spectrum obtained from a glycogen

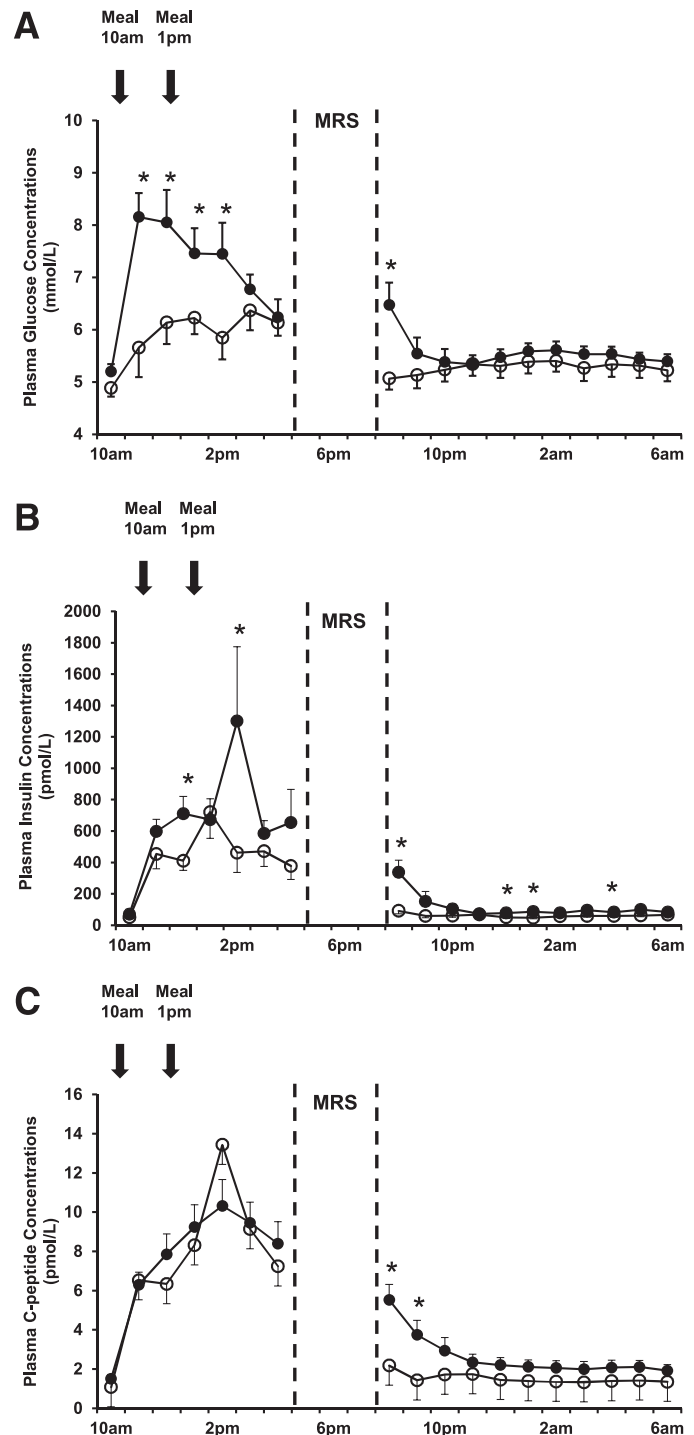


FIG. 1. Plasma concentrations in response to two carbohydrate-rich mixed meals ingested at 10 A.M. and 1 P.M. during a resting study. MRS occurred between 4 P.M. and 8 P.M., during which time no plasma samples were drawn. ○, young subjects (*n* = 12); ●, elderly subjects (*n* = 12). **A:** Plasma concentrations of glucose. **B:** Plasma concentrations of insulin. **C:** Plasma concentrations of C-peptide. **D:** Plasma concentrations of TG. **E:** Plasma concentrations of chylomicron-free TG. *n* = 9 for the elderly subjects. **F:** Plasma concentrations of FAs. **P* < 0.05.

phantom of known concentration using the same ¹³C observation coil as previously described (4).

