Changes in muscle strength in women following the menopause: a longitudinal assessment of the efficacy of hormone replacement therapy

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ABSTRACT

The effects of hormone deficiency at the menopause on muscle strength was examined in 10 healthy middle-aged women (1–3 years post-menopause) in a longitudinal trial over 39 weeks. Performance was compared with that of age-matched females (n = 11) taking a course of hormone replacement therapy (HRT). Muscle strength of the quadriceps was measured isometrically at 90° of knee flexion and at angular velocities of 1.05, 2.09 and 3.13 rad/s using an isokinetic dynamometer. Hand grip strength was assessed by means of a portable dynamometer. Measurements were taken every 13 weeks for 39 weeks. Significant decreases in isometric strength (−10%) and dynamic leg strength at 1.05 rad/s (−9%) were found in the post-menopausal women over 39 weeks. There was no change in strength in the HRT group. There were also no changes in leg strength at higher angular velocities or in grip strength for either the post-menopausal group or those taking HRT. While HRT preserved muscle strength, there was no evidence of a strengthening effect on skeletal muscle within this short period of treatment. A rapid loss of leg strength occurs post-menopausally in hormone-depleted women. HRT may offer protection against muscle weakness, although the hormone responsible for regulating strength is not evident using this model.

INTRODUCTION

The higher incidence of falls with age [1] has been attributed to muscle weakness [2], although impaired balance [3,4] and a deterioration in neuromuscular function [4] are also important risk factors for falling. A decline in strength is an inherent process of aging which has been reported extensively as a result of muscle atrophy [5–7]. A specific weakening of muscle, expressed as force per cross-sectional area (force/CSA), has also been demonstrated in aged human adductor pollicis (AP) [8] and hindlimb muscles in animals [9,10]. A closer examination of the time course of this specific muscle weakness in humans has revealed a disparity in its onset between males and females. A rapid decrease in force/CSA of the AP occurs from 50 years onwards in females, a trend that is not evident in males until 60 years of age [11]. Since the average age at which the menopause occurs is 50 years, these findings suggest a hormone-dependent loss of strength.

Whereas a hormonal component in the regulation of force production has been indicated for hand muscles, it is not known whether leg strength is also compromised as a result of ovarian failure in middle-aged women. Weakening of the quadriceps, the main weight-bearing muscle group concerned with ambulation and balance,
may result in a greater number of falls post-menopause. This would present important clinical implications for these women, who are already prone to losing bone at a rapid rate following the menopause [12–14]. Indeed, a high incidence of falls leading to an increase in Colles’ fractures has been reported previously in peri-menopausal women [1], although it would be imprudent to attribute this rate of falling to muscle weakness without concomitant assessment of leg strength.

The specific force of the quadriceps has been found not to differ when measured in young and old women [15], and, given the differences in reproductive status between these sample groups, it may be extrapolated that there are no hormonal influences regulating quadriceps strength. Conversely, Rutherford and Jones [16] reported a lower force-generating capacity of the quadriceps in osteoporotic females compared with healthy age-matched controls, which suggests a hormonal component of muscle weakness. Whereas computed tomography (CT) was used in the latter study to measure muscle size, Young et al. [15] employed ultrasound imaging. This technique does not yield the same resolution or sensitivity as CT scans, factors that are important in the estimation of the size of complex multi-pennated muscle groups such as the quadriceps. Cross-sectional comparisons of absolute strength may also disguise hormonal effects; Bassey et al. [17] failed to detect differences in absolute leg or grip strength in hormone replacement therapy (HRT) and oestrogen-depleted subjects. To overcome the problems of cross-sectional measurements and to determine the rate of strength loss 1–3 years post-menopause, we measured the maximal strength of a functional muscle group, the quadriceps, over 39 weeks in recently amenorrhoeic middle-aged women. Furthermore, based on the observation that muscle weakness is not manifest in women taking HRT [11], the role of hormone repletion in the regulation of force production was investigated to assess whether muscle strength is restored or maintained by HRT following the menopause.

Preliminary data have been presented to the Physiological Society [18].

**METHODS**

**Subjects**

A total of 21 women with a sedentary lifestyle volunteered to participate in the study. Subjects were recruited from the Menopause Clinic at Liverpool Women’s Hospital and through advertisements in a local newspaper. Eleven women (age 50.05 ± 3.84 years; height 1.59 ± 0.05 m; mass 67.50 ± 10.31 kg (means ± S.D.)) began taking HRT of various preparations at the onset of the study. The post-menopausal group comprised 10 women (age 51.97 ± 3.11 years; height 1.62 ± 0.07 m; mass 72.33 ± 14.57 kg) who had experienced the menopause within the previous 1–3 years from the time of testing, as determined retrospectively from questionnaire reports. A venous blood sample was taken to confirm high levels of follicle-stimulating hormone and luteinizing hormone (20 units/l). The women who began taking HRT had been referred to the Menopause Clinic for advice on taking the treatment.

