Tibolone does not affect muscle power and functional ability in healthy postmenopausal women

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ABSTRACT

Maintenance of neuromuscular function into old age is critical to maintain normal daily activity and functional independence. Maximal muscle strength declines with age, and the age-related loss in power might be even greater. An accelerated loss of muscle strength and power has been observed in women around the time of the menopause. The aim of the present study was to examine the effects of tibolone, a synthetic steroid with oestrogenic, progestogenic and androgenic activities, on muscle power, endurance and functional ability. A total of 85 healthy women, between 1 and 15 years postmenopausal, were recruited from local paper advertisements. Participants were randomly assigned to 2.5 mg of tibolone or to placebo pills of identical appearance; pills were taken daily for 12 months, orally in the morning. Muscle power was assessed as explosive leg extensor power. Endurance was measured on a 2 min walk test and a 3.5 m walk. Functional ability was determined with the timed Get Up and Go test and a Postural/Locomotor/Manual test. No significant between-group differences were observed for any of the parameters. Possible explanations for this lack of effect are either the absence of an effect of tibolone on muscle power and functional ability, or that our participants were too far above their strength-related functional limits to derive benefit from intervention. Further research is required to resolve this issue.

INTRODUCTION

Functional and physiological deterioration with advancing age influences the ability of older people to carry out daily activities [1,2]. Neuromuscular function is critical to maintain normal daily activity and functional independence. Maximal muscle strength declines in old age [3,4]; however, given the low importance of being able to exert maximal force under normal circumstances, the assessment of muscular endurance and power, rather than absolute strength, might be a more practical measure of neuromuscular function [5]. Muscular endurance, time until exhaustion and maximal explosive power have received only minimal attention in the literature. Explosive power is the product of force and velocity of contraction, and the age-related loss of power might be even greater than the loss of muscle strength.

The relationship between measures of muscle strength and functional ability is poorly understood. It is unclear if a gain in muscle strength and muscle mass alone can improve functional performance. An association has been established between muscle weakness and a decline in strength and functional capacity, not just for frail older people [6], but for all ages [7,8]. Studies in healthy elderly

Key words: functional ability, muscle power, postmenopausal, tibolone.
Abbreviations: ANCOVA, analysis of covariance; HRT, hormone replacement therapy; PLM test, Postural/Locomotor/Manual test; SI, simultaneity index; TMT, total movement time.
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people demonstrated little effect [9]. In the study of Carmeli et al. [1] an elderly group showed improved functional ability, similar to a younger group, without a gain in muscle strength. The possibility of a relationship between muscle strength, power and functional ability has not been investigated in middle-aged women. In a cross-sectional study on aging in healthy subjects, Samson et al. [10] observed an accelerated decrease in muscle strength and reduced speed in functional mobility tests in women around the age of 50 years. No effects were observed in walking tests and muscle power.

The mechanism behind the age-related loss of muscle function is unclear, but several hypotheses have been suggested. Lack of use of muscle may be an important contributor, but it does not explain observed losses in well trained senior athletes [11]. Also, age-associated changes in nerve–muscle relationships, including loss of spinal motor neurons and motor units, might result in muscle function loss [12]. Phillips et al. [13] have suggested an association between female sex steroid hormones and muscle strength, because of the steep decline in muscle strength that occurs during the years immediately following the menopause. Conflicting theories exist with regard to the cause of the menopause-related fall in muscle strength. Some investigators suggest that the fall in oestrogen concentration influences muscle strength [14], and others implicate the low progesterone levels, since both hormones are deficient at menopause [15]. Hakkinen et al. [16] mentioned the decreased testosterone concentration in aging females.

It has been observed that the postmenopausal loss of strength could be countered with hormone replacement therapy (HRT) [13,15,17], although studies on HRT and muscle strength are limited. There are even fewer studies on the effects of HRT on functional ability. In these studies, postural balance was assessed as a parameter of functional ability [18,19]. Studies conducted so far do not give an unequivocal answer as to the efficacy of hormone replacement strategies in improving muscle function [20].

In the present study, the aim was to examine the effects of tibolone on muscle power (explosive leg extensor power), endurance (2 min walking test and 3.5 m walk) and functional ability (timed Get Up and Go test and Postural/Locomotor/Manual (PLM) test) in healthy postmenopausal women. Tibolone is a synthetic steroid, which displays oestrogenic, progestogenic and mild androgenic activity following oral administration [21,22].

