Effects of hormone replacement therapy on muscle performance and balance in post-menopausal women

Alison L. ARMSTRONG, Janet OBORNE, Carol A. C. COUPLAND, Marion B. MACPHerson, E. Joan BASSEY and W. Angus WALLACE
Nottingham Osteoporosis Research Group, Department of Orthopaedic and Accident Surgery, University Hospital, Nottingham, U.K.

(Received 28 March/29 July 1996; accepted 19 August 1996)

1. A randomized controlled trial of the effect of oral hormone replacement therapy plus calcium compared with calcium alone on balance, muscle performance and falls was conducted over 48 weeks in 116 post-menopausal women (aged 45–70 years), all of whom had suffered a distal radial fracture during the previous 3 months. Treatment was with Prempak C or Premarin 0.625 mg in the test group with 1 g calcium daily (Sandoval) in both groups. Measurements were made of balance, assessed as sway, leg extensor power and self-paced walking speed, at 12-week intervals over 24 weeks. Hand grip strength was measured every 12 weeks for 48 weeks, and falls in the preceding 12 weeks were recorded at each visit.

2. There was no relation between initial levels of oestradiol and any other variable assessed, except body mass. Levels of follicle-stimulating hormone in the test group were in the premenopausal range. There was no significant change attributable to hormone replacement therapy at any time point in any of the outcome variables. The only significant difference was an increase of 4.2% (95% confidence interval 0.7–7.6%) in leg extensor power in the control group (calcium alone) compared with the group treated with hormone replacement therapy.

3. Of the total group, 37% fell again during the year, with three patients suffering a further fracture. Frequent fallers swayed significantly more often than the others, but there was no evidence that their muscle strength was poorer or that the group treated with hormone replacement therapy fell less frequently.

4. Hormone replacement therapy did not increase muscle performance, improve balance or reduce falls over a year in middle-aged women.

INTRODUCTION

Falls in elderly women are common [1] and are thought to arise from deterioration in balance [2]. Balance itself is under the control of the nervous system, but poor balance [3] and falls [4, 5] have also been related to lack of muscle strength. With increasing age, the number of neurons in the central nervous system declines and there is a deterioration in the response time for complex tasks [6]. Muscle strength [7, 8] also declines with age, such that the elderly may have only 40% of peak life-time strength [8]. Women are more vulnerable than men as they have lower leg strength in relation to their body mass, by about 30% [7, 8], and poorer balance [2].

Falls result in fracture if the bone mineral density is sufficiently low [9] and the cushioning provided by soft tissue is inadequate [10]. The increase in the number of falls as women get older is paralleled by an increase in minimal trauma fractures [1]. Consequently, preventing falls through the preservation of muscle strength and balance is important for the well-being of the elderly.

Recently it has been suggested that the loss of oestrogen that occurs at the menopause may be associated with the loss of balance [11] and strength [12–14] seen with increasing years in women. However, a recent randomized controlled trial has shown that hormone replacement therapy (HRT) is not associated with an increase in muscle strength, although the numbers in that study were small [15]. The following report examines this question in a larger group of women and includes measures of balance.

METHODS

A total of 116 Caucasian post-menopausal women (aged 45–70) who had suffered a wrist fracture within the previous 7 weeks were recruited from the fracture clinics of a large city hospital. A targeted history was taken from each woman and examination and biochemistry and gynaecological screen were performed to ensure that there was no contra-indication to HRT [16]. Follicle-stimulating...
hormone (FSH) and luteinizing hormone (LH) levels were checked in women without a uterus to ensure that they were of a post-menopausal pattern. The women were also screened for any overt neurological or neuromuscular condition that might impair their strength, balance or mobility, and none was being treated with drugs affecting balance. The subjects were then entered into a randomized controlled trial of HRT with calcium compared with calcium alone.

