Review

Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence

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Abstract

Introduction: Osteoporosis and fracture risk increase exponentially in postmenopausal females. This places a significant burden in terms of morbidity, mortality and costs that are likely to increase with an ageing population. Despite this there is very limited data on pharmacological management of osteoporosis in this high risk group.

Objectives of this review: To review the published literature on the clinical efficacy and safety of specific anti osteoporosis treatments in the reduction in fracture risk in females ≥75 years of age. The following major endpoints were used in this review:

1. Vertebral fracture reduction at 1 year and 3 years.
2. Non-vertebral fracture and hip fracture reduction at 1 year and 3 years.
3. Safety data in this group.

Search methods for identification of studies: We performed an electronic search of Medline (1970 to June 2007) and the Cochrane Library (1996 to June 2007). Our search strategy included MeSH terms for osteoporosis and treatments. We reviewed the reference list of identified articles for additional relevant published trials.

Results: Two hundred and fifty-two potentially relevant abstracts were identified. Only six publications were deemed to meet full eligibility criteria and one met most criteria. There is evidence for significant vertebral fracture relative risk reduction (RR) at 1 year for Risedronate (RR 81%; p < 0.001), Teriparatide (RR 65%; p < 0.05) and Strontium Ranelate (RR 59%; p = 0.002) and 3 years for Risedronate (RR 44%; p = 0.003), Alendronate (RR 38%; p < 0.05) and Strontium Ranelate (RR 32%; p = 0.013). There is evidence for significant non-vertebral fracture relative risk reduction at 1 year for Strontium Ranelate (RR 41%; p = 0.027) but not Teriparatide (p = 0.66) and 3 years for Strontium Ranelate (RR 31%; p = 0.011) but not Risedronate (p = 0.66). The only study to report a reduction in hip fracture at 3 years is the TROPOS study with Strontium Ranelate (RR 36%; p = 0.046).

Discussion: This review reinforces the irony that the least evidence is available for fragility fracture reduction in the group at greatest risk; the old old and those with non vertebral and hip fracture. Although there is good evidence for the benefit of the bisphosphonates (Alendronate and Risedronate), Teriparatide and Strontium Ranelate in vertebral fracture reduction, there are very limited data for non vertebral and hip fracture reduction. Strontium Ranelate is the only agent to date that has demonstrated a reduction in non vertebral and hip fracture events in this high risk elderly female population. Perhaps we need to adopt different strategies in managing older patients with osteoporosis as their fracture risks and treatment strategies may be quite different from younger populations.

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Introduction

Osteoporosis increases in prevalence with age such that it is common in the elderly [1–3]. For any bone mineral density (BMD) measurement, fracture risk is much higher in the elderly than in the young [4]. Age is one of the most important components of the fracture index derived by Black et al. [5]; and older age groups experience the greatest growth rate of osteoporosis risk in the population [6,7]. So although BMD is a strong risk factor for fragility fracture, its relative importance diminishes if there are other strong risk factors for fracture: advanced age, prior fragility fracture or family history of fragility fracture [4,8].

Older patients are at higher risk of falls [9] due to muscle weakness [10] and more than 90% of fractures occur after a fall [11–13]. Falls result in any fracture in 5% and specifically hip fracture in 1–2% of events [11]. Hence, in an ageing, osteoporotic population, fracture prevention through the optimisation of bone health as well as reducing falls risk should be important goals.

Epidemiological data worldwide have consistently demonstrated that the annual incidence of fragility fracture increases with age [14–19]. Above average fracture rates were described in Australian females residing in Dubbo [20] and Geelong [3] with an exponential increase in risk in the population groups over 74 years of age. The burden of fracture is expected to increase with an ageing population as the oldest old i.e. women ≥80 years of age comprise approximately 8% of the post-menopausal population but contribute >30% of all fragility fractures and 60% of hip fractures because of the high prevalence of osteoporosis and falls in this age group [21,22]. After age 75, hip fracture is the commonest fracture [23–25] with 1/3 of women and 1/6 of men estimated to sustain a hip fracture by the 9th decade [26] and is associated with significant morbidity and mortality [27–29] and financial burden [32,30–33].

Despite the high risk of osteoporotic fracture in older individuals, there is little data regarding treatment of this group. Studies have either included limited numbers or excluded older individuals due to strict entry criteria based on age and related factors. However, economic evaluations have suggested that if current anti-osteoporosis agents are as effective in older patients as in younger trial patients, the cost benefit ratios are more favourable given the higher absolute risk in older patients [34–36].

Objectives of this review

To review the published literature on the clinical efficacy and safety of specific anti-osteoporosis treatments in the reduction in fracture risk in females ≥75 years of age. The following major endpoints were used:
1. Vertebral fracture reduction at 1 year and 3 years.
2. Non-vertebral fracture and hip fracture reduction at 1 year and 3 years.
3. Safety data in this group.

