ORIGINAL RESEARCH

Effect of HRT on Serum Lipid, Apolipoprotein AI, Apolipoprotein B, and Lipoprotein (a) in Postmenopausal Women: Added Benefits of Dietary and Exercise Improvement

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ABSTRACT Objective: In this quasi-experimental study, we aimed to measure the effect of hormone replacement therapy (HRT) on serum lipid, apolipoprotein AI, apolipoprotein B, and lipoprotein (a). The study had three objectives: to replicate previous studies' findings on the effect of HRT on lipid and lipoprotein profiles; to integrate possible effects of dietary and exercise improvements (considered as independent predictors), covariates, and interaction variables; and to report effect sizes capable of estimating the impact of HRT on each outcome variable of the study. **Material and Methods:** The effect of HRT on serum lipid, apolipoprotein AI, apolipoprotein B, and lipoprotein (a) was determined in a case group of 86 postmenopausal women compared with that in a control group of 97 age-matched women who were not receiving HRT and who were not menopausal. **Results:** HRT had the expected salutary effect on all measured variables, except for apolipoprotein AI. The largest effect size was observed for high-density lipoprotein cholesterol, suggesting the need for replication and if necessary, further investigation of why HRT might be particularly beneficial for high-density lipoprotein cholesterol levels of postmenopausal women. **Conclusion:** Finally, the study found neither an independent nor interactive effect of diet or exercise on the effect of HRT.

Keywords: Hormone replacement therapy; postmenopausal; lipids; lipoprotein; apolipoprotein

Salutary effects of hormone replacement therapy (HRT) on lipids and lipoproteins are well-examined in scholarly literature. There are sound theoretical reasons as well as numerous empirical reasons supporting these effects. Evolutionarily, a decline in favorable lipid and lipoprotein profiles as a function of menopause can be interpreted as part of the coupling of reproductive and somatic senescence. As Croft et al. have argued, the phenomenon of prolonged post-reproductive lifespan (PRLSs) is relatively rare, primarily occurring in humans and certain insects and cetaceans.[1] Several possible reasons for prolonged PRLSs in human females have been proposed, including the role played by grandmothers when caring for their offspring and by contemporary advances in medicine.[2-4]

Regardless of the reasons for prolonged PRLSs in human females, reproductive senescence occurs after a steady decline in fertility and is also associated with declines in many markers of health, including bone health.[5-8] Yun and Lee have described declining health post menopause, with reference to the phrase "diseases of post-reproductive senescence".[9] Available biological evidence and the logic of evolutionary biology suggest that postmenopausal women are less protected from disease.[10]

In women, a decline in estrogen represents an increasing vulnerability to diseases, such as cardiovascular disease and osteoporosis.[11-13] In fertile women, estrogen provides protection against cardiovascular disease as well as other diseases; the existence of such a protective hormonal effect is not unique to humans and indicates how evolutionary forces would select for traits, feedback mechanisms, and structures that would enhance the chances of the young to live long enough to reproduce.[1,14-16]

The availability and increasing use of HRT affords women renewed protection against cardiovascular and other forms of disease.[17] In particular, HRT in postmenopausal women is associated with improvements in lipid and lipoprotein profiles.[18] Despite the extensive scholarly work on the usefulness of HRT with respect to lipid and lipoprotein profiles, there remain important gaps in the literature. One such gap is the failure of previous researchers to calculate and report effect sizes, including classic measures such as Cohen's *d* and Hedges' *g*.[19-21] Effect sizes are particularly useful in clinical settings because they convey information that is not conveyed by a *p* value, that is, the practical impact of an intervention.[21] Another gap in the literature is the absence of measurements of the lipid- and lipoprotein-protective effects, if any, of improved diet and exercise. In the context of anti-aging medicine, in particular, and also in the context of general medicine, physicians who administer HRT should make lifestyle recommendations for patients; such physicians would be particularly interested in a quantification of the added lipid- and lipoprotein-protective effects, if any, of improved diet and exercise.[22] Finally, physicians and researchers would benefit from reported effect sizes, for the added components of improved diet and exercise as well as for any changes in lipid and lipoprotein profiles. One point of lingering theoretical interest, for example, is why HRT might improve certain lipid or lipoprotein profiles to a greater extent than others. Such an effect, if it exists, can be identified through effect size estimations as well as through comparisons of the 95% confidence intervals of *t* statistics and related measures.