Localized ¹H spectra were acquired to assess IMCL from a voxel 10 × 10 × 10-mm³ centered in the soleus muscle using a stimulated echo-acquisition mode sequence, with three modules of water suppression. The total IMCL was estimated from comparison of a water-suppressed lipid spectrum and a lipid-suppressed water spectrum, with the appropriate peak for each spectrum

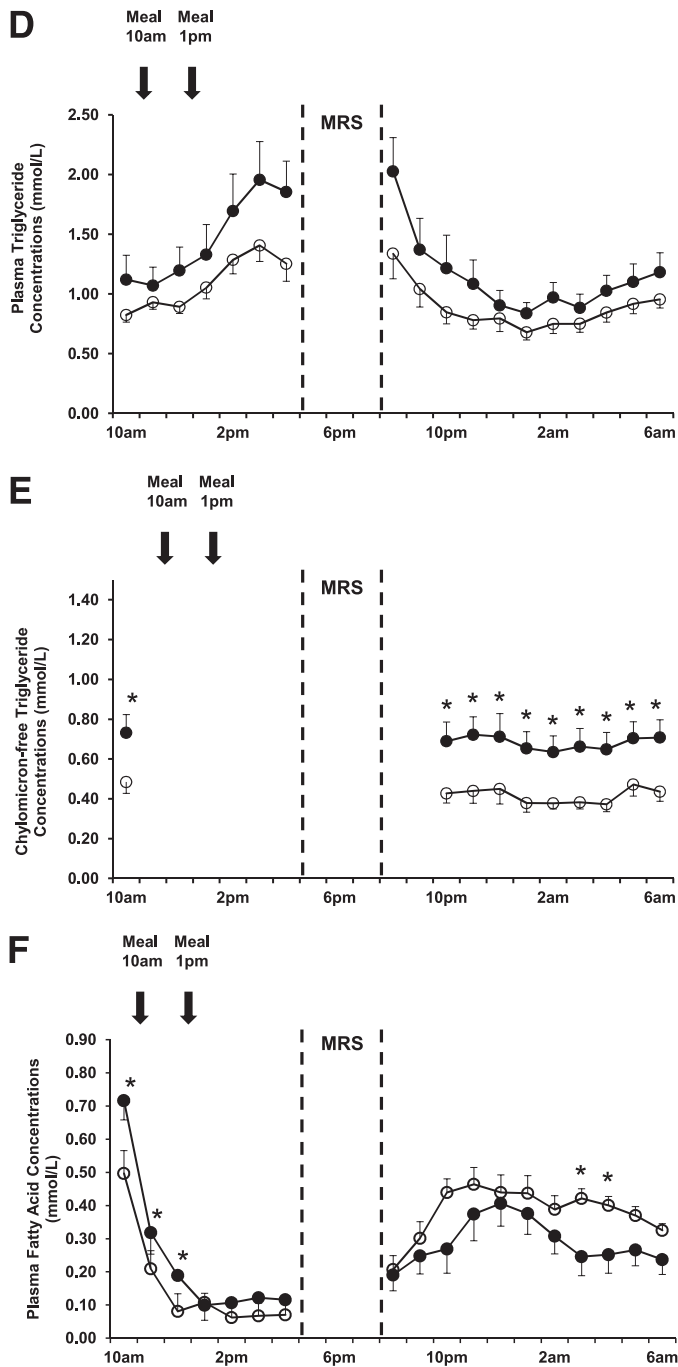


FIG. 1. Continued.

on-resonance. The IMCL and water resonances were corrected for T_1 and T_2 relaxation, and IMCL content was expressed as a percentage of the water content (4).

Liver glycogen content was measured with a second coil assembly composed of an 8-cm, circular ^{13}C coil and twin 11×14 -cm elliptical ^1H coils arranged in quadrature as described earlier (4). Liver glycogen concentrations were calculated from a glycogen phantom as previously described (3,4).

