TRL, IDL, and LDL Apolipoprotein B-100 and HDL Apolipoprotein A-I Kinetics as a Function of Age and Menopausal Status

Nirupa R. Matthan, Susan M. Jalbert, Stefania Lamon-Fava, Gregory G. Dolnikowski, Francine K. Welty, Hugh R. Barrett, Ernst J. Schaefer, Alice H. Lichtenstein

**Objective**—To determine mechanisms contributing to the altered lipoprotein profile associated with aging and menopause, apolipoprotein B-100 (apoB-100) and apoA-I kinetic behavior was assessed.

**Methods and Results**—Eight premenopausal (25 ± 3 years) and 16 postmenopausal (65 ± 6 years) women consumed for 6 weeks a standardized Western diet, at the end of which a primed-constant infusion of deuterated leucine was administered in the fed state to determine the kinetic behavior of triglyceride-rich lipoprotein (TRL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) apoB-100, and high-density lipoprotein (HDL) apoA-I. Data were fit to a multicompartmental model using SAAM II to calculate fractional catabolic rate (FCR) and production rate (PR). Total cholesterol, LDL cholesterol (LDL-C), TRL-C, and triglyceride levels were higher (50%, 55%, 130%, and 232%, respectively) in the postmenopausal compared with the premenopausal women, whereas HDL-C levels were similar. Plasma TRL, IDL, and LDL–apoB-100 levels and pool sizes (PS) were significantly higher in the postmenopausal than premenopausal women. These differences were accounted for by lower TRL, IDL, and LDL apoB-100 FCR (P < 0.05), with no difference in PR. There was no significant difference between groups in HDL-C levels or apoA-I kinetic parameters. Plasma TRL-C concentrations were negatively correlated with TRL apoB-100 FCR (r = −0.46; P < 0.05) and positively correlated with PR (r = 0.62; P < 0.01). Plasma LDL-C concentrations were negatively correlated with LDL apoB-100 FCR (r = −0.70; P < 0.001) but not PR.

**Conclusions**—The mechanism for the increase in TRL and LDL apoB-100 PS observed in the postmenopausal women was determined predominantly by decreased TRL and LDL catabolism rather than increased production. No differences were observed in HDL apoA-I kinetics between groups. *(Arterioscler Thromb Vasc Biol. 2005;25:0-0.)*

**Key Words:** apolipoprotein ■ lipids ■ lipoproteins ■ stable isotopes ■ menopausal status ■ aging

Cardiovascular disease (CVD) is the leading cause of death in the United States1,2 as well as in most developed countries.3–5 Based on data from the Framingham Heart Study, annual rates of first CVD event rise from 7 per 1000 in men 35 to 44 years of age to 68 per 1000 in men 85 to 94 years of age.6 In women, rates are comparable, but events occur 10 years later.6 This gender difference in risk has been attributed to a possible protective effect of endogenous female sex hormones.7

Among women, CVD death rates after menopause are 2 to 3× higher than women the same age before menopause.6,8 Several studies have also provided compelling evidence that CVD increases after oophorectomy and in women with premature menopause.9–11 In the Nurses’ Health Study, women who had undergone a bilateral oophorectomy had up to an 8-fold increase in CHD risk.10 Similarly, in the Women’s Health Initiative study, hysterectomized women, with or without ovarian preservation, had a significantly higher 10-year risk of myocardial infarction or coronary death, estimated using the Framingham algorithm compared with nonhysterectomized women.9

Data from cross-sectional12–25 and longitudinal studies12,18,21,26–29 have shown that menopause alters CVD risk factors. Postmenopausal compared with premenopausal women have higher plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglyceride (TG) levels. Differences in high-density lipoprotein cholesterol (HDL-C) levels have been inconsistent, with some reporting an increase,20 others a decrease,12,13,29 or no change16,17,19,22,24,25 after menopause. Hormone replacement therapy (HRT) does not reverse the apparent affects of a changed menopausal status on CVD outcomes.