Bayrak et al. measured the effect of HRT on lipid and lipoprotein profiles of 60 women who were divided into groups that received estrogen only and estrogen plus progesterone replacement. They found that both forms of HRT were associated with lipid and lipoprotein profile improvements. However, Bayrak et al. did not include a control group, measures of effect size, and covariates that could have helped to explain (for example, through moderation) the effects of both forms of HRT.[23]

Kim et al. found evidence on the effectiveness of HRT for reducing lipoprotein (a) and lipids in postmenopausal women.[24] In addition, Kim et al. found that HRT was associated with improvements in triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol profiles. They were interested in different treatment conditions, including (a) the addition of medroxyprogesterone acetate and (b) possible effects of hysterectomy. To assess the effects of these covariates, Kim et al. divided the case group into three groups. By doing so, however, Kim et al. lost potential statistical power as there was no need to place women with a hysterectomy into a separate case group; instead, the hysterectomy status could have been treated as a covariate and subsequently turned into an independent predictor [in ANOVA or analysis of covariance (ANCOVA)] or an interaction variable (such as hysterectomy * MPA) using an ANCOVA approach. Beca use of Kim et al.'s use of a repeated-measures *t*-test approach, they were not able to accommodate covariates in their model, resulting in the creation of an unnecessary case group and a corresponding loss of statistical power. The inclusion of appropriate covariates in an ANCOVA can address this kind of gap in the previous literature on the effects of HRT on the lipid and lipoprotein profiles of postmenopausal women.

This study has been structured as follows. First, a review of literature surveys and discussion on recent or notable findings on the effect of HRT on lipids and lipoproteins among postmenopausal women was done. Second, the methods of the study have been described. Third, the results have

been presented. Finally, the results have been discussed with reference to past findings, implications, and directions for future research.

MATERIAL AND METHODS

PROCEDURE

This was quasi-experimental study. Eighty-six women who had undergone HRT treatment volunteered to participate in data collection for this study. Of these women, 23 had had hysterectomies and the remaining 63 had intact uteruses. Each of these 86 women, who constituted the case group, received continuous 0.625 mg conjugated equine estrogen (CEE). Before each woman's first CEE treatment, her body mass index (BMI); VO_2 max; uterine status; and total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a) were measured. Each participant in the study underwent re-measurement of each of these variables at 6, 12, and 18 months after baseline. Each participant was, at baseline, offered a detailed brochure with exercise and diet recommendations; however, no active dietary or exercise intervention was staged. BMI and VO_2 max were treated as proxy variables for dietary improvement and exercise improvements, respectively, based on the hypothesis that improvements in BMI would reveal dietary improvements, whereas improvements in VO_2 would reveal exercise improvements

The control group included 97 age-matched women who were not postmenopausal. These women were patients who agreed to have their BMI; VO_2 max; uterine status; and total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipo- protein AI, apolipoprotein B, and lipoprotein (a) collected at baseline, 6 months, 12 months, and 18 months. Originally, 108 women were sampled for the control group; 11 became menopausal by the 18-month data collection period. Therefore, the final number of control group members was 97.

VARIABLES AND CODING

Variables of the study, accompanied by their names for statistical analysis using Stata software, were as follows:

■ Menopausal status (meno): Dichotomous nominal variable, with 0=not menopausal and 1=postmenopausal. No peri-menopausal women were included in the study.

■ Uterine status (hyst): Dichotomous nominal variable, with 0=uterus intact and 1=uterus removed.

■ Body mass index (BMI): Interval variable, measured to two significant figures.

■ Dietary improvement (diet): Measured as % decline in BMI from baseline. This variable was polytomous, with the following possible values: 1 = BMI increased by ≥5% vs. baseline, 2=BMI increased by up to 5% vs. baseline, 3=BMI decreased by up to 5%, and 4 = BMI decreased by >5%. These values were not intended to be ordinal; they only existed as category separators during data analysis.

■ Exercise improvement (VO_2): Measured as % increase in VO_2 max measured from baseline to the points of data collection. This variable was polytomous, with the following possible values: 1=VO_2 max increased by ≥5% vs. baseline, 2 = VO_2 max increased by up to 5% vs. baseline, 3 = VO_2 max decreased by up to 5%, and 4 = VO_2 max decreased by >5%. These values were not intended to be ordinal; they only existed as category separators during data analysis.

■ Total cholesterol (Cho): Measured as % change in total cholesterol (mg/dl), from baseline to the points of data collection.