Liver TG content was measured with a third coil assembly composed of a 12-cm, circular ^{13}C coil and twin (13×19) -cm elliptical ^1H coils arranged in quadrature as described (4,11) using a ^1H respiratory-gated stimulated echo acquisition mode sequence spectroscopy in a $15 \times 15 \times 15$ -mm 3 voxel (4). Spectra acquisitions were synchronized to the respiratory cycle and triggered at the end of expiration. Water-suppressed lipid spectra and lipid-suppressed water spectra were acquired in three different locations of the liver to account for liver inhomogeneity. A minimum of six spectra were acquired for each

subject, and the total liver lipid content was averaged and corrected for both T_1 and T_2 relaxation.

Analytical methods. Plasma glucose concentrations were measured using a YSI STAT 2700 Analyzer (Yellow Springs Instrument Co., Yellow Springs, CA). Plasma concentrations of insulin were measured with a double-antibody radioimmunoassay kit (Linco, St. Louis, MO). After centrifugation, plasma was split into two parts; one part was stored at -20°C until measurements of plasma FA and total TG concentrations. The second part was processed immediately by ultracentrifugation for purification and removal of chylomicrons and plasma TG extraction (6,7,12). Plasma FA and total and chylomicron-free TG concentrations were measured enzymatically (Roche Cobas Mira Plus; Roche Diagnostics) (13). Deuterium enrichments in palmitate and plasma water were measured by gas chromatography-mass spectrometry (5971A Mass Selective Detector; Hewlett-Packard, Wilmington, DE) as previously described (3,4).

Calculations. The ISI, which reflects whole-body insulin sensitivity, was calculated from OGTT plasma glucose and insulin concentrations as previously described (5,9).

Fractional rates of DNL were calculated as previously described (3,4). Area under the curve (AUC) of plasma hormone and metabolite concentrations was calculated using the trapezoidal rule (14).

Rates of glucose and lipid oxidation were calculated from the gas exchange measurements by using nonprotein values to the following equations (15): rates of glucose oxidation (mg/min), $([4.585 \times \text{VCO}_2] - [3.2255 \times \text{VO}_2])/\text{body weight (kg)}$; and rates of lipid oxidation, $([1.6946 \times \text{VO}_2] - [1.7012 \times \text{VCO}_2])/\text{body weight (kg)}$.

Statistical analysis. Statistical analyses were performed using paired Student t tests and Mann-Whitney U tests after log transformation of data without normal distribution (plasma insulin and liver TG content). Data are expressed as mean \pm SEM.

RESULTS

The groups were matched for sex, body weight, BMI, lean body mass, fat mass, nonsmoking status, and physical activity. The screening characteristics of the groups are shown in Table 1. The elderly subjects had higher fasting plasma glucose, total cholesterol and TG concentrations, and systolic blood pressure, although the latter was only moderately elevated. The elderly subjects were insulin-resistant as compared with the young subjects as reflected by the mean ISI, which was 37% lower ($P < 0.002$) in the elderly subjects compared with the young control subjects (Table 1).

The study was conducted after 3 days of a controlled eucaloric diet matched between the groups for percent fat, protein, and carbohydrate content. In the morning on day 1, fasting plasma glucose concentrations were slightly lower than at the time of screening but tended to be higher in the elderly than the young subjects (elderly, 5.20 ± 0.15 vs. young, 4.88 ± 0.16 mmol/L; $P = 0.16$). Postprandial plasma glucose concentrations were higher in the elderly than in the young subjects (Fig. 1A), and the AUC of plasma glucose concentrations over the course of the study tended to be higher in the older than the young subjects (elderly, 105.3 ± 3.0 vs. young, 94.2 ± 4.1 mmol/L/h; $P = 0.058$). Fasting plasma insulin concentrations also tended to be higher in the elderly subjects than the young subjects (69.5 ± 7.1 pmol/L vs. 49.5 ± 4.8 pmol/L; $P = 0.08$) and increased significantly more in the elderly subjects than the young subjects after each meal and remained higher for most of the postprandial period and the overnight period (Fig. 1B). Fasting plasma C-peptide concentrations were similar between the groups (elderly, 1.50 ± 0.22 vs. young, 1.07 ± 0.22 pmol/L; $P = 0.11$), but were higher in the elderly subjects than in the young subjects after the last meal at 8 P.M. (elderly, 5.52 ± 0.79 vs. young, 2.18 ± 0.54 pmol/L; $P < 0.002$) and at 9 P.M. (elderly, 3.74 ± 0.74 vs. young, 1.42 ± 0.35 pmol/L; $P = 0.003$; Fig. 1C).