A questionnaire was completed by all subjects for inclusion into/exclusion from the study. No subject had sustained fractures within the 5 years before recruitment, had suffered any pain or neuromuscular disease of the legs and hands, or was taking any treatment likely to affect performance. Physical activity levels of subjects were monitored upon recruitment using the Leisure Time Physical Activity Questionnaire [19]. Of the initial 27 subjects who were recruited, six dropped out (three from each group).

This study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and was approved by the Human Ethics Committee of Liverpool John Moores University and The Royal Liverpool Hospital Trust. Written informed consent was obtained from all participants.

**Procedure**

Body mass, height and blood pressure were recorded before strength testing. Subjects rested for 5 min before blood pressure was monitored using an automatic sphygmomanometer (Model 8111; DINAMAP, Critikom, Bracknell, U.K.). Values greater than 150/100 mmHg were recognized as hypertensive, and subjects were requested to seek medical advice before continuing with the study. A 5 min self-paced warm-up on a cycle ergometer (Monark) was performed before commencing the strength assessments.

Subjects attended a practice session 1 week before the baseline measurements to allow familiarization with the procedure and tests involved. Following the baseline test, measurements were taken on three occasions separated by 13-week intervals.

**Assessment of muscle strength**

**Quadriceps**

The maximal dynamic and isometric strength of the quadriceps was measured using the LIDO Active® isokinetic dynamometer (Loredan, Davis, CA, U.S.A.). The dynamic strength of the quadriceps was assessed at three angular velocities of 1.05, 2.09 and 3.13 rad/s. Subjects were seated in an adjustable chair, and the upper body was stabilized with straps secured across the shoulders, chest and hips. A resistance pad was also positioned on the thigh, proximal to the knee joint, to
localize the quadriceps and hamstring muscle groups. The axis of rotation of the dynamometer shaft was aligned with the axis of rotation of the knee joint, midway between the lateral condyle of the tibia and the lateral condyle of the femur. The cuff of the dynamometer’s lever arm was attached to the ankle, proximal to the malleoli. These positions were standardized for each subject. The range of motion was preset at 0–90°, and torque measures were corrected for gravity. Subjects performed four maximal reciprocal efforts through the entire range of motion, preceded by two submaximal warm-up trials. Each effort, undertaken with the arms folded, was supported by verbal encouragement. A 1 min rest period was allowed between measurements at each angular velocity. The order of testing at each angular velocity was standardized, beginning with dynamic leg strength at the lower angular velocity of 1.05 rad/s (Nm) (9.0%) 127.1 (7.6) 125.9 (7.7) 125.8 (7.6) 128.0 (7.8)

Table 1 Maximal muscle strength over 39 weeks in post-menopausal women with (n = 11) and without (n = 10) HRT

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Strength measure (CV%)</th>
<th>Baseline</th>
<th>Week 13</th>
<th>Week 26</th>
<th>Week 39</th>
<th>P values for group-by-time interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>Isometric (N) (10.1%)</td>
<td>114.7 (8.5)</td>
<td>114.0 (7.2)</td>
<td>113.8 (6.7)</td>
<td>112.4 (7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>122.3 (6.3)</td>
<td>123.8 (6.6)</td>
<td>113.5 (7.2)*</td>
<td>109.7 (6.5)*</td>
<td>0.007†</td>
</tr>
<tr>
<td>HRT</td>
<td>1.05 rad/s (Nm) (9.0%)</td>
<td>127.1 (7.6)</td>
<td>125.9 (7.7)</td>
<td>125.8 (7.6)</td>
<td>128.0 (7.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>127.5 (5.6)</td>
<td>131.0 (8.7)</td>
<td>122.8 (8.7)**</td>
<td>116.5 (8.4)**</td>
<td>0.01††</td>
</tr>
<tr>
<td>HRT</td>
<td>2.09 rad/s (Nm) (7.4%)</td>
<td>93.6 (4.8)</td>
<td>94.8 (5.0)</td>
<td>94.4 (5.8)</td>
<td>93.7 (4.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90.9 (5.3)</td>
<td>90.5 (7.0)</td>
<td>89.7 (6.5)</td>
<td>86.7 (6.4)</td>
<td>0.430</td>
</tr>
<tr>
<td>HRT</td>
<td>3.13 rad/s (Nm) (6.1%)</td>
<td>80.5 (4.5)</td>
<td>80.4 (5.0)</td>
<td>79.4 (4.3)</td>
<td>79.9 (4.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>76.8 (5.0)</td>
<td>77.4 (4.4)</td>
<td>78.0 (5.6)</td>
<td>75.3 (6.3)</td>
<td>0.416</td>
</tr>
<tr>
<td>HRT</td>
<td>Handgrip (kg) (7.8%)</td>
<td>27.2 (1.4)</td>
<td>26.2 (1.4)</td>
<td>27.4 (1.1)</td>
<td>26.2 (1.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>28.5 (2.2)</td>
<td>27.2 (2.1)</td>
<td>27.2 (2.2)</td>
<td>27.0 (2.1)</td>
<td>0.694</td>
</tr>
</tbody>
</table>