■ Triglyceride (Trig): Measured as % change in triglycerides (mg/dl), from baseline to the points of data collection.

■ Low-density lipoprotein cholesterol (LDL-c): Measured as % change in low-density lipoprotein cholesterol (mg/dl) from baseline to the points of data collection.

■ High-density lipoprotein cholesterol (HDL-c): Measured as % change in high-density lipoprotein cholesterol (mg/dl), from baseline to the points of data collection.

■ Apolipoprotein AI (Apoai): Measured as % change in apolipoprotein AI (mg/dl), from baseline to the points of data collection.

■ Apolipoprotein B (Apob): Measured as % change in apolipoprotein B (mg/dl), from baseline to the points of data collection.

■ Lipoprotein (a) (Lipoa): Measured as % change in lipoprotein (a) (mg/dl), from baseline to the points of data collection.

DATA ANALYSES

ANCOVA was adopted as the base model for the study. There were seven ANCOVAs, with separate ANCOVAs conducted for each of the seven dependent variables-representing changes in total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a). For better calculation of separate effect sizes of the relationship between HRT and each of these outcomes, a multiple analysis of covariance (MANCOVA) was rejected; the use of seven AN-COVA introduced a possible problem of Alpha inflation into the study. Effect sizes were calculated separately from ANCOVAs on the basis of descriptive statistics of mean, standard deviation, and *n* for each comparison group. All statistical analyses for the study were performed using Stata/SE 14.2 software. The level of statistical significance was 0.10.

RESULTS

The findings of the study have been divided into eight sections. The first section contains a single set of comparisons with accompanying descriptive statistics. The subsequent seven sections examined the impact of HRT administration-considered alongside the effects of dietary and exercise improvement-on changes in total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a).

DESCRIPTIVE STATISTICS

To determine the similarity between the HRT and non-HRT groups at baseline (that is, at month 0), independent samples *t*-tests were performed. Results of these *t*-tests have been presented in Table 1.

At a two-tailed α of 0.05, the HRT and non-HRT groups were, at the baseline, statistically comparable with respect to BMI, VO_2 max, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein (a). Therefore, subsequent disparities in these measurements can be more validly ascribed to HRT than to pre-existing differences.

Table 2 below includes a comparison of group outcomes, with means reported and standard deviations in parentheses.

COMPARATIVE FINDINGS

***t*-Tests and ANCOVAs.** Findings have been separately presented for total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, lipoprotein (a).

	M, Group	HRT M, Non-HRT Group	Difference	*t*	*p (t), two-tailed*
BMI	28.29	28.05	0.24	0.3216	0.7481
VO_2	47.76	48.46	-0.7	-0.8630	0.3893
Cho	200.33	199.33	1	0.2940	0.7691
Trig	126.86	129.38	-2.52	-0.4082	0.6836
LDL-c	139.31	142.17	-2.86	-0.6984	0.4914
HDL-c	42.42	42.06	0.36	0.5005	0.6173
Apoai	142.77	142.83	-0.06	-0.0293	0.9766
Apob	142.09	142.13	-0.04	-0.0127	0.9899
Lipoa	31.34	28.8	2.54	1.8014	0.0733

TABLE 1: Comparison of case and control groups at baseline.

	TABLE 2: Means and standard deviations of outcomes by group.							
	HRT Recipients (*n*= 86)				Non-HRT Recipients (*n*= 97)			
	0 Months	6 Months	12 Months	18 Months	0 Months	6 Months	12 Months	18 Months
BMI	28.29 (4.87)	27.91 (5.08)	27.92 (5.09)	27.85 (5.23)	28.05 (5.05)	28.08 (5.52)	28.08 (5.50)	28.09 (5.55)
VO$_2$ max	47.76 (5.85)	47.79 (6.00)	47.80 (6.06)	47.80 (6.09)	48.46 (5.13)	48.38 (5.00)	48.34 (4.95)	48.36 (5.11)
Cho	200.33 (25.60)	187.16 (26.45)	182.0 (26.65)	182.01 (26.65)	199.33 (20.63)	199.50 (20.71)	199.55 (20.70)	199.40 (20.88)
Trig	126.86 (42.58)	117.14 (42.78)	113.42 (42.53)	113.29 (42.52)	129.38 (40.97)	129.24 (40.95)	129.00 (41.10)	129.11 (40.99)
LDL-c	139.31 (29.34)	121.89 (29.73)	117.42 (29.60)	117.30 (29.57)	142.17 (26.66)	142.14 (26.67)	142.01 (26.56)	142.16 (26.68)
HDL-c	42.42 (4.94)	60.74 (9.88)	67.24 (10.58)	67.17 (10.82)	42.06 (4.78)	42.00 (4.83)	42.08 (5.03)	42.25 (5.26)
Apoai	142.77 (26.51)	150.00 (14.72)	156.29 (14.73)	156.12 (14.81)	142.83 (15.13)	155.58 (15.30)	155.53 (15.27)	155.61 (15.61)
Apob	142.09 (26.51)	134.13 (26.96)	129.56 (27.04)	129.52 (27.15)	142.13 (24.00)	142.04 (23.96)	142.16 (24.04)	142.19 (23.88)
Lipoa	31.34 (10.02)	15.20 (15.89)	8.21 (16.36)	8.22 (16.34)	28.80 (9.10)	28.55 (9.18)	28.60 (9.16)	28.56 (8.99)