Eligibility criteria for inclusion in review

Studies were randomised placebo or active comparator control trials or age comparison trials of at least 1 year duration and included post-menopausal females. Pooled analysis and published sub-group analysis, specifying the sub-groups ≥75 years were included.

Analysis

The following outcome and efficacy measures were predetermined:
1. The primary efficacy outcome was the proportion of women with incident vertebral fractures at 1 year and 3 years.
2. The secondary endpoint was non-vertebral and hip fractures at 1 and 3 years.
3. Vertebral fractures and non-vertebral fractures were required to be radiographically proven.
4. Safety measures included the following:
a) The proportion with any adverse event reported.
b) The proportion that withdrew due to adverse events.
c) The proportion with reported serious adverse events.
d) The proportion of deaths.
e) The proportion with any gastro-intestinal adverse event.

Search methods for identification of studies

An electronic search of Medline (1970 to June 2007) and the Cochrane Library (1996 to June 2007) using MeSH terms for osteoporosis and treatments was performed. We reviewed the reference list of identified articles for additional relevant published trials. We excluded studies specifically investigating hormone replacement therapy, calcium and vitamin D as a primary treatment measure in this review.

Abstracts of all possibly relevant articles were reviewed independently (AF and ML) for potential eligibility. Those records deemed eligible and those that did not have adequate information to confirm their inclusion underwent a full text review.
All data was summarised in a pre-formulated proforma including inclusion criteria, gender, age, type of study, duration and the main outcome measures. A third reviewer (CI) reviewed all publications meeting the inclusion criteria as well as those deemed to meet some criteria and or included patients from the target age groups and helped resolve difference in interpretation by reviewers AF and ML.

All studies, sub-group analysis or pooled analysis specifically reporting outcomes in the pre-specified age groups were included in the final review. No further or separate sub-group analyses were performed. Authors and industry sponsors were contacted for more information and clarification where sub-group analyses or additional data may be available for the relevant age group being assessed.

**Descriptions of studies**

Two hundred and fifty-two potentially relevant abstracts were identified. After excluding studies that did not meet eligibility criteria, 104 studies were fully reviewed for potential inclusion. The number of studies with each anti osteoporosis agent reviewed was as follows:

1. Alendronate 31
2. Clodronate 4
3. Etidronate 7
4. Ibandronate 10
5. Pamidronate 1
6. Parathyroid hormone (PTH 1–34 [Teriparatide]/PTH 1–84) 19
7. Raloxifene 12
8. Risedronate 11
9. Strontium Ranelate 6
10. Zoledronic acid 3

Only six publications were deemed to meet full eligibility criteria [37–42] and one met most criteria [43]. Two publications (Strontium Ranelate [37] and Risedronate [38]) met inclusion criteria based on publication of pooled subgroup analysis from previous studies including patients aged 80 years or older (but did not include patients from the 75–79 year group). Two publications [Teriparatide [39] and Alendronate [40]] met inclusion criteria for publication of subgroup analysis of patients aged 75 years and older from previously published studies. One study (Clodronate [41]) exclusively enrolled women ≥75 years of age. Where pooled analyses were published, the original studies were also independently reviewed. Although a full review of the original studies was completed, only data from the pooled and/or subgroup publications was considered for inclusion in this review, unless the pooled analysis and or subgroup differed from the subgroups described in the original study [42,43]. The HIP study (Risedronate) [42] met full inclusion criteria and the TROPOS study (Strontium Ranelate) [43] met partial criteria based on these criteria. The TROPOS study included patients from 74 years of age rather than the prespecified 75 years.

**Description of studies including outcomes in patients ≥75 years of age**

**Strontium Ranelate study**

The Strontium Ranelate study [37] was a pooled analysis of patients from the SOTI [44] and TROPOS [43] studies. The SOTI study assessed the anti vertebral fracture efficacy in 1649 white post menopausal women with osteoporosis and at least one prevalent vertebral fracture and the TROPOS study (5091 patients) assessed the anti non-vertebral fracture efficacy in 1977 white post menopausal women ≥74 years of age with osteoporosis and femoral neck BMD <0.68 g/cm² (measured by Hologic). Subjects were randomised to receive either Strontium Ranelate 2 g/day or placebo powder for three years. They also received supplemental calcium and vitamin D, if deficient. Of the total 6740 patients enrolled in both studies, 1488 (22%) were in the age range 80–100 years and were included in the pooled analysis [37]. The baseline characteristics of the patients are illustrated in Table 1.

