Resistance training enhances insulin suppression of endogenous glucose production in elderly women

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Honka MJ, Bucci M, Andersson J, Huovinen V, Guzzardi MA, Sandboge S, Savisto N, Salonen MK, Badeau RM, Parkkola R, Kullberg J, Iozzo P, Eriksson JG, Nuutila P. Resistance training enhances insulin suppression of endogenous glucose production in elderly women. J Appl Physiol 120: 633–639, 2016. First published January 7, 2016; doi:10.1152/japplphysiol.00950.2015.—An altered prenatal environment during maternal obesity predisposes offspring to insulin resistance, obesity, and their consequent comorbidities, type 2 diabetes and cardiovascular disease. Telomere shortening and frailty are additional risk factors for these conditions. The aim of this study was to evaluate the effects of resistance training on hepatic metabolism and ectopic fat accumulation. Thirty-five frail elderly women, whose mothers’ body mass index (BMI) was known, participated in a 4-mo resistance training program. Endogenous glucose production (EGP) and hepatic and visceral fat glucose uptake were measured during euglycemic hyperinsulinemia with [18F]fluorodeoxyglucose and positron emission tomography. Ectopic fat was measured using magnetic resonance spectroscopy and imaging. We found that the training intervention reduced EGP during insulin stimulation [from 5.4 (interquartile range 3.0, 7.0) to 3.9 (−0.4, 6.1) mol·kg body wt−1·min−1, P = 0.042] in the whole study group. Importantly, the reduction was higher among those whose EGP was more insulin resistant at baseline [higher than the median] (−5.6 (7.1) vs. 0.1 (5.4) mol·kg body wt−1·min−1, P = 0.015]. Furthermore, the decrease in EGP was associated with telomere elongation (r = −0.620, P = 0.001). The resistance training intervention did not change either hepatic or visceral fat glucose uptake or the amounts of ectopic fat. Maternal obesity did not influence the studied measures. In conclusion, resistance training improves suppression of EGP in elderly women. The finding of improved insulin sensitivity of EGP with associated telomere lengthening implies that elderly women can reduce their risk for type 2 diabetes and cardiovascular disease with resistance training.

liver; intra-abdominal fat; insulin resistance; resistance training; aging

Type 2 diabetes, cardiovascular disease, and frailty are common and frequently coexist among elderly people. Insulin resistance has been identified as an important risk factor for these conditions (2, 4). In addition, maternal obesity is emerging as a newly recognized predisposing condition for type 2 diabetes and cardiovascular disease based on large cohort studies (13, 14, 40). This study is part of an EU funded program—the Developmental ORigins of healthy and unhealthy AgeiNg—DORIAN, which aims to investigate the long-term impact of maternal obesity on health of the offspring (25).

Exercise, diet, and pharmacological interventions are used to enhance insulin sensitivity and reduce the accumulation of fat inside the abdomen and thus prevent or alleviate the progression of type 2 diabetes, cardiovascular disease, and frailty. Because decreased physical capacity is the hallmark of the frailty syndrome, resistance training is used to prevent and treat this condition (33). It has been previously shown that liver insulin sensitivity can be enhanced with aerobic exercise in young, middle-aged, and elderly people and with resistance training in adolescents (29, 30, 46, 50). We have recently shown that skeletal muscle insulin sensitivity can be enhanced with resistance training in the elderly offspring of obese mothers (7) who have an increased risk of type 2 diabetes and cardiovascular disease (13). However, the effects of resistance training on hepatic insulin sensitivity are unknown in elderly frail subjects.

