HRT affects skeletal muscle contractile characteristics: a definitive answer?

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In their paper entitled “Postmenopausal hormone replacement therapy modifies skeletal muscle composition and function: a study with monozygotic twin pairs,” Ronkainen and colleagues (9) remind us of an old friend, hormone replacement therapy (HRT), and revive the debate over whether the evidence is for or against a definitive answer in terms of the potential functional benefits of this therapy.

At first glance it appears debatable whether this is still a hot topic and whether the authors might not well have dug deeper in the literature to find an answer to their query: On balance, does HRT have noticeable effects on skeletal muscle structural and/or contractile characteristics? In fact, as evidenced below, the issue was far from resolved before the present work of these authors.

Stepping back slightly, we see that muscle force, which often correlates with measures of function, declines rapidly at the menopause (8). In fact, a loss of 15–25% of total muscle strength (on top of the decline associated with aging) has been found to coincide with the menopause (2, 4), and others support these findings (10).

HRT involves the supplement of one or more estrogens formulated either alone or opposed (i.e., with combined progesterones). Either way, studies have attempted to demonstrate that estrogens play a role in preserving muscle strength (e.g., Ref. 8). Functionally this translates into better postural balance [partly dependent on muscle strength (6)] in women receiving HRT (5). However, Skelton et al. (11) demonstrated that a 12.4 ± 1.0% muscle strength improvement seen with HRT was not an immediate consequence of increases in the levels of circulating estrogen. They showed that, whereas estrogens (estradiol and estrone) levels peaked early, strength increased more slowly. The evidence for or against the existence of noticeable effects of the therapy is thus still very much equivocal, not least because the definitive pathway (i.e., anabolic vs. antiapoptotic vs. metabolic vs. chronotropic vs. inotropic) for any estrogenic action is not clear.

While not all studies agree that HRT has muscle-strengthening effects (1, 12), caution in contrasting the conclusions of studies on any improved muscle contractile characteristic of HRT is advisable and a note should be made as to whether comparison is appropriate in the first place. For instance, methodologically are the two studies equivalent in terms of measurement of muscle force and size? Are formulation, dosage, and the duration of HRT usage parameters similar? Are these studies cross-sectional or longitudinal? What are the population characteristics, including lifestyle factors? Indeed, confounding factors could include the reliability of the muscle force measurement, differences in obesity status, physical activity, age, alcohol use, and smoking.

In this context, Ronkainen and colleagues (9) have cleverly used a design that minimizes the potential of genetic and/or physiological differences between users and nonusers (by using monozygotic twins), while optimizing the ability to tease out any HRT effects. The presented results are in favor of HRT having a significant positive impact on skeletal muscle functioning, given the strong relationship between muscle performance and HRT usage reported here. Through the robust design adopted here, this study therefore incrementally advances the field and in fact tips the balance toward a positive and measurable impact of HRT: HRT users have five times the levels of estrogen, walk 7% faster, jump 16% higher, and exhibit 8% greater relative lean tissue content and 5% smaller relative fatty tissue content compared with their nonusing counterparts.

There are nevertheless several issues related to muscle structural and contractile characteristics that may be further elucidated in future studies. Indeed, while the present study supports previous literature on the link between HRT and muscle contractile capacity, at least as far as muscle power is concerned, it disagrees with earlier data on a link between isometric strength and HRT usage (11, 13). The reader’s attention is drawn to the fact that this discrepancy with earlier literature may be linked to any factor including differences in study designs, HRT preparations, exposure time, etc.

The conundrum now is related to determining what the mechanisms for the effects of HRT may be so as to potentially delineate potential future targets for pharmacological interventions that may span not just the sexes but also the ages and varying physical activity groups. Indeed, there are several conditions and events that lead to muscle atrophy (sarcopenia) and weakness (asthenia). One possible candidate is a direct investigation of the events at the cross bridge level. A previous study (7) showed that absence rather than presence of HRT would appear to be associated with increased stretch-to-isometric force ratio at low activation levels. Such observations suggest that the force increment linked with HRT is possibly achieved either by changing the proportion of fiber types or simply by changing the frequency coding of electromyographic activity.

The documented long-term benefits of HRT use are numerous and range from substantial reduction in osteoporosis risk to improvement of some of the aspects of psychological functioning. However, on the negative end of the spectrum, a most common risk associated with the use of HRT is increased mammographic density and sensitivity, which has been linked to an increased likelihood of developing breast cancer. Nevertheless, in considering both risks and benefits of HRT, it is the general consensus that at least in women at risk of osteoporosis, the benefits far outweigh the risks (3). Indeed, osteoporotic fractures cause pain and disability and have a significant mortality effect (10–20% mortality rate within 6 mo of hip fracture). What is more, with aging a condition generally termed “aging-related sarcopenia” with related asthenia has seen many interventions linked to exercise and/or nutritional...
interventions. It may be that HRT could make a comeback with Ronkainen and colleagues’ present demonstrated positive impact on muscle contractile characteristics.

Also key to advancement in this field, future studies should specifically determine the impact of different formulations on the type of response to HRT. Indeed, in their study, Ronkainen et al. uncovered a trend toward differential response through different therapies whereby “estrogen-containing therapies (11 pairs) significantly decreased total body and thigh fat content, whereas tibolone (4 pairs) tended to increase muscle cross-sectional area.” Pinpointing the effects of each formulation is key to targeted and individualized therapeutic interventions of the future.

REFERENCES