**Risedronate study**

The Risedronate study [38] included patients from 3 studies: VERT-NA [45], VERT-MN [46] and HIP Study [42]; all were phase 3 clinical randomised double blind placebo controlled parallel group studies. The VERT studies were designed to determine the effect of Risedronate on vertebral fracture in women with post menopausal osteoporosis and the HIP study was designed to evaluate the effect of Risedronate on hip fracture in elderly women. In all three studies, patients received Risedronate or placebo daily for up to 3 years with supplemental calcium and vitamin D if considered deficient. Patients enrolled in VERT studies were post menopausal with osteoporosis i.e. 2 or more vertebral fracture or one fracture and a lumbar spine BMD of <0.83 g per cm² on Hologic BMD measurement. The HIP study included 2 cohorts of patients aged 70–79 years with osteoporosis and at least 1 non skeletal risk factor and patient who were 80 years or greater who had either ≥1 non-skeletal risk factor for fracture or a BMD showing osteoporosis at the femoral neck with the T score of less than −4.0 or a T score of −3.0 plus hip axis length of ≥11.1 cm.

The pooled analysis only included patients who were randomised to 5 mg Risedronate per day and had either femoral neck BMD T score <−2.5 or ≥1 prevalent vertebral fracture(s). Analysis included a total patient cohort of 6126 (Risedronate 5 mg or placebo) of which 1392 (23%) where aged 80 years and older. The baseline characteristics of the patients are illustrated in Table 1.

**Teriparatide study**

The Teriparatide subgroup study [39] was a pre-specified sub group analysis of the Fracture Prevention Trial (FPT) [47]. The focus of this analysis was to test whether older women (≥75 years) had similar safety and efficacy to that of younger women. The analysis compared whether there was a significant interaction between treatment (Teriparatide 20 μg versus placebo) and age (≤75 vs >75) at a significance level of p<0.10. All participants received calcium and vitamin D supplementation. The FPT was terminated early with median treatment duration of 19 months. Of the total 1637 postmenopausal women enrolled in the study, 244 (15%) were aged 75 years or greater with a mean age of 78 and a range of 75 to 86 years. The inclusion criteria were the presence of 1 or more moderate vertebral fracture or 2 mild vertebral fractures. The majority of patients (approximately 89%) had 1 or more fracture at enrollment. Patients who had less than 2 moderate vertebral fractures were required to have a BMD of the hip or lumbar spine T score of ≤−1.0. The baseline characteristics of the 75 years and older age group are illustrated in Table 1.

**Alendronate study**

The Alendronate study [40] is a sub group analysis of patients 75 years and older from the FIT study [48]. Subjects received either placebo or Alendronate 5 mg daily for 24 months, followed by 10 mg daily for 12 months plus supplemental calcium and vitamin D. In the original cohort there were 2027 postmenopausal women aged 55 to 82 with low femoral neck bone density and existing vertebral fractures (100%). Subjects were post menopausal females with a femoral neck BMD of ≤0.88 g/cm², which is equivalent to a T score of −2.0 (Hologic measurement) and at least 1 radiographic vertebral fracture. In total there were 539 (27%) subjects, 75 years or older with an age range of 75 to 82 and 100% of subjects had a previous vertebral fracture. The baseline characteristics of the patients are illustrated in Table 1.
Clodronate study

The Clodronate study [41] specifically randomised community-dwelling women ≥75 years of age who did not need to have proven osteoporosis or any other risk factor. Subjects were randomised to either Clodronate 800 mg daily or placebo for 3 years. Calcium or vitamin D supplements were not given as part of the study. A total of 5592 patients were enrolled equally. The baseline characteristics of the patients are illustrated in Table 1.

Vertebral fracture risk reduction in patients 75 years of age or older

The results are summarised in Table 2. There are limited published data on vertebral fracture risk reduction in this age group. There are published data at 1 year and 3 years for Risedronate and Strontium Ranelate, 1 year for Teriparatide and 3 years for Alendronate. There are no published data for Clodronate. There is evidence for significant vertebral fracture relative risk reduction at 1 year for Risedronate (RR 81%; p<0.001), Teriparatide (RR 65%; p<0.05) and Strontium Ranelate (RR 59%; p=0.002) and 3 years for Risedronate (RR 44%; p=0.003), Alendronate (RR 38%; p<0.05) and Strontium Ranelate (RR 32%; p=0.013). The Teriparatide study compared patients younger than 75 with those 75 or older and found no age-treatment interaction (p=0.42).

The Risedronate and Strontium Ranelate data only includes patients 80 years or older, making comparisons with the limited evidence available for the other treatment modalities unreliable. Limited comparisons are possible between these 2 groups which enrolled patients of similar age and body weight. However, Risedronate treatment group had a higher prevalence of vertebral fracture compared to placebo and the Strontium Ranelate group had lower femoral neck BMD at baseline compared to placebo. The Risedronate treated group appeared to have a greater proportional reduction in vertebral fracture risk at 1 year (81% vs 59%). However, the difference in risk reduction, although persistent for both groups was not as marked at 3 years (44% vs 32%).

