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Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy

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1. The time-course of the age-related decline in specific muscle force (maximum voluntary force per cross-sectional area) in men and women was determined by measuring the maximum voluntary force and cross-sectional area of the adductor pollicis muscle in 273 subjects aged 17–90 years (176 men, 30 pre-menopausal women and 67 peri- or post-menopausal women who were not receiving hormone replacement therapy).

2. To determine whether the loss of specific muscle force is hormone-dependent in women, we studied a further 25 women, aged 42–72 years, who were receiving hormone replacement therapy.

3. There was no significant difference in specific force between young men and pre-menopausal women. Around the time of the menopause there was a dramatic decline in specific force in women which was prevented by the use of hormone replacement therapy. In men the weakness started later (around the age of 60 years) and the decline in specific force was more gradual, reaching the level seen in post-menopausal women after the age of 75 years.

4. The protective effect of hormone replacement therapy on muscle strength is likely to be an important contributory factor to its proven action in preventing osteoporotic fractures. The dramatic peri-menopausal decline in muscle strength is a likely explanation for the known increases in falls and Colles' fractures around the time of the menopause.

INTRODUCTION

The muscle weakness associated with ageing has two components. There is weakness due to muscle atrophy [1–3], but a specific weakness of the remaining muscle of around 20% has also been shown by comparing maximum force with muscle cross-sectional area (CSA) in the adductor pollicis of young and elderly human subjects [4] and the hindlimb muscles of young and aged mice [5, 6].

The overall weakness is of the order of 40% and its time-course has been investigated [2, 3, 7]. Comparing measurements of grip-strength in male subjects reported over the past 150 years, it has been suggested that the onset of the weakness may now be occurring later, implying that environmental factors are capable of significant influence [8]. However, neither when the age-related decrease in specific force begins nor the time course by which it proceeds is known. Neither has the time course of the onset of muscle weakness in women previously been compared with that in men. We therefore report measurements of maximum voluntary force (MVF) and CSA in both men and women aged 17–90 years.

The cause of the specific loss of force is also unknown. We have tested the hypothesis that, in women, hormonal factors might contribute. This is suggested by the observations that patients with osteoporotic fractures have been shown to have specific muscle weakness [9, 10], and that bone loss can be prevented by hormone replacement therapy (HRT). We have therefore compared the results obtained in peri- and post-menopausal women not taking HRT with measurements of MVF and CSA from a further group of women on HRT (aged 42–72 years).

Preliminary accounts of this work have been presented to the Physiological Society [11–13].

METHODS

Subjects

Subjects were recruited from students, current staff and retired staff of University College London, pensioners of the Royal Hospital, Chelsea, London, a sports centre in London, a bowling club in Hastings, Sussex, and the menopause clinic at the Elizabeth Garrett Anderson Hospital, London. Altogether 298 subjects between the ages of 17 and 90 years were tested (176 men, 30 pre-menopausal

Key words: ageing, hormone replacement therapy, menopause, muscles.

Abbreviations: CSA, cross-sectional area; MVF, maximum voluntary force.

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women, 67 peri- or post-menopausal women who were not receiving HRT and 25 women aged 42–72 years who were receiving HRT).

Subjects were excluded if they: (1) had pain or stiffness of movements of the thumb, (2) had clinically evident wasting of hand muscles, (3) had generalized cardiovascular or neuromuscular disease, or (4) were regularly taking medication likely to affect muscle function or motivation.

The women on HRT (combined sequential oestrogen/progestin, or oestrogen alone in the five women who had had a hysterectomy) had been on therapy between 1 and 25 years (7.8 ± 1.3 years, mean $\pm$ SEM, $n=25$) and all except two had started peri-menopausally, one of these was 16 years post-menopausal, the other seven years post-menopausal, and they had received HRT for the last 9 and 5 years, respectively. The indications for HRT were menopausal symptoms or prophylaxis against osteoporosis.