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Mimicking the potential protective effect of endogenous with exogenous hormones has had disappointing results.\textsuperscript{30–32} Together, these data suggest that the premenopausal state and exogenous estrogen do not result in similar metabolic states.

Plasma lipoprotein levels are determined by the balance between production and catabolism. LDL production is dependent on the metabolism of its precursor, TG-rich lipoprotein (TRL), whereas clearance is largely mediated by LDL receptor uptake. Apolipoprotein B-100 (apoB-100) is synthesized in the liver and secreted in the form of TRL, which is subsequently delipidated to form LDL. ApoB-100 serves as a ligand for the LDL receptor and enables removal of LDL from plasma. ApoA-I is the main apolipoprotein associated with HDL. Assessing the kinetic behavior of the major apolipoproteins provides a unique opportunity to define mechanisms underlying the change in lipoprotein profiles associated with menopause. In the present study, we characterized the kinetic behavior of apoB-100 in 3 lipoprotein classes: TRL, intermediate-density lipoprotein (IDL), and LDL, as well as HDL apoA-I in premenopausal (younger) and postmenopausal (older) menopausal women.

Methods

Subjects

Study subjects were selected to maximize differences in sex hormone status. Consequently, perimenopausal women with irregular menses and postmenopausal women who attained menopause 12 months before the start of the study were excluded (predominantly women in the 40- to 50-year age range). Menopausal status was confirmed on the basis of plasma estradiol (30 ± 18 and 11 ± 7 pg/mL; \(P = 0.01\)) and follicle-stimulating hormone (5 ± 1 and 60 ± 26 mIU/mL; \(P < 0.0001\); premenopausal and postmenopausal women, respectively) levels. To further minimize potential confounding factors, only women free from chronic illness and not using HRT, oral contraceptives, or medications known to affect lipid metabolism (lipid-lowering drugs, fish oil capsules, \(\beta\)-blockers, or diuretics) were recruited. Subjects who smoked, had undergone a hysterectomy or oophorectomy, or reported consuming >2 alcoholic drinks per day were also excluded from participation. On the basis of hormonal status, they are referred to as premenopausal and postmenopausal women throughout this article. The final sample size for the apoB-100 kinetic study was 18 (8 premenopausal and 10 postmenopausal women). Six additional postmenopausal women who participated in the placebo phase of an estrogen or estrogen plus progexin study designed to measure HDL kinetics\textsuperscript{39} were included in the apoA-I kinetic data set (8 premenopausal and 16 postmenopausal women). Protocols were approved by the human investigation review committee of the New England General Clinical Research Center using identical protocols and methodologies.\textsuperscript{33}

Experimental Design and Diet

Eight premenopausal and 10 postmenopausal women were maintained for 6 weeks on a standardized Western diet providing 49% energy (%E) carbohydrate, 15% protein, 35%E (14% saturated fatty acids, 15% monounsaturated fatty acids, and 7% polyunsaturated fatty acids), and 180 mg cholesterol per 1000 kcal. All food and drink were provided to the subjects who reported to the metabolic research unit of Tufts University 4\(\times\) per week. Initial energy intakes were calculated using the Harris–Benedict equation, and adjustments made when necessary to maintain body weight. Six additional postmenopausal women were counseled to adhere to a similar diet, and after 4 weeks, HDL apoA-I kinetics were determined at the general clinical research center of Tufts-New England Medical Center using identical protocols and methodologies.\textsuperscript{13}

Measurement of Lipoprotein Kinetics

At the end of the lead-in period, a primed-constant infusion of deuterated leucine was administered to the women in the fed state to determine the kinetic behavior of TRL apoB-100, IDL apoB-100, and HDL apoA-I. After a 12-hour fast, subjects were fed the standardized Western diet hourly for 20 hours starting at 6 AM. Each identical meal consisted of 1/20 their daily caloric intake as described previously.\textsuperscript{14} Five hours after the first meal, subjects received an intravenous bolus dose (10 \(\mu\)mol/kg) followed by a constant infusion (10 \(\mu\)mol/kg per hour) of [5,5,5-\textsuperscript{2}H\textsubscript{3}] leucine over a 15-hour period. Blood samples (20 mL) were collected via a second intravenous line at 0, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, and 15 hours.