Liver insulin resistance is a major factor in the development and pathophysiology of type 2 diabetes and cardiovascular disease. A decreased ability of insulin to suppress endogenous glucose production (EGP; over 75% occurring in the liver) in both the fasting and postprandial state contributes to increased blood glucose levels. Decreased insulin-mediated glucose uptake (GU) in the postprandial state contributes to elevated postprandial glycemia, because the liver takes up approximately one-third of the ingested glucose load (32). Hepatic insulin resistance and increased blood glucose promote cardiovascular disease by increased VLDL production from the liver and reduced uptake of LDL from the circulation. An important driving force for liver and peripheral insulin resistance is ectopic fat accumulation around and inside abdominal organs such as the liver. Ectopic fat tissue releases free fatty acids (FFAs) and cytokines that interfere with insulin signaling, and fatty acids compete with glucose as an alternative source of energy in insulin-sensitive organs.

Telomeres are regions of DNA repeats at the end of chromosomes that protect the chromosomes from degradation. Telomere length is considered as a marker for cellular ageing.
because telomeres shorten over time due to defective copying of telomeres at cell division and DNA damage by oxidative stress. Telomere shortening beyond a critical length, called the Hayflick limit (20), triggers cell replicative senescence.

Leukocyte telomere shortening has been associated with an increased risk of type 2 diabetes and cardiovascular disease (19, 53). A progressive shortening of telomeres has been reported moving from subjects with normal glucose tolerance to subjects with impaired glucose tolerance and to diabetic patients (1, 15). In vitro studies have shown that exposure to free radicals and oxidative stress leads to a loss of telomeric DNA (31, 44). Consistently, in diabetic patients, a negative correlation was found between concentrations of lipid peroxidation products and leukocyte telomere length (1).

The inverse associations between telomere length and subclinical and clinical markers of diabetes (e.g., fasting glycemia, glycosylated hemoglobin, waist-to-hip ratio) and its related conditions such as atherosclerosis (36, 41) suggest that telomere shortening contributes to the onset or progression of chronic cardiometabolic diseases in which cell senescence plays a major role. In fact, shorter leukocyte telomere length predicts the development of type 2 diabetes over a 5.5-yr time range in a population of American Indians (55). In turn, Uziel et al. (49) reported that good glycemic control reduced telomere shortening in patients with type 1 or type 2 diabetes or coronary artery disease. We have recently shown that leukocyte telomere length associates with skeletal muscle insulin sensitivity (7). However, current knowledge about associations between telomeres and hepatic insulin sensitivity and intra-abdominal fat accumulation is very limited. According to a recent meta-analysis (34), whether physical exercise can slow or reverse telomere shortening remains uncertain.

In this report, we extend our previous findings from skeletal muscle in elderly women (7) by showing in the same study population that a 4-mo resistance training had a positive effect on EGP and that the exercise-induced reduction of EGP was associated with telomere elongation.

**MATERIALS AND METHODS**

**Subjects and design.** The subjects were recruited from the Helsinki Birth Cohort Study (HBCS). HBCS is a longitudinal cohort that includes 13,345 subjects born in Helsinki (Finland) between 1934 and 1944 (13). General characteristics of the study subjects are presented in Table 1 (7). Forty-six elderly women were recruited to this study. Thirty-five subjects, who were characterized as frail using a handgrip strength test, participated in the resistance exercise intervention, and 9 women with normal strength served as controls and did not participate in the intervention. Two additional frail subjects did not participate in the exercise intervention but were included in the baseline comparisons. Detailed inclusion and exclusion criteria have been described earlier (7). In brief, inclusion criteria for the whole study population were having an age 68-78 yr, and for participants with low muscle strength: 1) being in the lower half of grip strength in HBCS, and 2) having either lean/normal-weight (BMI \( \leq 26.3 \text{ kg/m}^2 \)), lower half of BMI) or overweight/obese (BMI \( \geq 28.1 \text{ kg/m}^2 \)), highest quartile of BMI) mother at the time of birth. Inclusion criteria for the control group were being in the upper half of grip strength and having a lean/normal-weight mother. Six of the participants had oral diabetes medication, and 16 had statin medication. The study protocol has been approved by the Ethics Committee of the Hospital District of Southwest Finland. The study was conducted according to the principles of the Declaration of Helsinki, and all participants gave their written informed consent for the study. This study has been registered at ClinicalTrials.gov (NCT01931540). Positron emission tomography (PET), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) studies were conducted twice, before and after the 4-mo exercise intervention in the frail group, and once in the nonfrail control group. The second PET and magnetic resonance measurements were performed approximately 2–3 days after the last exercise training session. After the intervention, two PET studies were cancelled due to lack of tracer, and two subjects withdrew their consent for the MRI and one for the PET study.