**MATERIALS AND METHODS**

**Participants**

A total of 85 healthy women [mean (S.D.) age 54.2 (4.7) years], between at least 1 year and at maximum 15 years after natural menopause, were enrolled in a randomized, double-blind, placebo-controlled trial. Participants were recruited by local paper advertisements. The study protocol was approved by the Medical Ethical Board of the University Medical Centre, and all participants gave written informed consent.

At screening, subjects underwent the following examinations: medical history, physical and gynaecological examination, and a mammography if not performed during the previous 12 months. Exclusion criteria were presence or history of sex-hormone-dependent malignancies; the use of HRT or other steroid medication or muscle-growth-affecting drugs during the 6 months preceding the start of the study; hypertension (> 170 mmHg systolic, > 105 mmHg diastolic); active liver disease or a history of this condition with a failure of liver function tests to return to normal; presence or history of endometrial hyperplasia with or without atypia; undiagnosed vaginal bleeding; presence or history of cardiovascular, cerebrovascular or thromboembolic disorders; consumption of more than four alcoholic drinks per day; porphyria; haemoglobinopathy; use of sex hormones, anabolics, corticosteroids, insulin, anticoagulants or enzyme-inducing drugs; participation in a clinical trial during the last 3 months; a body mass index below 18 kg/m² or above 29 kg/m²; and unwillingness to fill out a diary card for 12 months. Concomitant medication that could either interfere with the study drugs or influence muscle strength, as well as anticoagulants and enzyme-inducing drugs, were not allowed during the study period.

**Intervention**

The eligible participants were randomly assigned to 2.5 mg of tibolone (NV Organon, Oss, The Netherlands) or placebo pills of identical appearance; pills were taken daily for 12 months, orally in the morning. Randomization was done at a 1:1 ratio by the Department of Dispensing Services and Control, NV Organon. No person involved in the execution or monitoring of the study had access to the randomization list, other than through the Emergency Drug Identification Record. Compliance with treatment was monitored by means of a diary card and by counting the tablets remaining on each visit. The difference between the total number of tablets dispensed and the total number of tablets returned was divided by treatment duration, to calculate compliance (%). A special effort was made to keep the participants motivated, involving a dedicated 1 h session each week during which telephone queries were answered, and check-up calls after 1 and 9 months.

**Anthropometry**

Body weight was measured to the nearest 0.1 kg (Seca Alpha 770) and height to the nearest 1 mm using a wall-
Muscle power and functional ability

Assessments were performed at baseline and after 3, 6 and 12 months of treatment. To control for differences in activity patterns throughout the study period that could interfere with the main outcome measures, a habitual physical activity questionnaire [24] was administered at each visit. The questionnaire consisted of scores for household activities, sporting activities and other physical active leisure time activities, which together gave an overall activity score.

 Explosive leg extensor power

Explosive leg extensor power was measured using the Nottingham power rig [25]. The subject, seated and with arms folded, delivered power by pressing the footplate as hard and as fast as possible through a distance of 0.165 m, setting a flywheel in motion. Seat position was adjusted so that the knee angle at the start of the push was 90°. The measurement was repeated until no further improvement was seen, up to a maximum of 10 pushes. The highest recorded power outputs (measured in W) for both legs were averaged and used for analysis. The angles of the hip, knee and ankle during the push are somewhat similar were averaged and used for analysis. The angles of the hip, knee and ankle during the push are somewhat similar to those occurring during rising from a chair or climbing stairs. Repeated-measurements correlation for this test is 0.99 [10].

 Functional ability and endurance tests

Timed Get Up and Go test

Functional ability was assessed quantitatively with the timed ‘Get Up and Go’ test [26,27]. In this test, the time taken by an individual to rise from a standard armchair (46 cm high), walk 3 m, turn around, return and sit down again was measured. The subject sat with her back against the chair and her arms resting on the chair’s arms, and performed the test three times as quickly as possible. The fastest time (in s) was recorded.