The protocol for plasma lipid and lipoprotein characterization, quantification, and isolation of the apolipoproteins, isotopic enrichment determinations, and kinetic analysis were performed as described in detail previously.\textsuperscript{35–42} The fasting lipid and lipoprotein values reported are averages of 3 measurements taken at the end of the lead-in period. The nonfasting lipid and lipoprotein values are averages of 5 measurements corresponding to time points 1, 4, 8, 12, and 15 hours during the infusion protocol.

Kinetic Analysis

The kinetic parameters of apoB-100 in TRL, IDL, and LDL fractions, as well as apoA-I in HDL, were determined by fitting the multicompartmental model (Figures 1 and 2) to the tracer/tracee (TTT) ratio data using the SAAM II program (SAAM Institute) as described previously.\textsuperscript{39–42} After fitting the observed data to the respective models, fractional catabolic rates (FCRs; in pools per day)
Figure 2. ApoA-I compartmental model. Compartment 1 was the apolipoprotein precursor pool, defined by a forcing function representing the apoB-100 enrichment plateau. Compartment 2 was the intracellular delay compartment representing the time required for the synthesis and secretion of apoA-I from the intestine and liver. Compartment 3 represented the apoA-I T/T ratio with direct catabolism of apoA-I from this compartment.

and PRs (mg/kg per day) of apoB-100 and apoA-I were calculated.39–42

**Statistical Analyses**

Before statistical testing, data were checked for normality, and appropriate transformations were performed when necessary. Variables log transformed included body mass index (BMI), HDL-C, TRL-C, VLDL-C, and TGs. Untransformed data are presented in text and tables as means±SD. Student’s t test (SAS version 8; SAS Institute Inc) was used to assess mean differences between groups. Pearson correlation coefficients were calculated to test for association between plasma lipoproteins and apoB-100 and apoA-I kinetic parameters.

**Results**

**Baseline Characteristics and Lipoprotein Data**

Consistent with the study design, the postmenopausal women were significantly older (mean 62 [n=10] and 65 [n=16] years of age) than the premenopausal women (mean 25 years of age; Table 1). The group mean for BMI was higher for the postmenopausal (B) women compared with premenopausal women (mean 25 years of age) than the premenopausal women (mean 25 years of age; Table 1). The group mean for BMI was higher for the postmenopausal compared with premenopausal women (Table 1). Differences between postmenopausal women with apoB-100 kinetic data; †postmenopausal women with apoA-I kinetic data; ‡significantly different (P<.05) vs premenopausal women.

**ApoB-100 Kinetics**

Plasma TRL, IDL, and LDL apoB-100 levels were 112%, 58%, and 38% higher in the postmenopausal compared with the premenopausal women (all P values <.05; Table 2). A similar pattern was observed for TRL, IDL, and LDL pool sizes (PS; 107%, 70%, and 48%, respectively). These higher values were accompanied by a 45%, 51%, and 32% lower TRL, IDL, and LDL apoB-100 FCR in the postmenopausal relative to the premenopausal women (all P values P<.05). TRL rate constants in the delipidation pathway were ≈50%