**PET studies.** Details of the PET study procedure have been described earlier (7). In brief, the PET studies were performed after a 10- to 12-h overnight fast. Liver GU and EGP were measured during a euglycemic-hyperinsulinemic clamp using the 2-deoxy-2-[18F]fluoro-2-deoxy-glucose ([18F-FDG]) glucose tracer. The clamp protocol was done as previously described (10). [18F-FDG was injected 79 (SD 16) min from the clamp start and the liver and heart regions were scanned first for 35 min and then the abdominal area for 15 min. Tissue activity was measured from the images using Carimas 2.71 software (Turku PET Centre, downloadable at http://www.turkpetcentre.fi). Liver and adipose tissue GU were quantified using graphical analyses (16, 38) with lumped constants of 1.0 for liver and 1.14 for adipose tissue as previously described (26, 51). Endogenous glucose production was calculated as shown earlier (24).

Normoglycemia was well maintained during the hyperinsulinemia before [plasma glucose average 4.9 (0.43) mmol/l] and after the intervention [5.3 (0.42) mmol/l]. Insulin during hyperinsulinemic clamp was 83 [74–92] mU/l [498 (444–552) mU/l] before and 85 [76–94] mU/l [510 (456–564) mU/l] after the intervention. FFA concentration was similarly suppressed during clamp before [0.045 (0.025–0.070) mmol/l] and after the intervention [0.050 (0.025–0.070) mmol/l] (all P values > 0.05).

**Magnetic resonance measurements.** MRI was performed using a Philips Ingenia 1.5 T scanner (Philips Medical Systems, Best, the Netherlands) using a 20-cm-diameter head coil. The protocol included a single-shot T2-weighted spin echo (SE) of the whole brain, a proton density-weighted single-shot fast spin echo T2-weighted SE of the whole brain, a diffusion tensor imaging (DTI) of the whole brain, and a cine gradient echo phase-contrast sequence of the aortic arch and ascending aorta. Axial T1-weighted images of the brain were obtained to identify areas of increased signal intensity consistent with microbleeds.

### Table 1. Basic characteristics of the study subjects

<table>
<thead>
<tr>
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<th>Whole Group</th>
<th>OLM</th>
<th>OOM</th>
<th>CTR</th>
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<tr>
<td></td>
<td>Baseline (n = 35)</td>
<td>After intervention (n = 35)</td>
<td>Baseline (n = 19)</td>
<td>After intervention (n = 19)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>72 (69, 74)</td>
<td>72 (70, 74)</td>
<td>71 (68, 76)</td>
<td>71 (69, 75)</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>40 (6)</td>
<td>39 (5.5)</td>
<td>39 (6)</td>
<td>40 (5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (24, 30)</td>
<td>26 (24, 29)</td>
<td>26 (24, 29)</td>
<td>27 (24, 30)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92 (11)</td>
<td>91 (11)</td>
<td>92 (12)</td>
<td>92 (12)</td>
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<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.8 (5.4, 6.4)</td>
<td>5.9 (5.6, 6.3)</td>
<td>5.8 (5.5, 6.4)</td>
<td>6.0 (5.6, 6.4)</td>
</tr>
<tr>
<td>Fasting insulin, mU/l</td>
<td>8 (6, 12)</td>
<td>9 (6, 12)</td>
<td>9 (6, 11)</td>
<td>7 (5, 12)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/l</td>
<td>56 (40, 83)</td>
<td>63 (42, 83)</td>
<td>63 (42, 76)</td>
<td>63 (42, 83)</td>
</tr>
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</table>

Data represented as means (SD) or medians (interquartile range). OLM, offspring of lean/normal-weight mothers; OOM, offspring of overweight/obese mothers; whole group, frail intervention group (OLM + OOM); CTR, nonfrail controls. No differences between groups at baseline, or change after the intervention (P > 0.05). See Subjects and design for details. Data from Ref. 7.
Netherlands). Flexible surface and body coils were used for MRS. A single voxel was positioned in the liver parenchyma avoiding large vessels to obtain the 1H-MRS spectra for the measurement of liver fat as previously described (6).