Non-vertebral fracture risk reduction in patients 75 years of age and older

The results are summarised in Table 2. There are 1 year data for Strontium Ranelate (≥80 years) and Teriparatide (≥75 years) and 3 year data in the over 80 age group for Strontium Ranelate and Risedronate. Risedronate was demonstrated to reduce non vertebral fracture in a combined analysis of subjects in the HIP study (70–79 years and 80 years and over groups); relative risk 0.8 (95% CI = 0.7–1.0; p = 0.03); no benefit was demonstrated in the older cohort selected primarily on the basis of nonskeletal risk factors (p=0.43). There was no significant reduction in non vertebral fracture risk in the pooled analysis [38] which included subjects with either proven osteoporosis or a prevalent vertebral fracture (p=0.66); although benefit was demonstrated in subjects younger than 80 years; relative risk 0.61 (95% CI = 0.51–0.74; p<0.001). There are no published data for Alendronate and Clodronate.

There is evidence for significant non-vertebral fracture relative risk reduction at 1 year for Strontium Ranelate (RR 41%; p = 0.027) but not Teriparatide (p = 0.66) and 3 years for Strontium Ranelate (RR 31%; p = 0.011) but not Risedronate (p = 0.66).
Hip fracture risk reduction in patients 75 years of age and older

The results are summarised in Table 2. There are only 2 studies specifically designed to look at hip fracture as the primary outcome — the HIP study (Risedronate) and the Clodronate Study. A third study, TROPOS (Strontium Ranelate) reported hip fracture outcome as a secondary outcome in the subgroup ≥74 years, with more severe osteoporosis. The 80+ subgroup from the latter was also included in the pooled analysis by Seeman et al. [37] which reported hip fracture outcome as a secondary endpoint in patients 80 years or older.

The Clodronate study, with unselected community-dwelling women, reported no significant benefit at 1 year (HR 1.31; 95% CI = 0.82–2.03) and 3 years (HR 1.02; 95% CI = 0.71–1.47). The HIP study (Risedronate), which enrolled patients at least 80 years old with at least 1 non-skeletal risk factor for hip fracture or low femoral neck BMD, showed no significant benefit in hip fracture reduction at 3 years (p = 0.35) although hip fracture reduction was demonstrated in the osteoporotic 70–79 year age group (RR 40%; p = 0.009). The pooled Risedronate study [38] did not report hip fracture outcomes. The pooled Strontium Ranelate data demonstrated non-significant reduction in hip fracture at 3 years in patients at least 80 years of age (32%; p = 0.112). The only study to report a reduction in hip fracture at 3 years is the TROPOS study (Strontium Ranelate). However, it included the subgroup of patients from 74 years of age rather than our prespecified 75 years. The authors reported hip fracture RRR of 36% (p = 0.046) in a high risk subgroup aged at least 74 years of age with osteoporosis of the femoral neck on BMD.

Other studies with significant proportion of patients 75 years or older

Zoledronic acid

A double-blind, placebo controlled study by Black et al. [49] randomised 3889 postmenopausal, osteoporotic women, mean age 73 ± 5 (range 65–89) years, to either an annual infusion of zoledronic acid 5 mg or placebo at baseline with 12, 24 and 36 months of follow up. In this study 1452 (37.6%) of the placebo group and 1497 (38.6%) of the zoledronic acid group were included the subgroup of patients from 74 years of age rather than our prespecified 75 years. The authors reported hip fracture RRR of 36% (p = 0.046) in a high risk subgroup aged at least 74 years of age with osteoporosis of the femoral neck on BMD.

Table 2
Fracture efficacy in women ≥ 75 years randomised in osteoporosis studies

<table>
<thead>
<tr>
<th>Fracture risk</th>
<th>Vertebral fracture</th>
<th>Non vertebral fracture</th>
<th>Hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>3 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Alendronate studies</td>
<td>Placebo</td>
<td>NA</td>
<td>19.4%</td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>NA</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction* (p-value)</td>
<td>NA</td>
<td>38% (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>Risedronate</td>
<td>10.0%</td>
<td>24.6%</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction (p-value)</td>
<td>2.5%</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction (p-value): Pooled 80</td>
<td>81% (p &lt; 0.001)</td>
<td>44% (p = 0.003)</td>
</tr>
<tr>
<td></td>
<td>RRR: hip</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>RRR: Strontium Ranelate studies</td>
<td>NA</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction (p-value)</td>
<td>59% (p = 0.002)</td>
<td>32% (p = 0.013)</td>
</tr>
<tr>
<td></td>
<td>RRR: TROPOS ≥ 74</td>
<td>NA</td>
<td>151%</td>
</tr>
<tr>
<td>Teriparatide studies</td>
<td>Placebo</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Teriparatide</td>
<td>5.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction (p-value)</td>
<td>65% (p &lt; 0.05)</td>
<td>25% (NS p = 0.661)</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Placebo</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Clodronate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Relative risk reduction (p-value)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NS = Not significant; NA = Not available.