Of the subjects not on HRT, five had received treatment a year or more ago for a short time (between 1 and 6 months); all these subjects were 5–17 years post-menopausal.

None of the subjects had had other treatment for osteoporosis. Subjects completed a simple activity questionnaire.

MVF and CSA measurements

MVF of the adductor pollicis of the right hand was measured using a force transducer mounted on a metal bar placed between the bases of the proximal carpal bone of the thumb and the metacarpal bone of the index finger [14]. CSA was determined by measuring the thickness of the hand in the plane that bisects the adductor pollicis muscle by the difference in output from two linear potentiometers which were moved over the skin [15]. For each subject the MVF was a mean of four to nine maximum voluntary contractions and the CSA was a mean of two to four measurements. In this series mean coefficients of variations for each subject were 3.5% for MVF and 7.5% for CSA.

All subjects gave their informed consent. The study was approved by the ethical committees of University College London, University College Hospital and Hastings Health Authority.

Statistical analysis

Unpaired Student's t-tests were used to test for significant differences between data.

RESULTS

Fig. 1 shows MVF plotted against CSA for men aged 17–60 years and pre-menopausal women aged 22–45 years. MVF and CSA were strongly correlated in both groups (men: $n=148$, $r=0.83$; pre-menopausal women: $n=30$, $r=0.79$) and neither the regression lines nor the mean MVF/CSA values were significantly different. When the data for these subjects were pooled r was 0.86 ($P<0.001$).

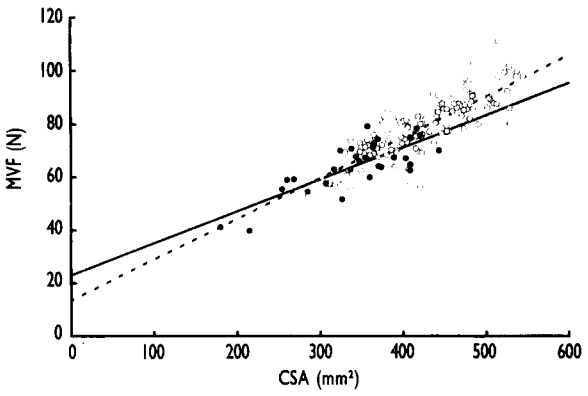

Fig. 1. Relationship between MVF and CSA in men aged 60 years and under (○) and pre-menopausal women aged 45 years and under (●). The regression lines for men (----) and women (——) are also shown. The regression line for men and women combined is not shown, but the equation for the line is $y=12+x0.16$.

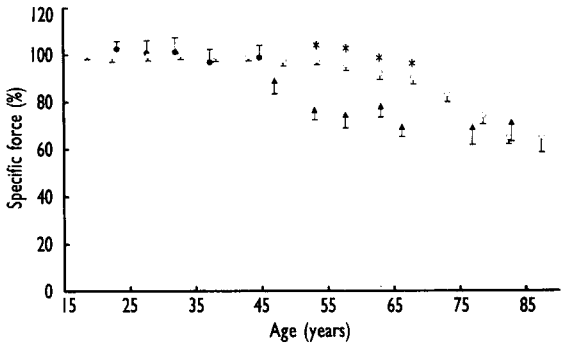

Fig. 2. Relationship between specific force and age for three groups of subjects: men (○), pre-menopausal women (●) and peri- or post-menopausal women (▲). Specific force is expressed as a percentage of the mean value for subjects aged 45 years and under. The points shown are means and SEMS; n ranges between 4 and 18 (mean = 12, men), 4 and 9 (mean = 6, pre-menopausal women) and 5 and 15 (mean = 10, peri- and post-menopausal women). Statistical significance: $^*P<0.02$ comparing men and women.