**Measurement of visceral adipose tissue volume.** Visceral adipose tissue volume was computed semiautomatically. Briefly, the abdominal region was defined to extend from the top of the diaphragm to the waist. The automated segmentations were performed in four steps: 1) whole body in-phase T1-weighted images were corrected for intensity inhomogeneity using the simultaneous correction method (52); 2) Otsu’s method (37) with two thresholds was used to classify pixels in the area representing adipose tissue, nonadipose tissue, and background; 3) arms were removed using simple morphological operations and removal of small objects in axial 2D slices; and 4) the inside lean tissue method was used to separate subcutaneous from other adipose tissue as described below. Pixels that had been incorrectly classified as adipose tissue were manually removed. Adipose tissue volumes were converted to masses using a density of 0.916 kg/l.

**The inside lean tissue (ILT) method.** When using the ILT method each pixel is given a probability that it is adipose tissue, lean tissue, or background. An ILT filter was applied to separate visceral (VAT) from subcutaneous adipose tissue (SAT) by identifying regions in the image that are inside lean tissue. Each pixel was given a probability value that it was lean tissue. When using thresholding, pixels are given the value 0 or 1 depending on the intensity of the pixel. The ILT filter then sums the total probability values of all pixels in several different directions for each pixel. A certain percentage of the directions with the highest values were then summed and used as the filtered value for that pixel. Heuristics showed that using 48 equally spaced directions is reasonably fast and accurate, and that using 40 percent of the directions gives good results. The obtained values were then normalized to the range of 0 to 1. Adipose tissue, where the value was smaller than 0.05, was considered to be subcutaneous, and the rest nonsubcutaneous. The value 0.05 was obtained by manually testing different values. Adipose tissue close to the spinal column, i.e., from the inter- and perimuscular regions (45), was removed manually as it is not considered to be visceral or subcutaneous.

The ILT method has been developed and evaluated on CT data (unpublished data). Evaluation on CT scans from 50 subjects showed excellent correlation (r) for manually performed reference segmentations and gave r values of 0.998 for VAT and 0.999 for SAT. Compared with the manual segmentation, the ILT method overestimated the depot with 4.6% for VAT and 2.6% for SAT. For this project the ILT method was adapted for analysis of MRI data. For validation manual reference segmentations of volumes containing VAT and SAT without other adipose tissue were performed in three slices near the umbilicus in five subjects and the volume of fat in these volumes was calculated using thresholding. Linear regression between these volumes and the volumes from the ILT method was performed, giving the r values of 0.9993 for VAT and 0.9995 for SAT. The volumes calculated using the ILT method were on average 2.40% greater for VAT and 0.32% greater for SAT.

**Liver fat measurement.** Livers in both the whole body scans as well as the dedicated liver scans were manually segmented using ImageJ (42). Liver fat percentage was analyzed from the 1H-MRS spectra using LCModel as previously described (6). To determine liver fat content for the cases where MRS measurement was not available for both before and after the intervention, fat index (FI1) was calculated as described earlier (5) for each pixel of all segmented liver images. In each liver image, the median FI1 of the pixels was used. A linear least-squares fit between FI1 and liver fat content measured using MRS was performed. This was done for all cases where both MR images and spectroscopic measurements were available for the same subject. The fitting was done separately for the data from the whole body scans and the dedicated liver scans. The coefficient of determination was r² = 0.884 for the whole body scans and r² = 0.929 for the liver scans. Liver fat content values were used in the following order of preference if both baseline and after-intervention values were available: MRS (n = 35) > liver MRI (n = 4) > whole body MRI (n = 9).