Randomization of the 116 women was blocked to ensure approximately equal numbers in each treatment group, and was stratified by age and time out of the fracture treatment device (cast or external fixator). Age stratification was above or below 61 years to allow for the effects of age on HRT response. Time out of fracture treatment device was stratified as before or after 3 weeks to allow for any effect of a temporary dip in neuromuscular function caused by the fractured wrist. All patients were entered within 3 months of the removal of their treatment device.

HRT – Prempak C or Premarin 0.625 mg (Wyeth) depending on uterine status – was given to the test group. Both the test and control group were given 1000 mg/day elemental calcium (Sandocal 1000, Sandoz Pharmaceuticals).

All measurements were made blind to treatment group using standard procedures as follows:

1. **Maximum leg extensor power.** This is a functional measure of explosive power, depending on the quadriceps muscle. The patient forcibly extends the leg against a foot place connected to a fly wheel. The best of up to nine attempts was recorded [17]. The coefficient of variation is 9% in naive subjects [17].

2. **Maximal grip strength.** Isometric hand grip strength was measured in the non-fractured wrist using a calibrated electronic dynamometer [18] (coefficient of variation 6% [19]).

3. **Sway.** Lateral sway was measured twice with the eyes open and then with the eyes closed using a Wright ataximeter [20] taking a mean of three measurements of 20 s of lateral sway with the feet together (coefficient of variation 14.7% in house).

4. **Self-paced walking speed.** This was timed over 147.25 m in a flat corridor with the patient walking 'at a normal pace' [21] (coefficient of variation 5% [22]).

5. **Falls.** The number of falls over each preceding 12-week period reported at each of the four visits was recorded. A fall was defined [23] as an episode in which the patient lost balance and hit the floor or another solid object.

All measurements were made every 12 weeks for 24 weeks for all variables, except for grip strength and falls, which were assessed over 48 weeks. Study numbers had a power of 90% to detect balance changes of 18% and strength changes of 8% between the treatment groups assuming study losses of 20% in the HRT group and 5% in the calcium group using data from Cauley et al. [13] and Crilly et al. [24].

To check that there were no substantial changes in the exercise taken by the patients during the study which might affect strength and balance measurements, an activity questionnaire modified from the Allied Dunbar National Fitness Survey was used at the beginning and end of the study [8]. Compliance with study medication was checked by tablet counting and measurements of FSH and oestradiol levels at every visit. Patients who were non-compliant with the medication were encouraged to complete attendance at the study so that the analysis of results could be on an intention-to-treat basis as well as for compliant patients.

The data were analysed by SPSS-PC. Cross-sectional data were analysed by calculating Pearson's product–moment correlations and stepwise multivariate linear regression analysis for identification of independent predictors of neuromuscular variables. Residual analysis was used to check the assumptions. Longitudinal data were analysed by using paired and unpaired Student's t-tests and analysis of covariance to allow for the effects of other variables on the treatment effect. Significance levels quoted are two-sided and probability levels of 5% or less were taken to denote statistical significance.

The patients gave informed consent to take part in the study, which was approved by the Ethics Committee of the University Hospital, Nottingham.

**RESULTS**

**Cross-sectional results**

*Initial values (see Tables 1 and 2).* There were no significant differences between the different treatment groups except that the group treated with HRT and calcium reported significantly more physical activity than the group receiving calcium alone ($P = 0.019$, Mann–Whitney U-test to allow for skewed distribution of variable) and the HRT group had a significantly lower body mass, but neither of these differences was of sufficient magnitude to influence any neuromuscular variable significantly.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>HRT and calcium group ($n = 57$)</strong></td>
</tr>
<tr>
<td><strong>Calcium group ($n = 59$)</strong></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Post-menopausal years*</td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
</tr>
</tbody>
</table>

*Based on 50 cases each group. †Calcium group significantly heavier ($P = 0.05$).
Table 2. Longitudinal neuromuscular, exercise and oestradiol results: analysis by intention to treat