Decline in MVF/CSA with age

In order to determine the time-course of the decline in specific muscle strength we plotted mean MVF/CSA for men and women in age groups spanning about 5 years (Fig. 2). This again emphasized the absence of any difference between men and women up to the time of the menopause. Thereafter there was a dramatic decline in strength in women followed by little change, whereas in men there was

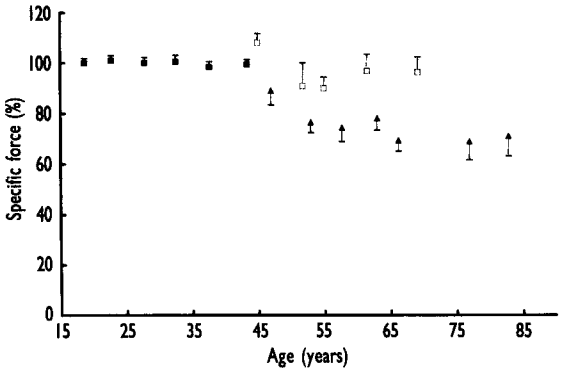

Fig. 3. Relationship between specific force and age in both men and pre-menopausal women aged 45 years and under (■), peri- or post-menopausal women (total 67) not on HRT (▲) and peri- or post menopausal women (total 25) on HRT (□). Specific force is expressed as a percentage of the mean value for subjects aged 45 years and under. Means and SEMS are shown; *n* ranges between 12 and 22 (mean = 18, men and pre-menopausal women), 4 and 15 (mean = 10, peri- and post-menopausal women not on HRT) and 4 and 6 (mean = 5, post-menopausal women on HRT).

a gradual decline which started much later (Fig. 2). For each of the four age groups between 53 and 68 years of age, the MVF/CSA for women was significantly lower than that for men of the same age group (Fig. 2). Only after the age of 75 years did the MVF/CSA produced by men and women once again reach the same level.

MVF/CSA with and without HRT

Fig. 3 shows the effect of HRT on specific force with age. Specific force is plotted in age groups spanning about 5 years. Data from men and pre-menopausal women were pooled, there being no significant difference between their specific forces, in order to simplify the presentation of the data.

To directly compare women on HRT with those who were not, we had to match the groups for age. Comparing subjects between 49 and 73 years of age gave the same mean age of 60 years, the same mean length of time post-menopause (11 years) and same average age at the time of menopause (48 years). There was no significant difference between these two groups in height (no HRT: 1.63 ± 0.01 m, $n=35$; HRT: 1.62 ± 0.02 m, $n=21$) or weight (no HRT: 66.7 ± 2.0 kg, $n=35$; HRT: 62.0 ± 2.8 kg, $n=21$). None of the women in these two groups was a trained athlete or dancer and there was no difference in their activity scores. However, MVF/CSA was very different between the two groups: those not on HRT were significantly weaker (0.140 ± 0.005 N/mm^2, $n=35$, $P<0.001$) than those on HRT (0.176 ± 0.006 N/mm^2, $n=21$). The MVF/CSA of the pre-menopausal group (0.190 ± 0.004 N/mm^2, $n=30$) was not different from that of the group on HRT.

DISCUSSION

The time course of the age-related decline in skeletal muscle MVF/CSA in men and women is very different. In men, MVF/CSA is maintained until the age of about 60 years, after which it declines. In women there is a dramatic reduction in MVF/CSA around the time of the menopause. This may elucidate the previously unexplained results of Winner *et al.* [16] showing a peri-menopausal increase in falls and Colles' fractures. Muscle weakness is associated with falls [17] and intuitively the association seems particularly likely when the onset of the weakness is rapid.

The fact that the reduction in MVF/CSA seen in very elderly women (>75 years) has actually occurred in the peri-menopausal years suggests a sex-hormone-dependent change. We tested this by examining the MVF/CSA of post-menopausal women receiving HRT and found that the menopausal decrease in specific force was prevented. The fact that HRT protects against loss of muscle strength as well as bone loss [18, 19] suggests an important additional role for this treatment in the prevention of osteoporotic fractures.