**Biochemical analyses and antilipolytic effect of insulin.** Plasma insulin was measured using automated electrochemiluminescence immunoassay (Cobas 8000, Roche Diagnostics, Mannheim, Germany). Plasma glucose for the clamp measurements was done in duplicate using the glucose oxidase method (Analox GM9, Analox Instruments, London, UK). FFAs were measured with an automated enzymatic assay (NEFA-HR2, ACS-ACOD, Wako Chemicals, Neuss, Germany; Cobas 8000, Roche Diagnostics).

**Leukocyte telomere length measurement.** Peripheral blood mononuclear cells (PBMC) were extracted from a whole blood sample with the Ficoll-Hypaque gradient technique (28), and DNA concentration, purity, and integrity were measured as previously described (7). The multiplex quantitative polymerase chain reaction (qPCR) method was used for the measurement of telomere length, as previously described (8). Samples were run in triplicate; the mean coefficient of variation of each triplicate was 6.0%, and the mean intra-assay CV% was 2.0%.

**Exercise intervention.** The resistance exercise program used in this study was conducted in accordance with current U.S. recommendations for the elderly population (48). The subjects participated in a 4-mo individualized circuit-type training program 3 times/wk under the supervision of a physiotherapist. The exercise program consisted of 8 different exercises to train different large muscle groups of the upper and lower body (leg press, chest press, seated row, abdominal crunch, back extension, seated leg extension, seated leg curl, and hip abduction) with three sets of 8–15 repetitions at medium intensity. Medium intensity was defined as 50–80% of estimated one-repetition maximum (12). Progress in the training was measured once per month, and the training loads were updated accordingly.

**Statistical testing.** The effect of exercise was tested using a paired t-test. The groups of offspring of lean/normal-weight mothers, offspring of overweight/obese mothers, and nonfrail controls before the intervention, and the difference between the groups in the exercise effect, were tested using ANOVA. ANCOVA was used to adjust for the possible effects of diabetes medication or statin use. Logarithmic transformation was used to convert right-tailed distributions to normal. In cases were normal distribution was not attainable, Mann–Whitney U-test was used for comparing groups before the intervention and Wilcoxon Signed rank test for the exercise effects. Associations between study variables were tested using the Pearson or Spearman correlation tests. P values ≤ 0.05 were considered statistically significant. Results are expressed as mean (SD) for normally distributed variables or median (interquartile range) for nonnormally distributed variables.

**RESULTS**

**Liver insulin sensitivity and fat content.** Insulin suppressed EGP more effectively after the exercise intervention in the whole intervention group (Table 2). EGP correlated significantly with the previously reported skeletal muscle and whole body insulin sensitivity (7) before the intervention in the whole study population (r = −0.457, P = 0.001; and r = −0.578, P = 2.76E-5, respectively). A more insulin-resistant EGP at baseline (higher than the median) predicted a better improve-ment in insulin-mediated EGP suppression after the interven- tion than insulin-sensitive EGP [−5.6 (7.1) vs. 0.1 (5.4) mmol·kg body wt−1·min−1, P = 0.015, Fig. 1]. Statin or diabetes medication did not influence the effect of intervention on EGP. Change in EGP after the intervention did not correlate with change in FFA or insulin average during hyperinsulinemic clamp; thus they do not explain the found effect of exercise on EGP. Exercise did not change liver GU or fat content (Table 2).
Table 2. Liver and adipose tissue results