**TABLE 1. Baseline Characteristics and Lipid and Lipoprotein Concentrations**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Premenopausal Women (n=8)</th>
<th>Postmenopausal Women (n=10)*</th>
<th>Postmenopausal Women (n=16)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>25±3</td>
<td>65±6‡</td>
<td>62±8‡</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64±9</td>
<td>68±13</td>
<td>70±11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23±3</td>
<td>26±4</td>
<td>27±4</td>
</tr>
<tr>
<td>Nonfasting values, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>3.6±0.7</td>
<td>5.5±1.0‡</td>
<td>5.5±0.9‡</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.0±0.7</td>
<td>3.3±0.9‡</td>
<td>3.3±0.8†</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>TRL-C</td>
<td>0.5±0.2</td>
<td>1.0±0.3‡</td>
<td>1.0±0.4</td>
</tr>
<tr>
<td>TGs</td>
<td>1.0±0.4</td>
<td>1.7±0.5‡</td>
<td>3.2±2.1†</td>
</tr>
<tr>
<td>Fasting values, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>4.5±0.8</td>
<td>6.1±0.9‡</td>
<td>6.2±0.9‡</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.8±0.8</td>
<td>4.0±0.9‡</td>
<td>4.0±0.8†</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.9±0.1</td>
<td>1.1±0.1</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>0.4±0.2</td>
<td>0.6±0.4</td>
<td>0.7±0.5</td>
</tr>
<tr>
<td>TGs</td>
<td>0.8±0.4</td>
<td>1.2±0.3‡</td>
<td>2.0±1.6‡</td>
</tr>
</tbody>
</table>

Values are mean±SD.

To convert values for cholesterol and TGs to mg/dL, multiply by 38.67 and 88.54, respectively.

*Postmenopausal women with apoB-100 kinetic data; †postmenopausal women with apoA-I kinetic data; ‡significantly different (P<.05) vs premenopausal women.

**TABLE 2. Kinetic Parameters of TRL, IDL, and LDL ApoB-100**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Premenopausal Women (n=8)</th>
<th>Postmenopausal Women (n=10)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRL apoB-100, mg/dL</td>
<td>3.2±1.5</td>
<td>6.8±5.0</td>
<td>0.04</td>
</tr>
<tr>
<td>PS, mg</td>
<td>97.5±54.9</td>
<td>202.0±132.3</td>
<td>0.04</td>
</tr>
<tr>
<td>FCR, pools/day</td>
<td>13.3±8.3</td>
<td>7.3±3.0</td>
<td>0.04</td>
</tr>
<tr>
<td>PR, mg/kg per day</td>
<td>15.5±3.6</td>
<td>18.6±8.5</td>
<td>0.32</td>
</tr>
<tr>
<td>IDL apoB-100, mg/dL</td>
<td>1.3±0.3</td>
<td>2.1±0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>PS, mg</td>
<td>39.1±13.4</td>
<td>66.4±36.6</td>
<td>0.05</td>
</tr>
<tr>
<td>FCR, pools/day</td>
<td>10.6±6.6</td>
<td>5.2±2.5</td>
<td>0.05</td>
</tr>
<tr>
<td>PR, mg/kg per day</td>
<td>5.8±2.3</td>
<td>4.9±2.9</td>
<td>0.47</td>
</tr>
<tr>
<td>LDL apoB-100, mg/dL</td>
<td>69.6±14.3</td>
<td>96.4±28.5</td>
<td>0.03</td>
</tr>
<tr>
<td>PS, mg</td>
<td>2020.7±583.2</td>
<td>2980.6±1116.7</td>
<td>0.03</td>
</tr>
<tr>
<td>FCR, pools/day</td>
<td>0.41±0.11</td>
<td>0.28±0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>PR, mg/kg per day</td>
<td>12.3±2.0</td>
<td>11.4±3.6</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Values are mean±SD.
lower in the postmenopausal compared with the premeno-
pausal women (Figure 1). A similar trend was also observed
with regard to TRL and LDL clearance rate constants.
There was no significant effect of menopausal status on PR in any
apoB-100 lipoprotein subclass (Table 2).