Data analysis

Means, S.E.M. values and percentage changes from baseline were calculated. A two-way analysis of variance (Statistical Package for the Social Sciences, 1993) with a repeated-measures factor (time) was employed to calculate strength changes between groups over time and differences in the relative force–velocity relationship. The Huynh–Feldt correction factor was used. Post-hoc tests (Scheffe) were carried out to determine differences between variables from the analysis of variance. Significance was set at the 5% level.

RESULTS

There were no significant differences in body mass between the two groups for the duration of the study (P = 0.430). Height was not significantly different between the two groups at the start of the study (P = 0.296), and did not change over the course of testing. Mean scores (+S.E.M.) for the isometric and dynamic strength of the quadriceps and handgrip strength are shown in Table 1.

Physical activity levels were assessed using the Leisure Time Physical Activity Questionnaire [19]. Subjects,
Figure 1 Changes in maximal isometric and dynamic strength (at 1.05 rad/s) between baseline and 39 weeks in post-menopausal women with (empty bars) and without (shaded bars) HRT. Results are means ± S.E.M. Differences between * and ** are significant at $P < 0.05$.

who all met the inclusion criteria of a sedentary lifestyle, did not report any leisure time physical activity above that of everyday household tasks. Additionally, subjects did not report any change in physical activity levels over the duration of the study.

Strength performance in women post-menopause

There was a significant group-by-time interaction over 39 weeks for isometric leg strength ($P < 0.01$) and dynamic leg strength at 1.05 rad/s ($P < 0.05$). There were no significant changes in strength at the higher angular velocities of 2.09 and 3.13 rad/s. Force in the HRT group remained constant across all angular velocities ($P < 0.05$). There was no significant change in grip strength over time for the two groups (Table 1).

Post-hoc power analysis, calculated using the methods of Pearson and Hartley [22], confirmed that the group-by-time interaction yields 85% power at the 5% significance level.

Percentage change in strength in post-menopausal women and those on HRT

The percentage change in strength between baseline and 39 weeks was significantly greater in post-menopausal women than in the HRT group for isometric strength ($-10.3\%$ and $-1.0\%$ respectively) and dynamic strength at 1.05 rad/s ($-9.3\%$ and $+1.5\%$ respectively) ($P < 0.05$). These results are plotted in Figure 1.

Standardized force–velocity relationships

Figure 2 shows a comparison of the speed-dependent change in relative force between baseline and 39 weeks in the post-menopausal (upper panel) and HRT (lower panel) groups. Force is expressed as a percentage of isometric force at each velocity. There were no significant differences in standardized force–velocity relationships over time or between groups ($P > 0.05$).

DISCUSSION

The present data suggest that muscle strength of the quadriceps declines at a rapid rate within the first 3 years post-menopause in women who do not take hormonal therapy. To our knowledge, this is the first longitudinal study to demonstrate that weakness occurs in a functional muscle group in response to the hormone deficiency at the menopause. This strength loss, which mirrors the accelerated loss of bone mineral density [13,14], presents a complex interaction between muscle weakness, bone loss and the associated risk of fracture.