Fasting as well as postprandial total plasma TG concentrations tended to be higher in the elderly subjects than the young subjects, although this was not significant (Fig. 1D).

In contrast, chylomicron-free plasma TG concentrations, which represent mostly VLDL, were 1.5-fold higher in the elderly as compared with the young subjects both at baseline (0.73 ± 0.09 vs. 0.48 ± 0.06 mmol/L; $P = 0.025$) and throughout the postprandial period (Fig. 1F). Fasting plasma nonesterified FA concentrations were $\sim 40\%$ higher in the elderly subjects than the young subjects (0.72 ± 0.07 and 0.50 ± 0.06 mmol/L, respectively; $P = 0.01$) and were completely suppressed in both groups after the last meal. During the overnight period, plasma FA increased similarly in both groups and was higher in the young at 3 and 4 A.M. (Fig. 1E).

Total cholesterol and HDL were both elevated in the elderly as compared to the young (Table 1), and LDL concentrations tended to be higher in the elderly than the young subjects, although this was not significant (Table 1).

Basal muscle glycogen concentrations tended to be lower in the elderly subjects than in the young subjects (72 ± 4 vs. 83 ± 4 mmol/L muscle; $P = 0.06$), and net postprandial muscle glycogen synthesis was 45% lower in the elderly subjects than in the young subjects ($P = 0.007$) (Fig. 2A).

Baseline IMCL content tended to be higher in the elderly subjects than in the young subjects (elderly, $1.39 \pm 0.19\%$ vs. young, $0.97 \pm 0.09\%$; $P = 0.056$), and although the

postprandial change in IMCL was similar between the groups (Fig. 2B), the postprandial IMCL content was 35% higher in the elderly subjects than in the young subjects (elderly, $1.47 \pm 0.16\%$ vs. young, $1.08 \pm 0.08\%$ respectively; $P = 0.04$).

Fasting liver glycogen concentrations were similar in both groups (elderly, 152 ± 16 vs. young, 181 ± 14 mmol/L; $P = 0.17$) and increased by 95 and 75% after the meals in the elderly subjects and the young subjects, respectively ($P < 0.0001$ vs. baseline in both groups) (Fig. 3A).

Fasting hepatic TG content was threefold higher in the elderly subjects than the young subjects (elderly, $0.97 \pm 0.31\%$ vs. young, $0.34 \pm 0.04\%$; $P = 0.006$). After the meals, the liver TG content increased by 15% in both groups and remained threefold higher in the elderly subjects than the young subjects ($P < 0.005$) (Fig. 3B).

Postprandial hepatic DNL, as assessed by the incorporation of $^2\text{H}_2\text{O}$ into plasma TGs, was twofold higher in the elderly subjects as compared with young subjects (elderly, $14.53 \pm 1.39\%$ vs. young, $6.88 \pm 0.66\%$; $P = 0.00015$) (Fig. 4) and was significantly correlated with the AUC of plasma insulin ($r = 0.66$; $P < 0.001$).