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. in group, 0–24 weeks (48 weeks)</th>
<th>Initial value</th>
<th>Final value (24 weeks except for §)</th>
<th>Change in value by 24 weeks (except for those marked §, in which case change by 48 weeks is shown)</th>
<th>Mean difference in change in value between groups (95% confidence intervals)</th>
<th>P-value for test versus control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean difference in change in value between groups (95% confidence intervals)</td>
<td>P-value for test versus control group</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>HRT and calcium 53</td>
<td>1.41 0.16</td>
<td>1.43 0.18</td>
<td>0.034 0.112</td>
<td>−0.1 0.64</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>Calcium 56</td>
<td>1.42 0.16</td>
<td>1.46 0.16</td>
<td>0.043 0.093</td>
<td>(−0.05 to 0.03)</td>
<td></td>
</tr>
<tr>
<td>Sway, eyes closed (degrees)</td>
<td>HRT and calcium 53</td>
<td>5.58 2.10</td>
<td>5.64 1.93</td>
<td>0.027 1.21</td>
<td>0.39 0.16</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Calcium 54</td>
<td>5.30 2.04</td>
<td>4.99 2.08</td>
<td>−0.36 1.61</td>
<td>(−0.16 to 0.93)</td>
<td></td>
</tr>
<tr>
<td>Sway, eyes open (degrees)</td>
<td>HRT and calcium 53</td>
<td>4.01 1.61</td>
<td>3.82 1.37</td>
<td>−0.19 1.23</td>
<td>0.02 (−0.40 to 0.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium 54</td>
<td>3.75 1.30</td>
<td>3.58 0.89</td>
<td>−0.21 0.93</td>
<td>(−0.40 to 0.44)</td>
<td></td>
</tr>
<tr>
<td>Grip strength (kg/§)</td>
<td>HRT and calcium 53§</td>
<td>25.5 5.2</td>
<td>25.7 6.1</td>
<td>0.64 3.51</td>
<td>−0.37 0.55</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Calcium 51§</td>
<td>27.0 4.8</td>
<td>27.6 4.8</td>
<td>1.01 2.69</td>
<td>(−1.59 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>Leg extensor power (N)</td>
<td>HRT and calcium 54</td>
<td>138 37</td>
<td>137 42</td>
<td>−0.76 17</td>
<td>−6.9 13.7</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td>Calcium 54</td>
<td>147 35</td>
<td>151 34</td>
<td>6.1 19</td>
<td>(−13.7 to 0.00)</td>
<td></td>
</tr>
<tr>
<td>Oestradiol level (pmol/l)§</td>
<td>HRT and calcium 51§</td>
<td>120 30–410</td>
<td>180 30–420</td>
<td>60 −190 to 240</td>
<td>0.002**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium 42§</td>
<td>120 50–290</td>
<td>120 70–200</td>
<td>0 −140 to 140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise (min/week)§</td>
<td>HRT and calcium 51§</td>
<td>280 0–1210</td>
<td>308 0–1440</td>
<td>30 −710 to 900</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium 50§</td>
<td>110 0–735</td>
<td>180 0–975</td>
<td>25 −420 to 565</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                          |                                      |               |                                     |                                                                                                  |                                                                                |                                     |
| Subjects treated with HRT and calcium took significantly more exercise initially than those receiving calcium alone: \( P = 0.019 \) (Mann–Whitney U test). *0.01 < \( P \leq 0.05 \); **0.001 < \( P \leq 0.01 \); ***\( P \leq 0.001 \).

Both groups were only moderately active, and values for strength and power were close to population norms [8]. Univariate correlations showed expected relations between neuromuscular and anthropometric variables. Oestradiol levels were not related to post-menopausal years or to any variable except body weight.

Multivariate analysis. Multivariate stepwise linear regression was used to examine the data and to look at the determinants of sway and strength, and in particular years since menopause or oestradiol levels. Either age or post-menopausal years, grip strength or leg power and sway with the eyes open or closed were included in the regression analyses in addition to height and weight.