* Any clinical fracture at 3 years HR, 0.80 (95% CI, 0.54–1.17); no treatment age interaction for any clinical fracture (p = 0.59) or vertebral fracture (p = 0.48).

+ Includes Hip study patients only — selected on the basis of non-skeletal risk factors for hip fractures rather than established osteoporosis.

= No treatment age interaction for new vertebral fracture (p = 0.35) although hip fracture reduction was demonstrated in the osteoporotic 70–79 year age group (RR 40%; p = 0.009).

= No treatment age interaction for new vertebral fracture (p = 0.046).

Adverse events reported in patients 75 years of age or older

There are limited published data on adverse outcomes in older patient subgroups. The most comprehensive data is published for Risedronate [38] and Strontium Ranelate [37] in the over 80 age group pooled analyses. Table 3 summarises the published adverse events. Neither Risedronate nor Strontium Ranelate resulted in more adverse events than placebo for the following categories: any adverse event, withdrawal due to adverse events, serious adverse events or deaths.

Strontium Ranelate pooled analysis suggested trends towards increased reporting of gastrointestinal (GI) side-effects i.e. nausea and diarrhoea although the statistical significance of this is not published. The adverse outcomes reported in the older groups were similar to the original study cohorts published. With the Risedronate trials there appeared to be no significant increase in adverse events involving the GI in the treated group versus the placebo group.
The Teriparatide subgroup study [39] did not specifically report the above prespecified adverse outcomes except the number of patients with at least 1 adverse event which was not different compared to placebo or between age groups. The study reported relevant treatment-emergent adverse events (TEAEs) with an incidence >3% in any treatment group and all TEAEs with significant treatment-by-age interaction (TAI) in patients younger than 75 versus those 75 and older. The TAI were similar between the age groups except for cataracts, deafness, pruritus and weight loss (commoner in the younger) and diarrhoea (commoner in the older) (TAI p<0.05). There was no increase in TEAEs compared to placebo in the older age group. Instead, the study reports statistically significant favourable outcomes compared to placebo in back pain (15% vs 25%), cataract (2% vs 10%) and pruritus (0% vs 5%) compared to placebo (p<0.05).

There are no published studies on adverse outcomes in the older age group for Alendronate or Clodronate. The main adverse outcomes described in the original cohort studies were mainly gastrointestinal i.e. nausea and dyspepsia.

Discussion

The current evidence

There is a significant paucity of evidence-based literature on randomised controlled trials in older patients with only some studies including patients over 75 years but the numbers are often small and infrequently analysed as subgroups. Hence, reliance on pooled analysis is required. There are published safety data for Strontium Ranelate, Risedronate and Teriparatide which demonstrate relative safety in the older age groups.

There is acceptable evidence to recommend the bisphosphonates (Risedronate and Alendronate), Strontium Ranelate or Teriparatide for vertebral fracture risk reduction. There are demonstrated benefits for Risedronate, Teriparatide and Strontium Ranelate; and data are consistent with randomised controlled trials in all younger age groups which demonstrate a significant early onset of benefit within 12 months with Teriparatide and Risedronate. There are no one year vertebral fracture endpoints for Alendronate or Clodronate. At three years, there is evidence for sustained benefit in vertebral fracture reduction with Risedronate, Strontium Ranelate and Alendronate with all three agents having similar relative risk reduction. There is no evidence for Teriparatide or Clodronate at 3 years in this age group.

Non-vertebral fracture data are limited. Most evidence is available for Strontium Ranelate which demonstrated a significant reduction in non-vertebral fractures in women 80 years or older by one year with a sustained benefit of 31% at three years. The 1 year study with Teriparatide and the 3 year pooled study with Risedronate demonstrate no benefit in non-vertebral fracture reduction. The main limitations in interpreting the significance of these latter 2 studies are that they are subgroup analyses with secondary endpoints and not powered to assess efficacy. In the Risedronate pooled study [38], the evidence indicates that patients aged 80 and over had an even more severe degree of osteoporosis than younger patients in this study. Despite this finding, only the younger group aged <80 years (mean age 72±5.5) demonstrated a reduction in non-vertebral fractures (p=0.025) at 3 years. The findings in the HIP study were similar with no demonstrated benefit in the older cohort, although the inclusion criteria of the older group without the requirement for demonstrated osteoporosis may be a limiting factor. Notwithstanding this, the lack of demonstrated benefit in older compared with younger cohorts raises questions about the difference in risk and effective pharmacological measures required to manage non vertebral fracture risk in older cohorts compared to younger cohorts. There are no published data for Alendronate and Clodronate. Based on the current evidence, Strontium Ranelate is the only agent with demonstrated benefit in non-vertebral fracture reduction in older women (>80 years).