The fasting respiratory quotients were similar between the elderly and young subjects and in both groups

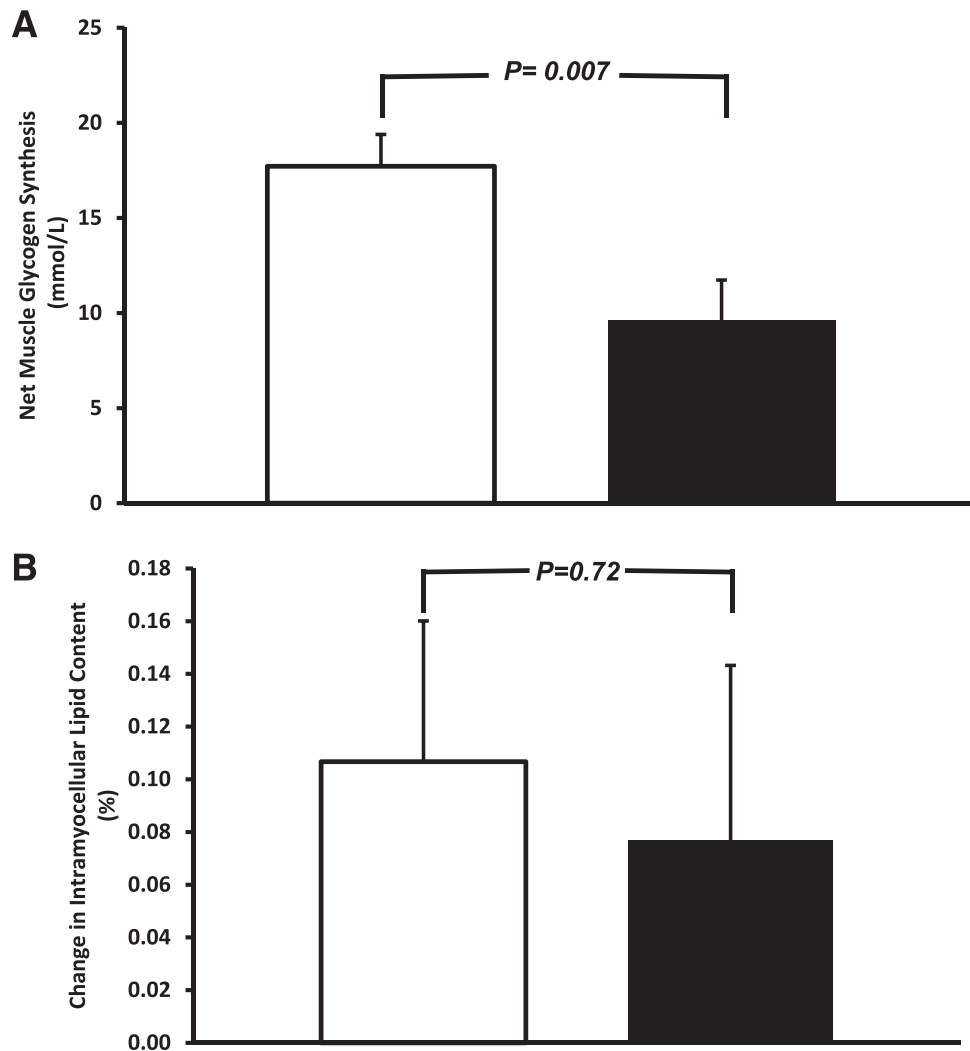


FIG. 2. ^{13}C and ^1H MRS measurements of changes in muscle glycogen concentrations (A) and IMCL contents (B) after two carbohydrate-rich mixed meals. Open bars, young subjects ($N = 12$); closed bars, elderly subjects ($N = 12$).