Key: Total cholesterol (cho); Triglycerides (trig); Low-density lipoprotein cholesterol (ldl-c); High-density lipoprotein cholesterol (hdl-c); Apolipoprotein AI (apoai); Apolipoprotein B (apob); Lipoprotein (a) (lipoa); BMI: Body mass index.

Total cholesterol findings. Total cholesterol of HRT recipients significantly decreased from the baseline to 6 months [–13.17 (*SE* = 3.96), *t*(170) = –3.3189; *p*=0.0006]. However, there were no further significant reductions in total cholesterol of HRT recipients; therefore, the only comparison for total cholesterol between the HRT and non-HRT groups was at 6 months. At 6 months, the mean total cholesterol of the HRT group (*M* = 187.16, *SD*=26.45) was significantly lower than that of the non-HRT group [(*M*=199.50, *SD* = 20.71), *t*(181) = –3.3538; *p* = 0.0003]. The effect of HRT treatment on cholesterol reduction remained significant [*F*(1) = 12.02; *p*=0.0007] when the dichotomous variables of major BMI loss [*F*(1)=0.06; *p*=0.8028] and major VO$_2$ increase [*F*(1)=0.75; *p*=0.3862] were added. Another interpretation of ANCOVA was that when HRT treatment was taken into account, there were no beneficial effects of BMI loss (as a proxy measure of healthier diet) and VO$_2$ max gain (as a proxy measure of exercise improvement) on total cholesterol reduction (Figure 1).

Triglycerides findings. Triglycerides of HRT recipients significantly decreased from the baseline to 6 months [-9.72 (*SE* = 6.51), *t*(170)=–1.4933; *p* = 0.0686]. However, there were no further significant reductions in triglyceride of HRT recipients; therefore, the only comparison for triglyceride between the HRT and non-HRT groups was at 6 months. At 6 months, the mean triglyceride of the HRT group (*M*=117.14, *SD*=42.78) was significantly lower than that of the non-HRT group [(*M* = 129.24, *SD*=40.95); *t*(181)=–1.9542; *p* =0.0261]. The effect of HRT treatment on triglyceride reduction remained significant [*F*(1)=3.86; *p*=0.0510] when the dichotomous variables of major BMI loss [*F*(1)=1.43; *p*=0.2326] and major VO$_2$ increase [*F*(1) = 0.36; *p*=0.5469] were added. Another interpretation of ANCOVA was that, when HRT treatment was taken into account, there were no beneficial effects of BMI loss and VO$_2$ max gain on triglyceride reduction (Figure 2).

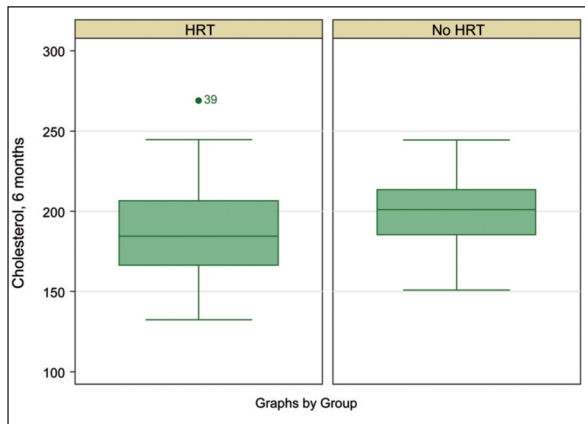**Low-density lipoprotein cholesterol findings**. Low-density lipoprotein cholesterol of HRT reci-