To determine whether the differences observed in plasma
TRL-C and LDL-C levels were associated with differences in
apoB-100 FCR or PR, correlation coefficients were calcu-
lated. Plasma TRL-C levels were correlated negatively with
TRL apoB-100 FCR \((r=-0.46; \, P<0.05; \, \text{Figure 3A})\) and
positively with TRL PR \((r=0.62; \, P<0.01; \, \text{Figure 3B})\) and
TRL apoB-100 and PS \((r=0.68; \, P<0.01 \text{ and } r=0.59; \, P<0.01, \text{respectively}).\) Plasma LDL-C levels were correlated
negatively with LDL apoB-100 FCR \((r=0.46; \, P<0.05; \, \text{Figure 3C})\) and positively with LDL apoB-100 and PS
\((r=0.68; \, P<0.01 \text{ and } r=0.59; \, P<0.01, \text{respectively).}\) Plasma
LDL-C levels and the PR of LDL apoB-100 were not
significantly related (Figure 3D).

ApoA-I Kinetics
Plasma apoA-I levels and PS did not differ significantly
among the premenopausal and postmenopausal women (Ta-
ble 3). There were no significant differences in apoA-I FCR
or PR between the 2 groups of women. Likewise, no significant
association was observed between plasma LDL-C levels and apoA-I FCR \((r=-0.12; \, P=0.58; \, \text{Figure 3E})\) or PR
\((r=0.36; \, P=0.10; \, \text{Figure 3F}).\)

**Table 3. Kinetic Parameters of HDL ApoA-I**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Premenopausal Women ((n=8))</th>
<th>Postmenopausal Women ((n=16))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL apoA-I, mg/dL</td>
<td>126.4±20.5</td>
<td>143.1±22.7</td>
<td>0.06</td>
</tr>
<tr>
<td>PS, mg</td>
<td>3654.3±616.1</td>
<td>4316.7±1104.3</td>
<td>0.10</td>
</tr>
<tr>
<td>FCR, pools/day</td>
<td>0.21±0.01</td>
<td>0.21±0.03</td>
<td>0.85</td>
</tr>
<tr>
<td>PR, mg/kg per day</td>
<td>11.9±4.1</td>
<td>13.3±3.4</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Values are mean±SD.

**Discussion**

Longitudinal studies \(^{12,18,21,26–29}\) have demonstrated that the transition from premenopause to postmenopause is associated with elevated TC, LDL-C, and TG levels. This finding is supported by cross-sectional studies \(^{12–25}\) including our data. The unique finding of the present study is that the metabolic basis for these effects is attributable to differences in TRL and LDL apoB-100 FCR, not PR.

Evaluating the independent association between meno-
pause and CVD risk is difficult because of the high corre-
lation between hormonal status and age. One solution is to
follow the same group of women in a longitudinal study. This
approach is hampered by weight gain and lifestyle changes
over time, the potential need for treatment to alleviate menopausal symptoms in some women, as well as the technical difficulties associated with conducting a stable
isotope kinetic study in a large number of individuals over
time.

Our primary goal was to determine whether loss of
endogenous sex hormones contributes to the atherogenic lipid
profile observed in postmenopausal women. Consequently,
by recruiting younger premenopausal and older postmeno-
pausal women, we were able to maximize this contrast in sex
hormone status. An alternate approach is to match subjects by
age or include a narrower age range and statistically adjust for
age. However, this would have resulted in the inclusion of
perimenopausal women with irregular menses and postmeno-
pausal women who had recently attained menopause, thereby
diluting the hormonal effect. Although our stringent exclu-
sion criteria eliminated the bias induced by oral contracep-
tive/HRT use and weight change, the design of the present
study limited the ability to partition out the independent
effects of menopause from aging, and this factor must be
taken into account when interpreting the results.