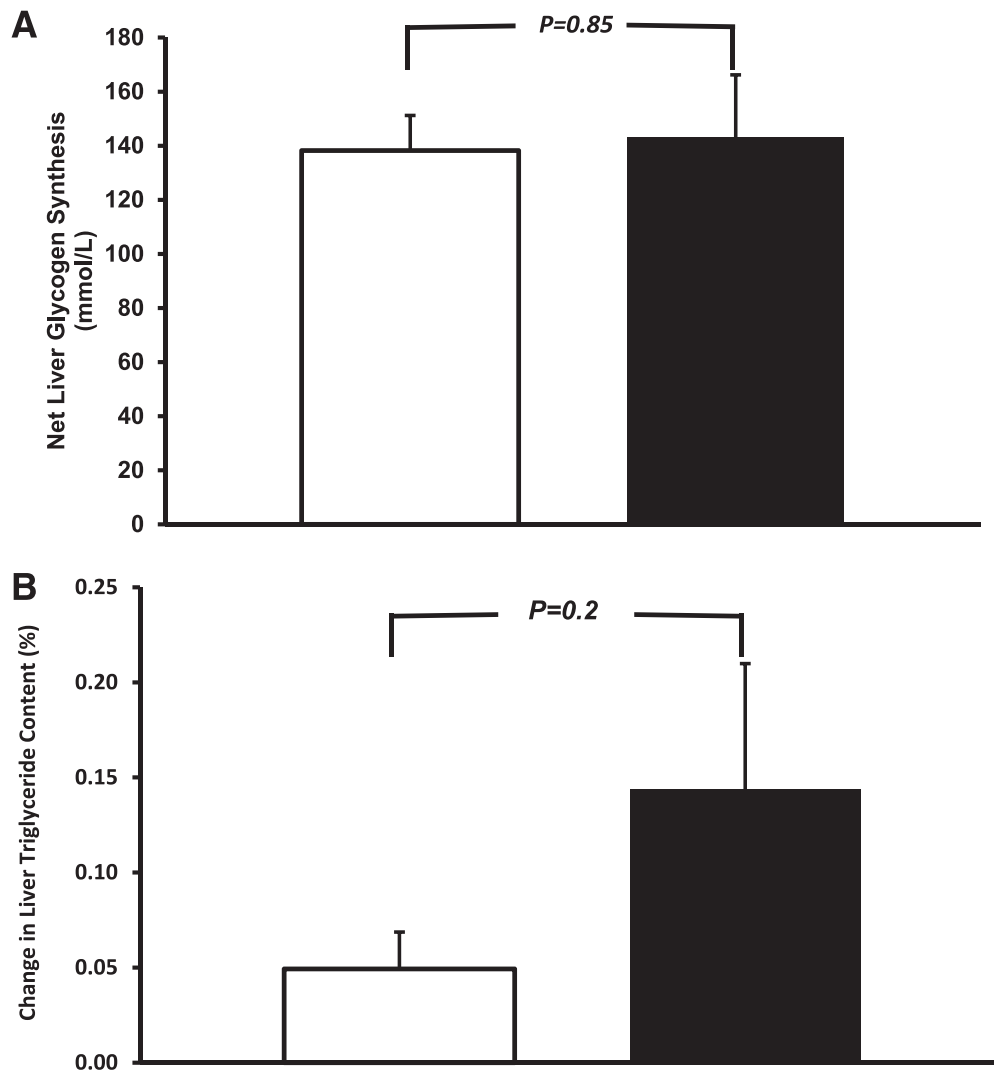


FIG. 3. ^{13}C and ^1H MRS measurements of changes in hepatic glycogen concentrations (A) and hepatic TG (B) contents after two carbohydrate-rich mixed meals. Open bars, young subjects ($N = 12$); closed bars, elderly subjects ($N = 12$).

increased significantly from the fasting to the postprandial state (Table 2). Rates of fasting glucose oxidation were lower in the elderly than in the young group ($P = 0.019$; Table 2). Rates of fasting lipid oxidation and postprandial glucose and lipid oxidation were similar between the elderly and the young (Table 2). There were no differences in rates of fasting energy expenditure between the elderly and the young subjects (Table 2).

DISCUSSION

In this study, we examined the effects of aging on the postprandial storage pattern of energy from two carbohydrate-rich meals with $\sim 2,500$ kcal containing 65% sucrose (equal amounts of glucose and fructose) into liver and muscle glycogen and TG as well as hepatic DNL in a group of healthy, normal weight, elderly subjects and a group of young individuals matched for sex, body weight, BMI, body composition, and activity. In contrast to the young individuals, who stored most of the ingested carbohydrate as liver and muscle glycogen, the elderly subjects had a marked defect in muscle glycogen synthesis resulting in diversion of their ingested carbohydrate into increased

hepatic DNL and increased plasma TGs. Taken together, these data suggest an important role of muscle insulin resistance in the pathogenesis of hypertriglyceridemia and NAFLD associated with aging.