Women taking HRT have higher muscle force/CSA ratios than age-matched females who are hormonally depleted [11]. In the present study, the possible role of exogenous hormones in preserving muscle strength was examined over 39 weeks, and a maintenance of leg strength was found to be associated with the initiation of HRT. While we did not find an increase in strength which would suggest that this weakening is reversible, Skelton et al. [23] reported a strengthening effect of HRT on the AP muscle in post-menopausal women of ~12% over 52 weeks. In contrast with the present findings, these workers did not report a decrease in strength in the non-hormone group. However, these women were older (62.8 years) than the post-menopausal women in the present study, and it is possible that they had already experienced the initial post-menopausal strength loss that we report. This would also explain the lack of change in leg strength measured at 0 and 1.05 rad/s over 11 months.
in hormone-depleted women aged 60–72 years [24]. The lack of strength gain in the HRT group in the present study compared with the data of Skelton et al. [23] may be also explained by the HRT preparations administered to the subject groups. Unlike in the study of Skelton et al. [23], it was not possible to standardize the preparations administered to subjects in the present study, as they were recruited from a menopause clinic. Nevertheless, it is apparent from both studies that HRT is capable of modulating muscle strength. By careful manipulation of HRT preparations in future work, it may be possible to discern the hormone responsible for these observations.

A loss of strength in women aged around 50 years was initially observed in the late 1970s [25], although Phillips et al. [11] were the first to confirm a sex-hormone-dependent loss of specific force in menopausal women, measured as force/CSA. There have been arguments raised since as to the validity of measuring ‘specific’ force using linear potentiometers to estimate muscle size [17], particularly in older women who experience an infiltration of fat into muscle [26] and the replacement of contractile material with connective tissue [27]. Estimating fat-free mass from skinfold measurements, Bassey et al. [17] claimed that post-menopausal women are more prone to accumulating fat in muscle compared with those taking HRT, leading to an overestimation of CSA of the AP in hormone-depleted women and a consequent underestimation of specific force. However, studies that have measured fat mass using dual photon absorptiometry have not found any differences between HRT and non-HRT women [28]. Even if HRT were associated with less fat deposition, it is unlikely that this would account for the 20% difference in specific force reported by Phillips et al. [11].

In a recent randomized controlled trial over 54 weeks, performance parameters, including leg power and grip strength, were not found to change in post-menopausal women aged 45–70 years [3]. These authors suggest that the decline in muscle strength reported after the menopause [11] can be explained by a decline in physical activity levels at this time [3]. Such a decline would not explain the strength changes we found for the quadriceps. Levels of physical activity were the same in the HRT and post-menopausal groups, but there was no change in leg strength in the women taking exogenous hormones. Furthermore, strength at higher angular velocities (2.09 and 3.13 rad/s) did not change, suggesting that factors other than activity levels are responsible for the loss in strength post-menopause.

While there is growing evidence that reproductive hormones are involved in the regulation of muscle strength, it is not known whether oestrogen or progesterone is primarily responsible, since both ovarian hormones are deficient at the menopause. In addition, HRT, which appears to confer protection against muscle weakness, may contain both oestrogen and a progestogen. Based on the findings that the force of the AP is highest at the pre-ovulatory peak in oestrogen in the menstrual cycle [29], loss of oestrogen is currently thought to be responsible for strength changes in post-menopausal women [11]. However, these claims are conjectural, as Greeves et al. [30] have provided unequivocal evidence that oestrogen is not the sole regulator of these strength changes. The maximal strength of the first dorsal interosseous muscle was measured in women receiving in vitro fertilization treatment, who experience changes in oestrogen comparable with those of post-menopausal women. Strength measured during a hypogonadal state following the down-regulation of hypothalamic pituitary receptors was not different from strength measured at supraphysiological oestrogen levels following a course of exogenous gonadotropins. We suggest that low progesterone levels may be responsible for the loss of strength during early post-menopause. Indeed, this is supported by the fact that progesterone is the first hormone to become deficient at the menopause due to the failure of corpus luteum formation [31]. The maintenance of strength we report in women taking HRT may therefore be mediated by the progestogen dose or by an interactive effect of progesterone and oestrogen in the combined preparations.

It is apparent from these observations that skeletal muscle is responsive to the deficiency in reproductive hormones during the early post-menopausal period. Although HRT appears to maintain the strength of the quadriceps, thereby reducing the risk of falling and sustaining a fracture, this treatment is contra-indicated in hormone-sensitive females. Future work is warranted to elucidate the exact hormonal milieu responsible for these strength changes. This will allow appropriate treatment to be offered to all post-menopausal women who are currently deprived of the possible protective benefits of progesterone.

ACKNOWLEDGMENTS

We thank Professor Alan Nevill for his assistance with the treatment of data and advice with the statistical analysis. The help of statistician Dr. Mike Kenward is also gratefully acknowledged.

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Received 3 December 1998/25 February 1999; accepted 8 April 1999