Evidence for hip fracture reduction is also limited. The TROPOS study (Strontium Ranelate) was powered to assess non-vertebral fracture as an endpoint. The subgroup analysis of patients over 74 years of age and at high risk of hip fracture was the only study to demonstrate a reduction in hip fracture in this age group. The HIP study (Risedronate) and Clodronate study specifically enrolled older patients and were powered to assess hip fracture as an outcome. However, there was no demonstrated hip fracture benefit in either study. The main limitation of both of the latter two studies was that enrollment of the older cohort was contingent on risk factors for hip fracture and did not require patients to be osteoporotic based on traditional BMD criteria and fracture history. Strontium Ranelate is the only agent with demonstrated benefit in hip fracture reduction in a high risk older subgroup.

The discrepancy in non vertebral fracture and hip fracture reduction between younger and older individuals may reflect differences in skeletal factors [52] and non-skeletal risk factors e.g. increased risk of falling with increasing age [53,54]. Osteoporosis of old age, “senile osteoporosis” as described by Riggs et al. [52], may need to be distinguished from other types of osteoporosis. Hip fracture is the predominant fracture after the seventh decade of life [23,24] and the strength of the hip neck area is reliant on preserved osteoblastic activity. Bone formation at this site is often impaired by the ageing process. By contrast, the incidence of fractures owing to increasing osteoclastic activity, a typical feature of post-menopausal osteoporosis, decreases in the older population. [55]. This may explain some of the potential difference in benefit of current antiresorptive agents in younger women with predominantly high bone turnover osteoporosis and older women with “senile osteoporosis”. Hence, reducing bone remodelling rates without improving bone formation rates may be inadequate in older populations who sustain predominantly non-vertebral plus hip fractures and less frequent vertebral fractures compared with younger age groups.

Strontium Ranelate has weaker antiresorptive properties compared to bisphosphonates, but similar benefits in fracture reduction. Although the exact mechanism of action of Strontium Ranelate is unknown, it may have some anabolic effects on bone that may explain its unique benefit in fracture reduction in the older age group [46,56,57]. Teriparatide is a potent anabolic agent with demonstrated benefit in improving BMD and reducing vertebral and non vertebral fracture risk in studies [47]. Its main role may be to treat severe osteoporosis with very low BMD or recurrent fragility fractures. Older patients fit this description extremely well.
in terms of risk. However, there are very limited and only short term data in this group. The magnitude of benefit demonstrated as early as 1 year i.e. relative risk reduction of 65% which was non-
inferior to treatment in younger age groups of patients with prior
fragility fracture is promising.

The cost effectiveness of treating older women with currently
available agents has been demonstrated in numerous analyses [34–
36] but is based on the assumption that this population responds
similarly to treatment compared to younger study populations. One
study suggested that the age-specific intervention threshold for cost-
effectiveness was exceeded in every person 80 years of age or older
without any further risk stratification [36]. The National Institute for
Clinical Excellence (2007 – Technology Appraisal Guidance 87)
recommends that women aged 75 and older with prior fragility
fracture should be offered antiresorptive treatment without further
risk stratification (secondary prevention). Based on current literature,
it is not possible to make this recommendation for bisphosphonates
in primary prevention in view of the findings of the study by McClung et
al. [42] and McCloskey et al. [41] which suggested that age and risk
factors alone in women over 80 years and 75 years respectively,
without pre-existing fracture, was not adequate to justify Risedronate
or Clodronate treatment. This hypothesis has not been tested for
Teriparadise or Strontium Ranelate. It may be more important in the
older individual to consider multifactorial intervention strategies to
address fracture risk.

Fracture is a consequence of a triad of factors including bone
quality, a precipitating event, e.g. fall or trauma and the interphase
between the bone and the contact surface. In older individuals,
falls is a significant factor in fracture presentation and is probably
the strongest single risk factor [58–60] in over 90% of hip fractures.
Improving calcium and vitamin D status [61], and the use of hip protectors [62–64] are demonstrated as important
adjunctive strategies.

Conclusions

Teriparadise, Risedronate, Alendronate and Strontium Ranelate
demonstrate significant benefit in vertebral fracture reduction but
Strontium Ranelate is the only agent to date that demonstrates
reduction in non-vertebral and hip fracture events in a high risk
elderly female population.

This review reinforces the irony that the least evidence is
available for fragility fracture reduction in the group at
greatest risk, who are likely to sustain the greatest potential harm in terms
of disability and mortality and at the greatest cost to society.

Randomised controlled trials to provide more robust evidence for
treatment of this patient group, who are likely to place increasing
demands on limited per-capita health care resources in future
decades, are needed. Older individuals have unique needs and
differ quite significantly from younger populations in terms of their
fragility fracture risk and new pharmacological strategies need to
be explored. It is important that physicians apply a multi-factorial
and multi-disciplinary approach to fracture reduction in addres-
sing the triad of osteoporosis, falls risk and reducing the impact
of injury.