This study is first to directly measure fasting and postprandial liver and muscle glycogen synthesis in healthy elderly subjects. Using this approach, we found that healthy elderly subjects have a severe impairment in insulin-stimulated muscle glycogen synthesis, which was 45% lower than the young activity BMI-matched control subjects and is most likely the explanation for the severe peripheral insulin resistance we have previously observed in a similar group of healthy lean individuals during a hyperinsulinemic-euglycemic clamp (5). Although reductions in lean body mass associated with aging also contribute to reduced insulin-stimulated glucose metabolism associated with aging (16), the ^{13}C MRS technique directly measures muscle glycogen content per volume muscle and is therefore independent of changes in lean body mass associated with aging. These data therefore directly demonstrate an important contribution of muscle insulin resistance to whole-body insulin resistance associated with aging independent of sarcopenia.

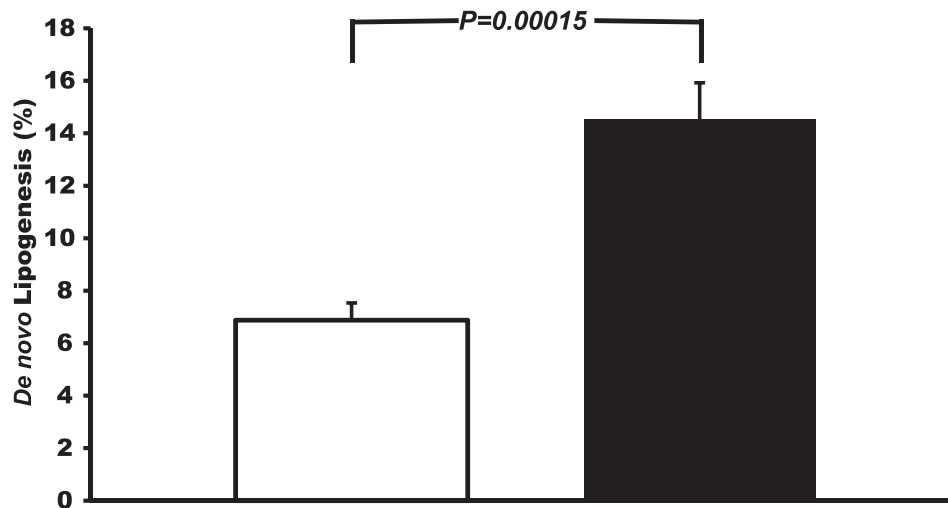


FIG. 4. Hepatic DNL after the ingestion of two carbohydrate-rich mixed meals. Open bars, young subjects; closed bars, elderly subjects.

We have previously shown that age-associated muscle insulin resistance is linked with increased IMCL content, which is likely due to age-dependent decreases in mitochondrial oxidative-phosphorylation activity (5,17). In most groups of sedentary individuals, IMCL content is strongly correlated with muscle-specific insulin resistance; however, the IMCL content is most likely a marker of intramuscular content of specific lipid metabolites, such as diacylglycerols, which are likely the direct cause of muscle insulin resistance through activation of protein kinase C θ , resulting in decreased insulin signaling at the level of insulin receptor substrate-1 tyrosine phosphorylation (18,19).

Both fasting and postprandial hepatic glycogen concentrations were similar between the young and elderly subjects. Although plasma insulin levels were increased in the elderly as compared with the young, the elderly had severely impaired muscle glycogen synthesis, whereas glycogen synthesis in the liver was similar to the young group. In both groups, hepatic glycogen concentrations reached

~300 mmol/L in liver, which is similar to the hepatic glycogen concentrations we measured in our previous studies of young healthy volunteers after carbohydrate ingestion (20,21).