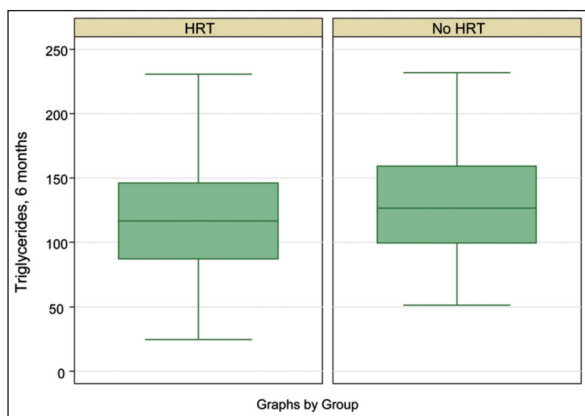**FIGURE 1:** Box plot of cholesterol at 6 months after HRT of the case and control groups.

FIGURE 2: Box plot of triglycerides at 6 months after HRT for the case and control groups.

pients significantly decreased from the baseline to 6 months [−17.42 (SE=4.50), $t(170)$=−3.8685; p = 0.0001]. However, there were no further significant reductions in low-density lipoprotein cholesterol of HRT recipients; therefore, the only comparison for low-density lipoprotein cholesterol between the HRT and non-HRT groups was at 6 months. At 6 months, the mean low-density lipoprotein cholesterol of the HRT group (M = 121.89, SD=29.73) was significantly lower than that of the non-HRT group [(M=142.14, SD=26.67); $t(181)$=−4.8564; $p < 0.0001$]. The effect of HRT treatment on low-density lipoprotein cholesterol reduction was no longer significant [$F(1)$=0.50; p= 0.4794] when the dichotomous variables of major BMI loss [$F(1)$=0.05; p =0.8199] and major VO_2 increase [$F(1)$=0.12; p =0.7248] were added. One possible interpretation of this ANOVA is that missing

instrumental variables might be responsible for the loss of HRT's significance when major BMI loss and major VO_2 increase were taken into account (Figure 3).

High-density lipoprotein cholesterol findings. High-density lipoprotein cholesterol of HRT recipients significantly increased from the baseline to 6 months [18.29 (SE=1.19), $t(170)$=15.3601; $p<$ 0.0001]. However, there were no further significant increases in high-density lipoprotein cholesterol of HRT recipients; therefore, the only comparison for high-density lipoprotein cholesterol between the HRT and non-HRT groups was at 6 months. At 6 months, the mean high-density lipoprotein cholesterol of the HRT group (M=60.74, SD =9.88) was significantly higher than that of the non-HRT group [(M=42.08, SD=5.03); $t(181)$= 16.5480; $p<0.0001$]. The effect of HRT treatment on high-density lipoprotein cholesterol reduction remained significant [$F(1)$=273.97; $p<0.0001$] when the dichotomous variables of major BMI loss [$F(1)$=1.81; p =0.1806] and major VO_2 increase [$F(1)$=0.12; p 0.7332] were added. Another interpretation of ANCOVA was that, when HRT treatment was taken into account, there were no beneficial effects of BMI loss and VO_2 max gain on high-density lipoprotein cholesterol increase (Figure 4).

Apolipoprotein AI findings. Apolipoprotein AI of HRT recipients significantly increased from the baseline to 6 months [7.22 (SE=2.18), $t(170)$ =
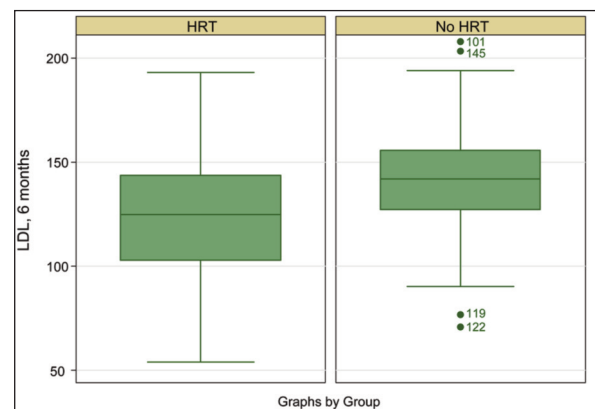