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<th>Whole Group</th>
<th>OLM</th>
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<tr>
<td>EGP, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td></td>
<td></td>
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<tr>
<td>Liver GU</td>
<td>5.4 (3.0, 7.0)</td>
<td>6.1 (3.7, 6.6)</td>
<td>4.9 (2.5, 9.3)</td>
<td>5.5 (1.8, 8.7)</td>
</tr>
<tr>
<td>Liver fat content, %</td>
<td>2.7 (1.9, 5.8)</td>
<td>2.8 (2.0, 6.5)</td>
<td>2.5 (1.5, 5.1)</td>
<td>3.0 (1.6, 8.8)</td>
</tr>
<tr>
<td>Mesenteric fat GU, ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>28 (20, 37)</td>
<td>28 (24, 32)</td>
<td>30 (17, 44)</td>
<td>29 (16, 33)</td>
</tr>
<tr>
<td>Visceral fat mass, kg</td>
<td>3.4 (2.2, 4.2)</td>
<td>3.4 (2.3, 4.4)</td>
<td>2.7 (2.1, 4.2)</td>
<td>3.8 (3.1, 4.7)</td>
</tr>
<tr>
<td>Telomere length, repeats/reference gene$§</td>
<td>1.01 (0.84, 1.27)</td>
<td>1.01 (0.85, 1.30)</td>
<td>1.08 (0.81, 1.24)</td>
<td>1.00 (0.87, 1.09)</td>
</tr>
</tbody>
</table>

Data represented as medians (interquartile range). *\( n = 13 \) for PET measurements. †Significant change compared with baseline, \( P = 0.042 \). ‡Trend for change compared with baseline, \( P = 0.060 \). No differences between groups at baseline in any of the studied measures or change after the intervention for variables other than EGP (\( P > 0.05 \)). §§ for the whole group = 29, OLM = 16, OOM = 13.

Age or initial handgrip strength did not explain our findings since age did not correlate with EGP at the beginning or end of the experiment and the initial handgrip strength did not correlate with EGP at baseline.

In contrast to our previous study, there were no differences between offspring of lean/normal-weight mothers and offspring of overweight/obese mothers. The intervention groups and nonfrail participants had similar EGP or liver GU, and fat content at baseline (Table 2). Furthermore, the intervention outcomes were similar among the intervention groups, although a trend for improved EGP suppression was observed in offspring of overweight/obese mothers alone.

Visceral adipose mass and insulin sensitivity. Mesenteric fat GU and the amount of visceral adipose tissue were not changed during the exercise intervention (Table 2). Mesenteric fat GU and visceral fat mass were similar among nonfrail and frail offspring of lean/normal-weight and overweight/obese mothers before the intervention. There were no differences in the antilipolytic effect of insulin between the groups before the intervention or change after the intervention.

Telomere length. Those participants who had telomere elongation had a considerably higher improvement in EGP suppression \([-5.2 (5.8) \text{ vs. } 1.6 (4.3) \mu \text{mol} \cdot \text{kg body wt}^{-1} \cdot \text{min}^{-1}, \ P = 0.002, \text{Fig. 2} \] and tended to have a favorable change in visceral fat mass \([-0.21 (0.36) \text{ vs. } 0.02 (0.30) \mu \text{kg}, \ P = 0.079 \] compared with those with telomere shortening. However, telo-

![Fig. 1. Endogenous glucose production (EGP) during clamp in the frail participants with low (low IR) and high hepatic insulin resistance (high IR) before the resistance training intervention. White bars, preintervention; black bars, postintervention. The middle, bottom, and top edges of the boxes represent median with 1st and 3rd quarters, and notches are calculated as \( 1.58 \times \text{interquartile range/sqrt} (n) \) (95% confidence interval for the median). The error bars extend to the furthest case inside 1.5 interquartile range from the box. If notches do not overlap, there is evidence for a difference between medians. *\( P = 0.015 \) for change after the intervention.](https://appliedphysiology.org/doi/10.1152/japplphysiol.00950.2015)