The similar net postprandial hepatic glycogen storage between the young and the elderly supports the hypothesis that the additional carbohydrate load, which was not stored as muscle glycogen, was diverted away from the muscle and into de novo hepatic lipid synthesis. This is further supported by the more than twofold higher DNL in the elderly, which was strongly correlated with postprandial plasma insulin levels. This association between plasma insulin concentrations and DNL is consistent with our previous studies in young, lean individuals with muscle-specific insulin resistance (3). Chronic hyperinsulinemia leads to upregulation of the sterol regulatory element-binding protein-1c and liver X receptors, transcription factors that promote DNL (22–24), and accordingly, the elderly subjects also had higher fasting plasma TG levels as well as higher postprandial VLDL concentrations. Chronic increases in hepatic DNL likely contribute to the increased hepatic lipid accumulation observed in the elderly in this study as well as previous studies (5) and long-term development of NAFLD, as suggested by a study examining DNL from diet and nonesterified FAs by tracer distributions in liver biopsies from obese patients with NAFLD in which DNL accounted for ~26% of hepatic TGs (25). The twofold increased hepatic DNL in the elderly is similar to the increased DNL previously observed in healthy, young, lean, insulin-resistant individuals and occurred despite an ~20% reduction in caloric content in the meals compared with our previous study in young individuals (5,17) due to limitations in what the elderly subjects were comfortable ingesting.

Increased hepatic DNL resulting in hypertriglyceridemia has been associated with decreased HDL levels because of cholesteryl ester transport protein activity, in which a VLDL particle donates a TG molecule to HDL and thus results in cholesterol-rich VLDL remnant particles and TG-rich, cholesterol-depleted HDL particles (26). Further modifications of the TG-rich, cholesterol-depleted HDL particles lead to dissociation of the Apo A-I protein, which is cleared more rapidly than HDL-associated Apo A-I, leading to reduced circulating Apo A-I and HDL (26). This is apparently

TABLE 2

Fasting and postprandial RQ, rates of whole-body glucose and lipid oxidation, and energy expenditure in young and elderly subjects

	Young	Elderly	<i>P</i> value
Fasting state			
RQ	0.82 ± 0.01	0.79 ± 0.01	NS
Rates of glucose oxidation (mg/[kg BW · min])	1.56 ± 0.19	0.99 ± 0.12	0.019
Rates of lipid oxidation (mg/[kg BW · min])	0.86 ± 0.06	0.97 ± 0.10	NS
Energy expenditure (kcal/[kg BW · 24 h])	20.1 ± 0.7	18.1 ± 0.9	NS
Postprandial state			
RQ	0.92 ± 0.02	0.92 ± 0.01	NS
Rates of glucose oxidation (mg/[kg BW · min])	3.63 ± 0.45	3.27 ± 0.19	NS
Rates of lipid oxidation (mg/[kg BW · min])	0.41 ± 0.13	0.52 ± 0.09	NS
Energy expenditure (kcal/[kg BW · 24 h])	25.2 ± 1.1	24.3 ± 1.3	NS

BW, body weight; RQ, respiratory quotients.

not the situation in these elderly individuals in whom total HDL was higher than in the young subjects. Although the reasons for this are unknown, it is possible that alterations in the composition of the HDL particle in plasma associated with aging make it a poorer substrate for lecithin-cholesterol acyltransferase (27).

Taken together, this study demonstrates that age-induced skeletal muscle insulin resistance results in decreased postprandial muscle glycogen synthesis and diverts carbohydrates toward de novo lipid synthesis in the liver, resulting in dyslipidemia and hepatic lipid accumulation. These findings have important implications for the underlying cause of the development of the metabolic syndrome, NAFLD, and type 2 diabetes in aging and suggest that the initiating pathogenic event in age-related dyslipidemia and hepatic steatosis is skeletal muscle insulin resistance and the resulting compensatory hyperinsulinemia. Further studies to reverse or improve muscle insulin sensitivity, such as exercise or dietary restriction, may serve as preventative or therapeutic measures of this pattern of alterations in postprandial energy storage by improving postprandial muscle glycogen synthesis and lowering hepatic DNL in the elderly, as has recently been shown in young, insulin-resistant individuals (4).

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C.F., S.D., R.R., G.I.S., and K.F.P. researched data and were involved in the analysis and interpretation of data and writing of the manuscript. C.F. and K.F.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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