FIGURE 3: Box plot of low-density lipoprotein cholesterol at 6 months after HRT for the case and control groups.
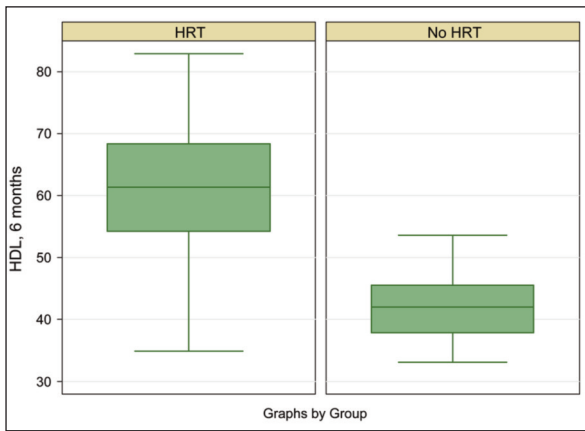
–3.3144; p =0.0011]. At 6 months, the mean apolipoprotein AI for the HRT group (M =150.00, SD = 14.72) was significantly lower than that for the non-HRT group [(M =155.59, SD =15.31); t(181) = –2.5141; p =.0064]. By 12 months, however, there was no significant difference in apolipoprotein AI of the HRT (M =156.29, SD =14.73) and non-HRT groups [(M =155.53, SD =15.27); t(181) =0.3644; p =0.7287]. At 18 months as well, there was no significant difference in apolipoprotein AI between the HRT (M =156.12, SD =14.81) and non-HRT groups [(M =155.61, SD =15.61); t(181) =0.2247; p =0.8225]. However, the effect of HRT treatment on apolipoprotein AI reduction became significant [F(1) =6.39; p =0.0123] when the dichotomous variables of major BMI loss [F(1) =0.61; p =0.4371] and major VO$_2$ increase [F(1)<0.01; p =0.9843] were added, suggesting possible apolipoprotein AI-affecting properties of diet and exercise change or related variables (Figure 5).

Apolipoprotein B findings. Apolipoprotein B of HRT recipients significantly decreased from the baseline to 6 months [–7.96 (SE=4.08), t(170)= –1.9510; p=0.0263]. However, there were no further significant reductions in apolipoprotein B of HRT recipients; therefore, the only comparison for apolipoprotein B between the HRT and non-HRT groups was at 6 months. At 6 months, the mean apolipoprotein B of the HRT group (M = 134.13, SD = 26.96) was significantly lower than that of the non-HRT group [(M =142.04, SD = 23.96); t(181) =

–2.1016; p=0.0185]. The effect of HRT treatment on apolipoprotein B reduction remained significant [F(1)=4.44; p = 0.0366] when the dichotomous variables of major BMI loss [F(1)=0.72; p =0.0366] and major VO$_2$ increase [F(1)=0.10; p =0.7470] were added. Another interpretation of ANCOVA was that, when HRT treatment was taken into account, there were no beneficial effects of BMI loss and VO$_2$ max gain on apolipoprotein B reduction (Figure 6).