![Fig. 2. Association between the change in EGP and the change in telomere length after the resistance training intervention. Black triangles, frail offspring of lean/normal-weight mothers; white circles, frail offspring of overweight/obese mothers. The curves indicate a 95% confidence interval for the mean. Subjects with a full suppression of EGP before the intervention (EGP < 0 \mu \text{mol} \cdot \text{kg body wt}^{-1} \cdot \text{min}^{-1}; n = 3) are not included in the graph (outliers). Spearman \( \rho = -0.596, \ P = 0.001 \) without removal of outliers.](https://appliedphysiology.org/doi/10.1152/japplphysiol.00950.2015)
mere length was not associated with EGP, liver GU, liver fat content, mesenteric fat GU, or visceral fat mass at baseline (all $P$ values $> 0.05$). Furthermore, there was no difference in telomere length between baseline and after the intervention in the whole intervention group or in offspring of lean/normal-weight and overweight/obese mothers (Table 2). Statin or diabetes medication did not alter the found associations.

**DISCUSSION**

In this study we demonstrated that regular resistance training for 4 mo was sufficient to improve insulin-mediated suppression of EGP in elderly women with low muscle strength, without attendant changes in hepatic lipid content or glucose uptake. This observation has clinical relevance because aged people are more susceptible to develop insulin resistance due to muscle weakness, and EGP is an important factor in the progression toward overt type 2 diabetes. In addition, telomere elongation was associated with reduction in EGP. Offspring of overweight/obese and lean/normal-weight mothers did not significantly differ at baseline or in outcomes of the intervention in any of the measured studies.

Before the intervention, hepatic insulin resistance measured during euglycemic hyperinsulinemia was greater in our study (median EGP 5.4 μmol·kg$^{-1}$·min$^{-1}$) than in the previously reported aerobic exercise studies among middle-aged overweight (mean EGP approx. 3.4 μmol·kg$^{-1}$·min$^{-1}$) (46) and elderly normal-weight (mean EGP ~3.5 μmol·kg$^{-1}$·min$^{-1}$) (29) subjects; however, insulin resistance was lower than in obese patients with prediabetes (EGP ~6.6–9.5 μmol·kg$^{-1}$·min$^{-1}$) (30). The resistance training intervention decreased EGP by 28% in the whole intervention group. This response was similar to reports using middle-aged subjects (46) but less than the difference found earlier between sedentary and aerobic exercise-trained elderly individuals and among prediabetic patients (29, 30). The minor difference indicates a possibly lower effect of resistance training but could be also due to lower amount of exercise (3 vs. 5–6 times per week), although our protocol was intense enough to induce improvements in whole body and skeletal muscle insulin sensitivity in offspring of overweight/obese mothers (7). Not surprisingly, the improvement in suppression of EGP induced by exercise was found in those participants whose EGP was above the median before intervention. Changes in hyperinsulinemic clamp insulin or FFA averages after the intervention did not correlate with the found changes in EGP; therefore they do not explain the enhancement in suppression of EGP.

Several reports (1, 41) show that shorter telomeres in patients with glucose intolerance and insulin resistance have a progressive loss of telomeric DNA as impaired glucose homeostasis deteriorates into diabetes. Also, inverse correlations between telomere length and markers reflecting cardiometabolic risk factors such as BMI, waist-hip ratio, blood levels of C-reactive protein, glycosylated hemoglobin, and carotid intima-media thickness have been shown (1, 36, 55). The above data primarily result from cross-sectional data. However, recently, short leukocyte telomere length was shown to predict type 2 diabetes in a large longitudinal cohort of American Indians (55), which suggests a substantial contribution of telomere loss to the onset of the disease. Increased exposure to reactive species, oxidative-stress, and inflammation, which all are biological markers associated with cell ageing, has been postulated as the main mechanism underlying the relationship between short telomeres and diabetes (31, 41, 44). In addition, earlier studies have shown correlations of telomere length/shortening in leukocytes and in key metabolic organs, liver, skeletal muscle, and adipose tissue (9, 11), providing evidence for intraindividual synchrony in telomere length across somatic cells in humans. However, further studies are warranted.