The following relationships were derived:

- Sway (eyes open) (degrees)
  \[= 3.24 + 0.04 \text{weight (kg)} - 0.013 \text{leg power (W)} \quad R^2 = 0.14\]

  The associations of age and walking speed disappeared once leg power was entered in the regression equation.

- Leg power (W)
  \[= 75.9 + 1.28 \text{weight (kg)} - 1.40 \text{post-menopausal years} \quad R^2 = 0.31\]
  or
  \[= 160 + 1.32 \text{weight (kg)} - 1.72 \text{age (years)} \quad R^2 = 0.31\]
  or
  \[= 29.7 - 0.27 \text{post-menopausal years} \quad R^2 = 0.15\]
  or
  \[= 45.7 - 0.32 \text{age} \quad R^2 = 0.13\]

The variance explained in all regression equations was very low, except for leg power. There was no evidence for a hormonal influence on neuromuscular variables.

Longitudinal results

Compliance. Non-compliance with the study medication by 1 year was 21% (12 patients) for the test group and 7% (four patients) in the control group. Non-attendance for measurement was 7% (four patients in each treatment group). Measurements of FSH levels showed levels lying in the premenopausal range for the test group. Measurements of oestradiol levels (see Table 2) showed that the test group had a significant increase in their hormone levels compared with both the control group and the initial values \( P = 0.0001 \). The changes in hormone levels were associated with significant improvements in the mean bone density in the lateral spine after 48 weeks of 6.1% (95% confidence interval 2.1–10.1%) and 1.0% (95% confidence interval 0.1–1.9%) to 3.6% (95% confi-
Effect of HRT and calcium on neuromuscular variables as compared with calcium alone (see Table 2). The results presented are by intention to treat. Similar results were obtained if the analysis was for compliant patients. No significant differences in the changes in neuromuscular parameters between the test and control group were found, except for leg extensor power. This difference occurred because of an increase in the leg power of the calcium group of 4.2% (95% confidence interval 0.7–7.6%) compared with the HRT group, in which leg power remained unchanged. Exercise levels increased in both groups during the year, significantly so for the control group \( (P = 0.04) \), but sway was unchanged. However, using analysis of covariance to adjust for age, weight, the initial value of the variable, the change in exercise levels during the year and the dominance of the hand (grip strength only) made no difference to the outcome in any neuromuscular parameter.

The percentage change in oestriadiol levels and grip strength over the 48 weeks of measurements (Fig. 1) shows that, whereas oestriadiol levels changed markedly, no such change was observed in grip strength.

Falls. Thirty-seven per cent of all patients fell at least once during the year; 7.4% fell two or three times. There were no statistically significant differences in the numbers falling by treatment group when analysed by a \( \chi^2 \) test, whether the analysis was done according to intention to treat \( (P = 0.12) \) or on compliant patients only \( (P = 0.20) \). Patients who fell two or more times in the 48 weeks had significantly worse sway with the eyes open \( (29\%, P = 0.048) \) and closed \( (40\%, P = 0.011) \) than patients who fell once or not at all during the year. However, there were no differences in grip strength, leg power, walking speed or oestriadiol level. Three patients sustained further minimal trauma fractures. Two had fractures of the wrist and one to the neck of the humerus (one from the HRT group and two from the calcium-only group).