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Sarcopenia: etiology, clinical consequences, intervention, and assessment

T. Lang · T. Streeper · P. Cawthon · K. Baldwin · D. R. Taaffe · T. B. Harris

Abstract The aging process is associated with loss of muscle mass and strength and decline in physical functioning. The term sarcopenia is primarily defined as low level of muscle mass resulting from age-related muscle loss, but its definition is often broadened to include the underlying cellular processes involved in skeletal muscle loss as well as their clinical manifestations. The underlying cellular changes involve weakening of factors promoting muscle anabolism and increased expression of inflammatory factors and other agents which contribute to skeletal muscle catabolism. At the cellular level, these molecular processes are manifested in a loss of muscle fiber cross-sectional area, loss of innervation, and adaptive changes in the proportions of slow and fast motor units in muscle tissue. Ultimately, these alterations translate to bulk changes in muscle mass, strength, and function which lead to reduced physical performance, disability, increased risk of fall-related injury, and, often, frailty. In this review, we summarize current understanding of the mechanisms underlying sarcopenia and age-related changes in muscle tissue morphology and function. We also discuss the resulting long-term outcomes in terms of loss of function, which causes increased risk of musculoskeletal injuries and other morbidities, leading to frailty and loss of independence.

Keywords Aging · Falls · Imaging · Muscle strength · Sarcopenia · Skeletal muscle

Introduction

Skeletal muscle contractions power human body movements and are essential to maintaining stability. Skeletal muscle tissue accounts for almost half of the human body mass and, in addition to its power generation role, is a crucial factor in maintaining homeostasis of glucose metabolism. Given its central role in human mobility and metabolic function, any deterioration in the contractile, material, and metabolic properties of skeletal muscle has an extremely important effect on human health. Because the population in the USA aged 65 and over is expected to approximately double over the next 15 years [1], age-related losses in skeletal muscle mass and function present an extremely important current and future public health
issue. Loss of mobility, one of the major consequences of age-related skeletal muscle deterioration, is one of the primary determinants of the need for nursing home care, a public health cost which the US Health Care Finance Administration predicts may exceed 183 million dollars by 2010 [2]. The term coined by I.H. Rosenberg, which is widely used to describe skeletal muscle loss, is sarcopenia, from the Greek roots sarx (flesh) and penia (loss). Although this term is clinically applied to denote loss of muscle mass, it is often used to describe both a set of cellular processes (denervation, mitochondrial dysfunction, inflammatory and hormonal changes) and a set of outcomes such as decreased muscle strength, decreased mobility and function, increased fatigue, increased risk of metabolic disorders, and increased risk of falls and skeletal fractures. In this review, we (1) summarize current understanding of the mechanisms which underlie sarcopenia, (2) relate this information to age-related changes in muscle tissue morphology and function, and (3) describe the resulting long-term outcomes in terms of loss of function, which cause increased risk of musculoskeletal injuries and other morbidities, finally leading to frailty and loss of independence.

Muscle fiber structure and the neuromuscular junction

This section is derived from a number of excellent reviews of muscle cell structure and function [3, 4]. All of the body’s skeletal muscles are composed of multinucleated cells called fibers. Each fiber incorporates the contractile proteins myosin and actin, along with numerous other regulatory proteins, which are organized into thick and thin filaments, respectively. The myosin and actin filaments are arranged in periodic bands within structures called sarcomeres, and a repeated sequence of sarcomeres form tubelike structures called myofibrils. Each muscle fiber contains a large number of parallel myofibrils, and the force generated by the muscle fiber is proportional to the number of myofibrils it contains. Muscles are innervated by motor neurons. In the case of small muscles used for fine motor control, motor neurons may innervate only a few small fibers. In larger muscles, a fiber is innervated by a single branch of a motor neuron, and the motor neuron innervates many muscle fibers. The combination of a single motor neuron and the muscle fibers innervated by its branches is called a motor unit. The hierarchic organization of muscle tissue is diagrammed in Fig. 1.

A skeletal muscle motor unit is activated when a signal is generated in the motor cortex of the brain, traveling though the spinal cord, and is transmitted as an action potential through the motor neurons to each fiber in the motor unit, resulting in a simultaneous contraction of the fibers. When the nerve impulse reaches the junction between the motor neuron branch and the fiber, acetylcholine is released from the axon end of the neuron. A wave of electrical changes are produced in the muscle cell when the acetylcholine binds to receptors on the fiber cell surface, causing release of calcium from the sarcoplasmic reticulum, which activates the contractile machinery to generate power.

The power generated in a muscle contraction is provided by the interaction of the actin and myosin components within the sarcomere. In the broadest terms, this occurs when the myosin component attaches to the actin framework. Following a sequence of chemical transformations via actin-induced breakdown of adenosine triphosphate (ATP), free energy is released to generate both force production and movement of actin within the sarcomere, thereby causing the whole muscle to generate force and movement. Several reviews describing this process are provided in the following references [5–12].