The mechanism whereby hormonal changes result in loss of specific muscle force in ageing female muscle, which can be prevented by HRT, is speculative. We have previously shown that the specific decrease in force seen in very elderly subjects is not due to failure of activation [14]. In the mouse model the decreased maximum force/CSA seen in muscles from aged animals can be restored by applying a rapid stretch during the contraction [6]. This phenomenon is thought to result from a change in an equilibrium, at the level of the cross-bridges, between high- and low-force states. When the muscle is being rapidly stretched all the cross-bridges exert the same maximum force whichever state they are in at the onset of stretch [6, 20]. Similar behaviour, that is decreased isometric force which can be restored by stretch, is also seen in fatigued muscle [21] and can be brought about experimentally by increasing intracellular P_i [22] or lowering H^+ concentration (pH) [23]. Observations so far suggest that there are no significant changes in P_i or pH in aged mouse [23a, 24]. However, it remains a possibility that hormonal influences could alter the sensitivity of the cross-bridges to such metabolites or that some other factor affects the cross-bridge reducing force development with ageing. Our current results show that in women oestrogen is able to prevent the action of this unknown factor.

The corresponding hormonal influence in men might be androgens or the relationship between androgens and oestrogen. Free testosterone levels decline in men from around 60 years of age [25,

26], which is consistent with the time course in reduction in MVF/CSA shown in the present study. This decrease in free testosterone is probably due to decreased Leydig cell mass and function [26]. The administration of testosterone to older men (>50 years) causes a general increase in muscle mass and strength but has no effect on young men, whereas castration is known to cause a reduction in muscle mass and strength [8]; the effect on MVF/CSA has not been studied. In normal men, the peripheral aromatization of androgens is an important source of oestrogens. It is not clear what happens to the levels of oestrogens with age in men [25] and both androgens and oestrogens should be estimated in any study to investigate the possible role testosterone might play in maintaining MVF/CSA in men.

As well as oestrogen replacement preventing menopausal bone loss in women [18, 19], testosterone replacement therapy has been shown to restore bone mass in osteoporotic men [27]. It is not known if these are direct actions of the respective hormones on bone [27]. It is an intriguing possibility that the primary abnormality may be a hormone-related loss of specific muscle strength and that bone loss is secondary to this muscle weakness.