Little is known about the effect of natural menopause on
lipoprotein kinetics. Our data show that nonfasting plasma
TC, LDL-C, TRL-C, TG, and apoB-100 levels were higher in
postmenopausal compared with premenopausal women. This
was accompanied by lower TRL and LDL FCR. One possible
explanation is the reduction in endogenous hormone secre-
tion. Conjugated equine estrogen replacement therapy in-
creases TG levels,\(^ {44} \) an effect presumably resulting from the
hepatic first pass of this steroid. Oral 17\( \beta \) estradiol raises TG
levels by increasing PR of large and small VLDL, with no
significant change in FCR.\(^ {23,44} \) This effect may result from an
increase in hepatic apoB mRNA transcription and incorpora-
tion into nascent VLDL.\(^ {45} \) Inhibition of hepatic fatty acid
\( \beta \)-oxidation by estrogen\(^ {46} \) promotes increased TG synthesis
and decreased intracellular degradation of newly synthesized apoB-100, contributing to increased apoB secretion in large VLDL. Transdermal 17β estradiol, considered to more closely reflect the physiological effect of endogenous estrogen, has little effect or causes a slight reduction in TG levels.47

Changes in body composition observed after menopause may contribute to changes in TG levels. Differences in BMI was borderline significant (P=0.07) between the women who participated in the apoB-100 part of the kinetic study. No association was observed between BMI and TRL, IDL or LDL apoB100 FCR, or PR, regardless of menopausal status (data not shown). It has been suggested that increased fat mass could elevate plasma free fatty acid levels, causing overproduction of TG by hepatocytes and resulting in excess TRL apoB-100 production. This would decrease conversion of IDL to LDL and delay FCR of LDL via downregulation of hepatic LDL receptor activity. This hypothesis is partially supported by the slower TRL delipidation and clearance rate constants and lower TRL, IDL, and LDL apoB-100 FCR observed in the postmenopausal compared with premenopausal women.

The LDL apoB-100 kinetic studies collectively demonstrate that estrogen, irrespective of type or route of administration, decreases plasma LDL-C levels by increasing LDL apoB-100 FCR, potentially mediated via upregulation of hepatic LDL receptor mRNA transcription.45,53 Based on these results, loss of endogenously produced estrogen may have the reverse effect and decrease clearance of LDL and subsequently increased plasma LDL-C levels. This was observed in the present study.

Conflicting results have been reported on the effect of menopause and plasma HDL-C levels. Although most studies, including the current data, find no significant difference between premenopausal and postmenopausal women, others report either an increase or a decrease.12,13,29

The HDL apoA-I kinetic studies collectively demonstrate that estrogen, irrespective of type or route of administration, decreases plasma HDL-C levels after oral HRT to increased apoA-I PR50,54 or decreased apoA-I FCR.55 Brinton et al reported that FCR was the major determinant of HDL-C levels in women with a wide range of HDL-C levels and ages. The effect of age or menopausal status was not addressed. However, mean HDL-C (1.9 and 1.8 mmol/L) and apoA-I (4.6 and 4.1 mmol/L) levels were similar in the 12 premenopausal and 3 postmenopausal women, respectively (assuming a mean menopause age of 52 years), precluding further distinctions between the 2 groups. Interestingly, transdermal estrogen, bypassing the liver, had little effect on HDL-C levels or kinetic rates.44 In the current study, the finding of no significant difference in HDL apoA-I kinetic behavior between the premenopausal and postmenopausal women supports the conclusion that loss of endogenous estrogen does not markedly impact plasma HDL-C levels.

In conclusion, results of the present study demonstrate that lower TRL and LDL FCR rather than higher PR was the putative factor in modulating TRL and LDL apoB-100 PS and plasma levels in postmenopausal women. There was little effect of menopausal status on HDL-C or apoA-I levels or kinetic parameters. The potentially adverse consequence of a shift toward a more atherogenic lipoprotein profile in postmenopausal women emphasizes the need for better understanding, prevention, and treatment of heart disease in postmenopausal and oophorectomized women.

Acknowledgments

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References


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**Figure I**: Tracer/Tracee (T/T) ratios for TRL apoB-100 (■), IDL apoB-100 (□), LDL apoB-100 (△) and HDL apoA-I (*) versus time after a primed constant infusion of [5,5,5-\(^2\)H\(_3\)]-L-leucine over a 15 hour period in premenopausal (A) and postmenopausal (B) women. T/T values shown for each timepoint are averages with standard deviations for all subjects.