**DISCUSSION**

These patients had values for strength and power that were similar to representative data for their age group \[8\] despite having been selected as a group with increased vulnerability to falls and wrist fracture. Within the group there were age-related differences in grip strength \[8, 13\], leg power \[8, 17\] and leg strength \[26, 27\] that are consistent with other studies. Although in regression analysis the variation in strength was explained by postmenopausal years and weight (for leg power), age explained almost as much variance as postmenopausal years, suggesting that strength is not especially related to the menopause. In addition, there were no statistically significant associations between strength and the natural levels of oestradiol despite a substantial range of hormone values. These findings do not support the view that postmenopausal lack of oestrogens contributes to muscle weakness in older women \[13, 14\]. Our findings are consistent with the outcome of a randomized controlled trial in which the effects of HRT and exercise were evaluated \[15\]. Although Cauley et al. found a univariate correlation between grip strength and both oestriadiol levels \[28\] and HRT use \[13\] this association disappears in multiple linear regression analysis, leaving the only independent predictors of grip strength as age, height and physical activity. Phillips et al. \[14\] report an association with force per cross-sectional area in the adductor pollicis when comparing post-menopausal women on HRT with those who were not, but do not comment on absolute strength levels.

No relation was found in the present study between sway and natural oestriadiol levels. Sway has a low reliability, so it is possible that a weak association could have been missed, but this seems unlikely as the sway measurements had sufficient power to distinguish the more frequent fallers from the rest.

Cross-sectional studies are easily biased; for example, HRT users are known to be thinner, better educated, to drink more alcohol and to take more physical activity \[29\]. A longitudinal study of the same group conducted in a substantial prospective randomized controlled trial provides more secure evidence, and the clear-cut findings of the present study were that HRT was not associated with improvements in any neuromuscular variable. The numbers of women in this study and the duration provided ample power to find effects on muscle performance. Muscle strength improves with training in a matter of weeks \[30, 31\], and muscle remains responsive to such anabolic provocation until extreme old age, so the findings of this and other studies \[13, 14\] are unlikely to be explained by irreversible loss of muscle strength at the
menopause against which HRT could provide protection.
Over the year both groups reported increased physical activity. The increase was significant compared with the initial value for the calcium group, but not compared with the increase in the HRT group. The activities reported were not too strenuous and were evidently not sufficient to produce increases in neuromuscular variables, except for a small, but significant, increase of 4% in leg extensor power in the calcium group. This change was significantly different from that in the HRT group and remained after controlling for changes in activity levels, so it is possible that the HRT had a negative influence on muscle power. This has been found in two studies of young women [32, 33].

The evidence from this study lends no support to the suggestion that the menopause is associated with a loss of muscle strength caused by falling oestrogen levels or that reversing the menopausal loss of oestrogen levels will restore strength to levels enjoyed earlier in life. If there is a decline in strength at the menopause, which is not found in representative studies [34], then it is likely to be due to changes in activity levels; disuse is a long-established cause of muscle weakness [26]. Furthermore, studies have shown that with disuse or atrophy muscle may be infiltrated by fat [35] or fibrous tissue [36], which could lead to a decrease in force per cross-sectional area without a decrease in the overall force. This could explain the findings of Phillips et al. [14].

The number of further falls over the year was surprisingly high and confirmed that this group of women was vulnerable to falls. The patients in this study fell significantly more often (χ² = 5.73, P < 0.02) than those in a comparable population study [1], even after adjusting for the differences in age distributions. Fallers had worse sway, which is consistent with other studies [2], but they did not differ in HRT status or muscle performance. It appeared, therefore, that neurological factors affecting balance were responsible, suggesting that strength training programmes will not reduce the incidence of falls in middle-aged women unless they also reduce sway and improve balance.

In conclusion, increased plasma levels of oestri-diol produced by HRT were not associated with increased muscle performance, improved balance or a reduced incidence of falls over a year in middle-aged women after distal radial fracture.

ACKNOWLEDGMENTS
This study was funded by the Wishbone Trust and the Special Trustees for the Nottingham Hospitals. At the request of the authors, the drugs used in this study were provided free of charge from Sandoz Pharmaceuticals (Sandopak 1000) and Wyeth (Premarin C and Premarin 0.625 mg). The biochemical analyses were performed by the Department of Clinical Chemistry, City Hospital, Nottingham, and we are grateful to Drs C. Marenah and C. Selby for their help.

REFERENCES