Lipoprotein (a) findings. Lipoprotein (a) of HRT recipients significantly decreased from the baseline to 6 months [–16.14 (SE=2.02), t(170)= –7.9696; p <0.0001]. However, there were no further significant reductions in lipoprotein (a) of HRT recipients; therefore, the only comparison of li-
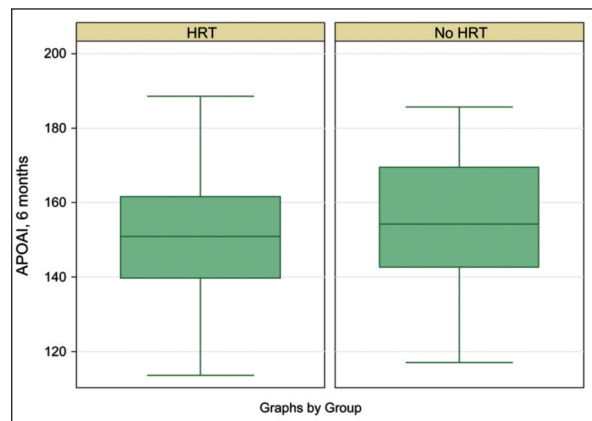
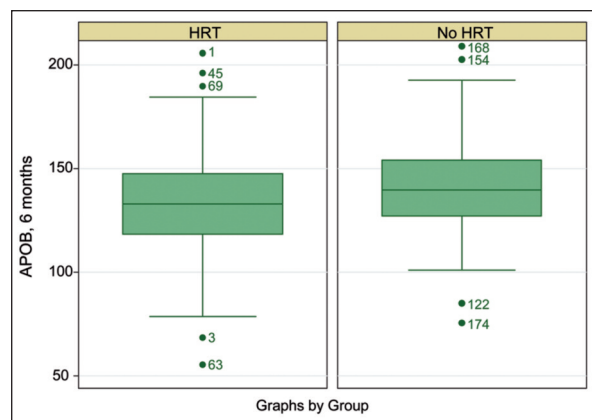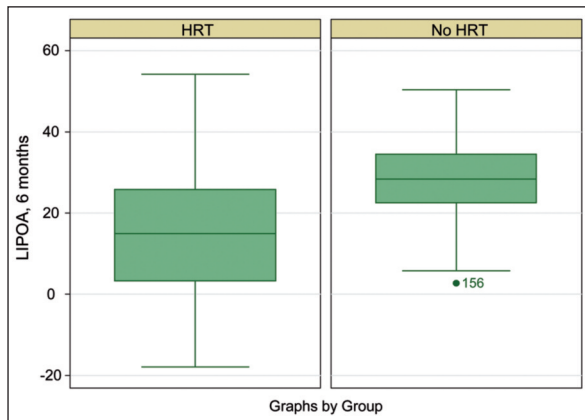**FIGURE 7:** Box plot of lipoprotein (A) at 6 months after HRT for the case and control groups.

poprotein (a) between the HRT and non-HRT groups was at 6 months. At 6 months, the mean lipoprotein (a) for the HRT group ($M = 15.20$, $SD = 15.89$) was significantly lower than that for the non-HRT group [($M = 28.55$, $SD=9.18$); $t(181) = -7.0530$; $p < 0.0001$]. The effect of HRT treatment on lipoprotein (a) reduction remained significant [$F(1)=50.88$; $p<0.0001$] when the dichotomous variables of major BMI loss [$F(1)=0.52$; $p=0.4703$] and major VO_2 increase [$F(1)=3.04$; $p=0.0829$] were added. Another interpretation of ANCOVA was that, when HRT treatment was taken into account, there were no beneficial effects of BMI loss, but that the interaction of VO_2 max gain on the group was significant [$F(1)=4.63$; $p=0.0327$]. However, this effect was minuscule (Figure 7).

EFFECT SIZES

The effect sizes of the difference between the HRT and non-HRT groups at 6 months have been presented in Table 3 below. The comparison of the effect

sizes indicates that the largest effect size in the study was that for high-density lipoprotein cholesterol, indicating that the salutary effect of estrogen administered to postmenopausal women might be greater for high-density lipoprotein cholesterol than for the other measures in Table 3. It should also be noted that 0 was not found in any of the 90% confidence intervals for the effect sizes. This point was particularly important with respect to apolipoprotein AI, for which no statistically significant difference was found between HRT and non-HRT groups.

DISCUSSION

The only unexpected finding in this study was the absence of a significant difference in apolipoprotein AI between the HRT and non-HRT groups. This result could have been caused by a statistical error. One possibility was that a change in apolipoprotein AI as a result of HRT administration interacted with exercise and dietary change, but there were no significant interactions between (a) apolipoprotein AI, group, and major BMI decrease [$F(1)=1.07$; $p=0.3022$]; (b) apolipoprotein AI, group, and major VO_2 max increase [$F(1)=0.84$; $p = 0.3593$]; and (c) (a) apolipoprotein AI, group, major BMI decrease, and VO_2 max increase [$F(2)=0.72$; $p =0.4867$]. For reasons discussed in the literature review and introduction, the absence of a significant difference in apolipoprotein AI between the HRT and non-HRT groups was unexpected, and this finding was also not aligned with the other changes in lipid and lipoprotein observed in the study. Therefore, the absence of a significant difference in apolipoprotein AI between the HRT and non-HRT groups should not be taken as a basis for interpreting existing fin-

TABLE 3: Effect Sizes of HRT treatment vs. No HRT treatment, 6 months.				
	Cohen's *d*	**Hedges' *g***	**Glass's Delta 1**	**Glass's Delta 2**
Cholesterol	-0.523	-0.521	-0.466	-0.595
Triglycerides	-0.289	-0.288	-0.282	-0.295
Low-density lipoprotein cholesterol	-0.719	-0.716	-0.681	-0.759
High-density lipoprotein cholesterol	2.450	2.440	1.893	3.866
Apolipoprotein	-0.372	-0.370	-0.380	-0.365
AI Apolipoprotein	-0.311	-0.309	-0.293	-0.330
B Lipoprotein (A)	-1.044	-1.040	-0.840	-1.453

dings or theories about the relationship between estrogen and lipid/lipoprotein profiles.