 PLM test

The PLM test was performed using an optoelectronic device, a MacReflex 2D motion analysis system (Qualysis AB, Sävedalen, Sweden). It provides a simple non-invasive method of assessing motor performance. In this test, a camera projected and detected infrared flashes at a sampling frequency of 50 Hz. The flashes were reflected from six markers placed on the subject’s body (head, right shoulder, upper right arm, just above right hip joint, 10–15 cm above right ankle, and toe of left shoe) and one marker on a hand-held object. The hand-held object consisted of a plastic disc base to which was attached a cylinder and handgrip. The subject, starting from the upright position, picked up the object from the floor (postural- or P-phase), walked forward (locomotor- or L-phase) and placed it on a shelf at chin height (manual- or M-phase), which was positioned at a fixed horizontal distance of 1.5 m from the initial position of the hand-held object on the floor. The subject had to continuously move the object from the floor to the shelf and back without pausing. Data were recorded only when the subject was moving in the forward direction, i.e. towards the shelf. The P-, L- and M-phases were determined automatically from the computer by calculating the marker co-ordinates. Total recording time was 20 s.

 Modifed Cooper test

The modified Cooper test is a 2 min walking test, which appears to be highly correlated with the 12 min Cooper test [28]. It is a reproducible measure of endurance. The subject is asked to walk as quickly as possible (without starting to run) for 2 min, and the distance covered (m) is recorded.

 Walking speed

The time taken (s) to walk 3.5 m as quickly as possible was recorded with a stopwatch attached to infrared detectors. Passing the first detector started the stopwatch and passing the second detector stopped it.

 Protocol

The measurements were performed in a room free from external distractions, in which only the investigator and the subject were present. All tests were demonstrated by the assessor, before being performed by the volunteer. During all tests verbal encouragement was given. Tests were performed in a set order, with rests in between to avoid fatigue.

 Statistical analysis

Data were analysed using the intent-to-treat analysis. For analyses of explosive leg extensor power, the mean values of the peak results for the right and left sides were used. The analyses of the timed Get Up and Go test, the modified Cooper test and the walking speed test were based on the fastest or best attempt. Analyses of the PLM tests were based on total movement time (TMT) and simultaneity index (SI). The SI is defined as the sum of the duration of the three phases (P, L and M) divided by TMT.

 Each of the parameters was analysed by means of an analysis of covariance (ANCOVA) model. This model incorporated treatment group as a factor and the baseline value as a covariant. Scatter plots of the values found at last visit against the baseline values (not shown) and an examination of residuals were used to assess the adequacy
of the ANCOVA and to detect outliers. To assess the efficacy of tibolone, estimates of the treatment differences with 95% confidence intervals and two-sided $P$ values were calculated. A $P$ value < 0.05 indicated statistical significance.

In addition, a Student’s paired $t$ test was used to test for differences in mean values between last visit and baseline per treatment group. All analyses were performed using SAS version 6.12 for PC (WinNT vs. 4.0).

**RESULTS**

A total of 85 women were randomly allocated into groups and started treatment. Of these, 81 women contributed to the analysis (tibolone, $n = 39$; placebo, $n = 42$). These women were classified as the intent-to-treat population. The demographic and clinical characteristics of each group at baseline are presented in Table 1. Random allocation to either the tibolone or the placebo group resulted in no significant differences between the groups for any of the baseline characteristics.

Nine subjects (tibolone, $n = 4$; placebo, $n = 5$) reported a hysterectomy in their medical history. In total, five subjects (5.9%) discontinued participation in the trial (tibolone, $n = 3$; placebo, $n = 2$). Of these, four out of five were within the first months after enrolment in the study, and therefore had no post-baseline assessment. Reasons for dropout were malaise (tibolone, $n = 2$); clinically significant abnormal mammography (placebo, $n = 1$); poor compliance (tibolone, $n = 1$) and private problems unrelated to the study (placebo, $n = 1$). This last subject dropped out of the trial in month 7. Overall compliance with treatment was 98–99%.

**Leg extensor power**

No significant between-group difference was observed for leg extensor power at the final visit (Table 2). Although it seemed that the baseline values (mean ± S.D.) for the tibolone group (185.7 ± 60.6 W) were slightly higher compared with the placebo group (162.3 ± 63.1 W), this was not statistically significant. In both groups a significant difference in mean values was observed between baseline and the final visit. At the final visit the values for leg extensor power were: tibolone group, 198.2 ± 66.0 W; placebo group, 178.8 ± 62.5 W.

**Timed Get Up and Go test**

No treatment or between-group effect was observed at the final visit for the Get Up and Go test (Table 2). However, in each treatment group a small but significant increase in the mean value was observed between baseline and the final visit.