In our study we found that telomere elongation is associated with improved EGP suppression and a trend for reduced visceral fat in women who underwent a 4-mo exercise training program. In addition, we have shown earlier that leukocyte telomere length is positively associated with skeletal muscle insulin sensitivity (7). Consistently, an improvement in glycemic control was reported to reduce telomere shortening in both diabetic and CHD patients (49). Although here we did not observe difference in telomere length between offspring of lean/normal-weight and overweight/obese mothers, we have recently found in a much larger study population that maternal pregnancy BMI correlates with telomere length in the elderly offspring (17).

Data exploring the effect of exercise training report controversial results including a positive, negative, and U-shaped relationship between physical activity and telomere length (34). Notably, most of the studies exploring the associations between cardiovascular fitness, maximum oxygen consumption, and telomere length have a lack in the characterization of glucose homeostasis. We expanded this observation by hypothesizing that, to observe a reduction of telomere shortening and even telomere elongation, exercise training should translate into a significant improvement in glycemic homeostasis. However, this needs to be studied further to provide evidence for causality.

Insulin-mediated hepatic GU is a key factor in controlling postprandial glycemia since the liver takes up approximately one-third of an ingested glucose load (32). Unexpectedly, before the intervention, hepatic GU was 38% higher in this study population compared with younger nondiabetic women in earlier studies from our group (21, 22). Because blood glucose was well-controlled, a likely explanation for the large difference favoring the older population of the current study is that the insulin levels during clamp were 40% higher in the subjects of this study compared with participants from our earlier studies despite using a similar insulin infusion rate. The higher insulin levels are possibly caused by decreased insulin degradation related to ageing (23). There is little knowledge about the effects of resistance training on hepatic GU in humans. Exercise intervention did not change hepatic insulin-stimulated GU; therefore resistance exercise seems to be ineffective for improving hepatic GU. However, it is possible that the lack of improvement is due to insulin sensitivity of hepatic GU being already high before the intervention.

Resistance exercise had no effect on liver fat in this study. This is likely because the median liver fat content in the study population was already normal (2.7%) before the intervention. This interpretation is supported by a review of the literature, where the resistance training studies which found a decrease in liver fat content had subjects with nonalcoholic fatty liver disease (3, 18, 54), while the one with no effect of exercise (47) had participants with normal liver fat content (35).
We did not find changes in visceral fat mass and GU or antilipolytic effect of insulin after the intervention. According to a meta-analysis by Ismail and colleagues (27), resistance training has no independent effect on visceral fat mass. A meta-analysis of studies with obese participants suggests that the best outcome on body composition would be achieved with combined resistance and aerobic training (43). To our knowledge only one study addressed the effect of exercise on visceral fat GU in humans (39). In that study, Reichkendler and colleagues (39) found that aerobic exercise intervention improved skeletal muscle but not visceral fat GU during an insulin clamp in young sedentary overweight males. Based on these results and ours, resistance training seems to have little effect on visceral adipose tissue.

This study has some limitations. The study groups were relatively small, because limitations on availability of imaging resources reduced the possibilities to extend the study groups. Men were not studied because after menopause, women’s risk for frailty, cardiovascular disease, and type 2 diabetes increases rapidly, and elderly women would have therefore especially benefited from an exercise intervention. Participant selection was based on handgrip strength; the treatment effects might have been more pronounced using additional criteria of frailty. However, the frequent comorbidities found in a frail population would have introduced difficult confounders and likely decreased the participation rate and compliance.

In conclusion, in this study we have shown that with resistance training, in addition to improving skeletal muscle insulin sensitivity, elderly women can improve their glycemic control by enhancing insulin-mediated suppression of EGP and thus reduce their risk of frailty, type 2 diabetes, and cardiovascular disease. These improvements were attained without changes in body adiposity except in decreased intramyocellular lipid content among offspring of overweight/obese mothers observed in our previous study (7). In addition, hepatic and visceral adipose tissue glucose uptake remained unchanged. Furthermore, the improved EGP suppression was associated with telomere elongation, and higher skeletal muscle insulin sensitivity was correlated with longer telomeres (7) suggesting that favorable metabolic changes may be related to slower cellular ageing.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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