The aspect of the study that deserves additional interest is the difference in effect sizes. One question of immediate interest raised in Table 3 is why was the effect of HRT on high-density lipoprotein cholesterol so much greater than that on the other tested outcome variables. Again, this result could be a statistical artifact more than a clinical clue; however, if future researchers apply effect sizes and find similar gaps in effect sizes, there would be more justification to re-focus research agendas on how and why estrogen replacement might be more beneficial to high-density lipoprotein cholesterol than to other lipid and lipoprotein profiles. In the absence of replication, it is not clear whether such a research agenda is even necessary. In particular, given that previous researchers have not generated effect sizes, there is a need for future studies to include such measures to determine whether HRT might be having different impacts on different lipid and lipoprotein profiles. Such differential profiles, if they exist, could point the way to identifying mechanisms and characteristics of estrogen that might be more protective for some lipid and lipoprotein profiles than others.

Another unexpected finding of the study was that major BMI loss and major VO_2 max increase were neither independently predictive of improvements in lipid and lipoprotein profiles nor, except in one case, significant moderators of the impact of HRT. There are several possible reasons for this finding. One possible reason is that the definition of major improvement utilized in this study (5% for BMI loss and 1% for VO_2 max gain) is insufficient as a measure of effect. Perhaps the lipid- and lipoprotein-protective effects of dietary and exercise improvement manifest themselves at greater magnitudes of improvement.

Another possibility is that of inaccurate measurement, particularly for BMI. BMI was calculated by weighing subjects and measuring their heights. Participants were weighed in their clothes, minus shoes; however, participants were not directed to wear the same clothing at the 6-, 12-, and 18-month marks, and it is also possible that they were not weighed in the same conditions (for example, some participants might initially have been weighed before going to the bathroom and subsequently weighed after going to the bathroom). The possibility of such measurement errors suggests that procedures for obtaining BMI were deficient.

There is also a possibility that BMI loss is an inappropriate proxy variable for dietary improvement. Researchers have argued that the quantification of dietary improvement is difficult; while measuring BMI change is a means of avoiding the definitional and conceptual problems that attempts to measure the quality of diet, the drawback of a BMI-based approached is that BMI can fall for reasons, such as illness, that are unrelated to dietary quality.[25-32]

We were not experts in VO_2 max measurement, which admitted the possibility of measurement error. In addition, a 1% improvement in VO_2 max might have been an inappropriate threshold; one that failed to capture true improvements in cardiovascular exercise capacity. Finally, it should be noted that the measurement of VO_2 only captures changes in aerobic exercise capacity-not anaerobic capacity, which is also an excellent, and independent, measure of overall physiological health and exercise capacity.

CONCLUSION

The present study had two complementary agenda. The first agenda was to replicate past measurements of the effect of HRT on lipid and lipoprotein profiles among postmenopausal women. The second, and more important, agenda was to demonstrate novel approaches to what is now a well-defined and well-studied research topic. Although effect sizes and ANCOVAs represent elementary statistical methods, they can add substantial value to studies on the relationship between HRT and lipid/lipoprotein profiles. ANCOVAs allow for the measurement of interaction between the effect of HRT and other variables. In this study, major BMI change and VO_2 max change were included as independent predictors and group interaction variables in ANCOVA models; however, future researchers can insert any number of covariates of interest in such models.

In addition, the benefit of calculating effect sizes is that researchers can go beyond determining whether the effects of HRT on lipid/lipoprotein profiles are statistically significant and generate more clinically useful information. As far as an effect size is a measurement of the impact of a predictor variable or an intervention, it provides clinicians and other practitioners with a useful, practical estimate of the outcome of an intervention. Although the study had numerous limitations, it provided a demonstration of how going beyond *t*-tests can add both theoretical and empirical value to analyses of HRT effects on lipid/lipoprotein profiles, particularly in the case of estrogen when administered to postmenopausal women.

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