**PLM test**

Since no between-group difference (treatment effect) was observed for TMT values (Table 2), no further analysis was performed on the SI or the separate phases ($P$, $L$ and $M$). At the final visit, the mean TMT was slightly lower in both groups (tibolone, $1.30 ± 0.26$ s; placebo group, $1.35 ± 0.25$ s) compared with baseline values.

**3.5 m walk test**

No treatment effect was observed at the final visit (Table 2), and nor were there any significant differences in mean values observed at baseline and at the final visit for either group.

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**Table 1** Baseline demographic subject characteristics of postmenopausal women treated with tibolone 2.5 mg ($n = 39$) or placebo ($n = 42$) daily for 1 year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group</th>
<th>Tibolone group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.0 (4.1)</td>
<td>54.4 (5.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.8 (6.0)</td>
<td>71.1 (8.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5 (5.4)</td>
<td>167.2 (5.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1 (2.2)</td>
<td>25.4 (2.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133.4 (14.4)</td>
<td>134.8 (14.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.3 (10.2)</td>
<td>81.2 (9.1)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.8 (9.1)</td>
<td>75.6 (9.3)</td>
</tr>
<tr>
<td>Leg extensor power (W)</td>
<td>162.3 (63.1)</td>
<td>185.7 (60.6)</td>
</tr>
<tr>
<td>Get Up and Go test (s)</td>
<td>1.91 (0.7)</td>
<td>3.85 (0.7)</td>
</tr>
<tr>
<td>3.5 m walk test (s)</td>
<td>1.72 (0.3)</td>
<td>1.64 (0.2)</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>1.99 (0.3)</td>
<td>2.04 (0.2)</td>
</tr>
<tr>
<td>2 min Cooper test (m)</td>
<td>224.5 (19.9)</td>
<td>228.0 (22.9)</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of treatment effects at final visit after 1 year of therapy by means of ANCOVA for tibolone 2.5 mg daily ($n = 39$) and placebo ($n = 42$)

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Least squared means</th>
<th>95% confidence interval</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEP (W)</td>
<td>186.7</td>
<td>189.4</td>
<td>14.9, 9.5</td>
</tr>
<tr>
<td>Get Up and Go test (s)</td>
<td>4.12</td>
<td>4.22</td>
<td>0.37, 0.17</td>
</tr>
<tr>
<td>3.5 m walk test (s)</td>
<td>1.71</td>
<td>1.67</td>
<td>0.05, 0.13</td>
</tr>
<tr>
<td>2 min Cooper test (m)</td>
<td>230.5</td>
<td>235.6</td>
<td>11.5, 1.3</td>
</tr>
<tr>
<td>PLM TMT (s)</td>
<td>1.332</td>
<td>1.317</td>
<td>0.06, 0.09</td>
</tr>
</tbody>
</table>
Modified Cooper test
In the placebo group, a significant difference was observed between mean values at baseline \((224.5 \pm 19.9\, \text{m})\) and at the final visit \((233.9 \pm 26.3\, \text{m})\). In other words, at the final visit the placebo group walked further in 2 min than they did at the start of the study. No difference compared with baseline was observed in the tibolone group (baseline, \(228.0 \pm 22.9\, \text{m}\); final visit, \(233.2 \pm 25.9\, \text{m}\)). No between-group difference was observed at the final visit (Table 2).

DISCUSSION
Studies in the literature on muscle function and HRT have assessed muscle mass and strength as an index. It has been shown that oestrogen and tibolone users had greater isometric knee extensor strength compared with non-users [29]. With respect to postural balance, participation in physical activity seems to outweigh any influence of HRT [29]. In the present study we were unable to demonstrate any effect of tibolone, compared with placebo, on muscle power and functional ability in a 1-year intervention study in healthy postmenopausal women.

The participants in our study were relatively active and without any problems related to the performance of daily activities. At baseline, leg power scores were comparable with those reported in a group of premenstrual women [30] and higher than in a group of postmenopausal women studied by Armstrong et al. [19]. With respect to the timed ‘Get Up and Go’ test, a sample of adults, without balance problems, could complete this test in less than 10 s [27]. In a sample of people dependent in most activities of daily living and mobility skills, the test took more than 30 s [31]. In our population the average time to complete the test was about 4 s. Finally, walking speed is an objective measure of functional ability in elderly people. Subjects who either have fallen or have a fear of falling walk more slowly than people without balance problems [32]. The normal walking speed for females aged 19–29 years is approx. \(1.23 \pm 0.11\, \text{m/s}\), and that for 70–79-year-olds is \(1.11 \pm 0.13\, \text{m/s}\) [33]. In our study population the average walking speed was \(2.0\, \text{m/s}\). Although we instructed our participants to walk as quickly as possible, these results confirm the good health of our subjects.