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REFERENCES

1. Essen-Gustavsson, B. & Borges, O. Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiol. Scand. 1986; **126,** 107–14.
2. Kallman, D.A., Plato, C.C. & Tobin, J.D. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J. Gerontol. 1990; **45,** M82–8.
3. Vandervoort, A.A. & McComas, A.J. Contractile changes in opposing muscles of the human ankle joint with aging. J. Appl. Physiol. 1986; **61,** 361–7.
4. Bruce, S.A., Newton, D. & Woledge, R.C. Effects of age on voluntary force and cross-sectional area of human adductor pollicis muscle. Q. J. Exp. Physiol. 1989; **74,** 359–62.
5. Brooks, S.V. & Faulkner, J.A. Contractile properties of skeletal muscles from young, adult and aged mice. J. Physiol. (London) 1988; **404,** 71–82.
6. Phillips, S.K., Bruce, S.A. & Woledge, R.C. In mice, the muscle weakness due to age is absent during stretching. J. Physiol. (London) 1991; **437,** 63–70.
7. Narici, M.V., Bordoni, M. & Cerretelli, P. Effect of aging on human adductor pollicis muscle function. J. Appl. Physiol. 1991; **71,** 1227–81.
8. Larson, L. Aging in mammalian skeletal muscle. In: Pirozzolo, F.J. K Maletta, G.J., eds. The aging motor system. New York: Praeger, 1982: 60–98.
9. Bruce, S.A., Ghattaora, R., Phillips, S.K., Sheikh, A. & Woledge, R.C. Hip fracture patients have weak hand muscles. Age Ageing 1992; **21** (Suppl. 1), P12.
10. Jones, D.A. & Rutherford, O.M. Effect of ageing and osteoporosis on the force-generating capacity of the quadriceps muscle in women. J. Physiol. (London) 1990; **423,** 84P.
11. Bruce, S.A., Phillips, S.K. & Woledge, R.C. Strength and cross sectional area of adductor pollicis muscle in men and women. J. Physiol. (London) 1992; **446,** 226P.
12. Rook, K.M., Phillips, S.K., Bruce, S.A. & Woledge, R.C. The effects of ageing on muscle strength in men and women. J. Physiol. (London) 1992; **452,** 25P.
13. Phillips, S.K., Bruce, S.A., Woledge, R.C. & Siddle, N.C. Force and cross-sectional area of adductor pollicis muscle in post-menopausal women, with and without hormone replacement therapy. J. Physiol. (London) 1992; **446,** 364P.
14. Phillips, S.K., Bruce, S.A., Newton, D. & Woledge, R.C. The weakness of old age is not due to failure of muscle activation. J. Gerontol. 1992; **47,** M45–9.
15. Bruce, S.A., Newton, D. & Woledge, R.C. Effect of subnutrition on normalised muscle force and relaxation rate in human subjects using voluntary contractions. Clin. Sci. 1989; **76,** 637–41.
16. Winner, S.J., Morgan, C.A. & Grimley-Evans, J. Perimenopausal risk of falling and incidence of distal forearm fracture. Br. Med. J. 1989; **298,** 1486–8.
17. Wickham, C., Cooper, C., Margetts, B.M. & Barker, D.J.P. Muscle strength, activity, housing and the risk of falls in elderly people. Age Ageing 1989; **18,** 47–51.
18. Lindsay, R., Aitken, J.M., Anderson, J.B., Hart, D.M., MacDonald, E.B. & Clarke, A.C. Long-term prevention of postmenopausal osteoporosis by estrogen. Lancet 1976; **1,** 1038–41.
19. Smith, R. Osteoporosis: cause and management. Br. Med. J. 1987; **294;** 329–32.
20. Lombardi, V. & Piazzesi, G. The contractile response during steady lengthening of stimulated frog muscle fibres. J. Physiol. (London) 1990; **431,** 141–71.
21. Curtin, N.A. & Edman, K.A.P. Effects of fatigue and reduced intracellular pH on segment dynamics in 'isometric' relaxation of frog muscle fibres. J. Physiol. (London) 1989; **413,** 159–74.
22. Elzinga, G., Steinen, G.J.M. & Versteeg, P.G.A. Effect of inorganic phosphate on length responses to changes in load in skinned rabbit psoas muscle. J. Physiol. (London) 1989; **415,** 132P.
23. Curtin, N.A. Force during stretch and shortening of frog sartorius muscle: effects of intracellular acidification due to increased carbon dioxide. J. Muscle Res. Cell Motil. 1990; **11,** 251–7.
23a. Phillips, S.A., Wiseman, R.W., Woledge, R.C. & Kushmerick, M.J. Neither changes in phosphorus metabolite levels nor myosin isoforms can explain the weakness in aged mouse muscle. J. Physiol. (In press).
24. Taylor, D.J., Crowe, M., Bore, P.J., Styles, P., Arnold, D.L. & Radda, G.K. Examination of the energetics of aging skeletal muscle using nuclear magnetic resonance. Gerontology 1984; **30,** 2–7.
25. McKinlay, J.B. Prog. Clin. Res. 1989; **320,** 163–92.
26. Vermeulen, A. Clinical review 24: androgens in the aging male. J. Clin. Endocrinol. Metab. 1991; **73,** 221–4.
27. Marcus, R. Skeletal ageing: understanding the functional and structural basis of osteoporosis. Trends Endocrinol. Metab. 1991; **2,** 53–8.