Since our participants were in good physical shape, this might have undermined the possibility of obtaining an improvement upon intervention. Furthermore, it is unclear whether HRT itself can improve muscle power and function, or whether a combination of HRT and exercise is needed. For example, it appears that premenopausal women show greater increases in bone mineral density than postmenopausal women after participating in exercise programmes [34]. Oestrogen status appears to influence the degree of adaptation of bone mineral density to habitual activity levels. This interaction might also be observed with regard to the effects of HRT, muscle strength and training programmes. The interaction might be synergistic, additive or attenuative [35].

No treatment effects of tibolone were observed for any parameter, but most subjects, in both the tibolone and the placebo groups, showed improved scores at the final visit. This finding might suggest that participating in a double-blind, placebo-controlled intervention study is beneficial for your health, regardless of treatment group. It is more likely that an increase in physical activity during the 1 year of intervention would have affected the results. However, at all visits questionnaires were obtained to calculate the amount of energy used in habitual physical activities [24]. The association between functional ability parameters and habitual physical activity scores was calculated by the use of the Spearman correlation. All calculated correlation coefficients appeared to be very small and non-significant. Thus in neither the tibolone nor the placebo group could an increment in physical activity explain the improved scores at the final visit. Therefore the observed improvement suggests a learning effect with regard to the functional ability tests. Protocols with familiar tasks and discrete starting and end points appear to achieve the greatest reliability in this context [36].

Of equal importance is the fact that movements with more than one constraint may add an element of ambiguity to these tests. In such cases, the subject may make an interpretation, deciding whether speed or strength is more important; that decision may vary from one test to the next. This might have influenced the assessment of leg explosive power in particular, since both speed and strength contribute to the best performance. For this reason, measurements on this test were done more times (up to 10 pushes for each leg), to allow the subject to produce her best effort. With regard to the other tests, the volunteers were instructed to perform the tests as quickly as possible, without starting to run on the walking tests. A fast protocol is preferable over a self-paced protocol, because of smaller intra-subject variability [10].

Because of the non-linear relationship that exists between muscle strength and mobility, an increase in strength will not automatically affect functional ability. For ‘normal’ performance a critical amount of strength is needed, but above this threshold a further increase in strength will not enhance the performance of a task [37]. For example, professional athletes may be stronger than average adults, but athletes do not walk several times faster than the average adult does. Most of their strength is a physiological reserve and is not used during normal walking.

Hence, in order to detect functional limitations, the role of factors other than muscle strength needs to be
identified and investigated [38]. For instance, delayed reaction time, inadequate sensation, poor balance, joint function impairment, pain and fear might negatively influence the ability to perform a task. During dynamic movements, as opposed to maximal isometric contractions, central nervous system co-ordination or activation might be a contributory factor [39,40]. Furthermore, the loss of muscle power is greater and more closely related to physical disability than the loss of muscle strength [41,42]. The decline in power is steeper because it is magnified by the loss of velocity. In a cross-sectional study, the loss in quadriceps strength averaged 1.5% per year, whereas the decline in explosive leg extensor power was approx. 3.5% per year [43].

Summarizing, in the present study we could not demonstrate an effect of tibolone on muscle power and functional ability. Two explanations are possible: either that tibolone does not exert an effect on muscle power and functional ability, or that our participants were too far above their strength-related functional limits to derive benefit from intervention. More research is recommended, especially in women with or close to functional restrictions. The ability to transfer a gain in strength into an improved performance of daily activities would be most beneficial in frail elderly people.

Acknowledgments

This research was supported financially by NV Organon, Oss, The Netherlands. The support included manufacture and provision of tibolone and placebo tablets, statistical advice, and monitoring of the study according to the guidelines of Good Clinical Practice (GCP). We thank Wim Jansen, Sylvia Engelen, Pieter Wouters and Ad Theeuwes (NV Organon) for their help with the statistical analysis.

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Tibolone, muscle power and functional ability


Received 20 April 2001/6 August 2001; accepted 8 October 2001