Motor units are differentiated into three main types based on the specific type of myosin expressed in the fibers. Slow motor units contain the smallest number of fibers and consist of type 1 myosin, which transduces energy at a relatively slow rate. Thus, these fibers/motor units contract with relatively slow velocity. Type I fibers in slow motor units are especially rich in mitochondria and myoglobin, which make them reddish in color and which allow for a high capacity for sustained delivery of ATP from oxidative metabolism of triglycerides and carbohydrate. The oxidative ATP synthesis process characteristic of type I fibers is relatively slow to ramp up and can be sustained for long periods of time, making these motors units well-suited for sustained aerobic exercise such as distance running. Additionally, the low contraction velocity means that these slow motor units are also heavily recruited in precise finite motor activities and in opposing gravity. Fast fatigable motor units generate more force and have higher velocities than slow motor units, both because they have the highest number of fibers and because the individual fibers have the largest cross-sectional area (CSA) and the highest contractile velocity. These motor units express type IIx myosin, which transduces energy at a faster rate than type I myosin. These fibers are relatively poor in mitochondria, and the primary source of ATP is through glycolysis of glycogen, which can provide considerable energy over a relatively short time period. Fast fatigable motor units are typically recruited during activities such as weightlifting or sprinting, which require maximal power generation. In addition, there is a third type of motor unit, the fast fatigue-resistant motor unit, which transduces energy at a rate which is intermediate between slow and fast fatigable motor units. Fast fatigue-resistant motor units contain type IIa myosin and are intermediate in CSA between type I and type IIx and are also intermediate in
terms of the number of fibers and in velocity of contraction. Contractile force, normalized by CSA, is similar across fiber types, but the maximum power, normalized for fiber CSA, of the fast fatigable motor units is at least four times greater due to the higher contractile velocity compared to the slow type I motor units.

Age-related changes in muscle contractile properties

The term “sarcopenia” has been employed to describe the loss of muscle tissue that occurs over a lifetime and is also commonly used to describe its clinical manifestation as well. Age-associated processes bring about changes in the mass, composition, contractile properties, and material properties of muscle tissue, as well as in the function of tendons. These changes translate to alterations in muscle power, strength, and function, leading to reduced physical performance, disability, increased risk of fall-related injury, and, often, frailty. This section will provide a brief review of some of the age-related changes that affect the contractile and material properties of muscle as well as the function of tendons.

Age-related changes in muscle morphology

The age-related loss of muscle mass results from loss of both slow and fast motor units, with an accelerated loss of fast motor units. In addition to the loss of fast motor units, there appears to be fiber atrophy, or loss of CSA, of type II fast glycolytic fibers [13, 14]. As motor units are lost via denervation, an increased burden of work is transferred to surviving motor units, and as a potential adaptive response, remaining motor units recruit denervated fibers, changing their fiber type to that of the motor unit. Thus, there is a net conversion of type II fibers to type I fibers, as the type II fibers are recruited into slow motor units (Fig. 2). As a result, although there is relatively little change in the average CSA of type I fibers, the percentage of the total muscle cross-sectional area occupied by type I fibers tends to increase with age, whereas not only are type II fibers lost but the CSA and the aggregate power-generating capacity of the remaining fibers also decrease dramatically. Finally, while in young muscle tissue there is a mosaic-like appearance corresponding to presence of both types of fibers, in aged muscle, the recruitment of denervated fibers by surviving motor units causes a clustering of similar fiber types [13, 14].

The loss of both type I and accelerated loss of type II fibers results in sharp age-related changes in muscle function. The loss of fast motor units and the concomitant loss of type II fibers result in loss in muscle power necessary for actions such as rising from a chair, climbing steps, or regaining posture after a perturbation of balance. The extent of skeletal muscle power loss with age has been confirmed by studies of cycle ergometry in which the cycle velocity at maximal power was measured. In a study of human volunteers ranging in age from 20 to 90 years, Kostka et al. found that velocity at maximal power decreased by roughly 18% between ages 20–29 and 50–59 and by a further 20% between 60–69 and 80–89 [15]. In addition to studies examining muscle power and contrac-
tion velocities, other studies have cross-sectionally examined age-related changes in strength, showing strength declines as great as 30–35% [16]. These alterations in strength have been linked primarily to declines in muscle mass as well as reductions in power per unit area and force per unit area, as nonmuscle tissue components replace lost muscle fiber [17].

Another morphologic aspect of aging skeletal muscle is the infiltration of muscle tissue components by lipid, which can be contained within adipocytes as well as deposited within muscle fiber. The aging process is thought to result in increased frequency of adipocytes within muscle tissue. As with precursor cells in bone marrow, liver, and kidney, muscle satellite cells can express both adipocytic and a myocytic phenotypes, and recent studies have reported that expression of the adipocytic phenotype is increased with age [18–21]. This process is still relatively poorly understood in terms of its extent and spatial distribution. Another well-known source of adiposity in muscle tissue is through increased deposition of lipid within muscle fibers [22–28]. This type of lipid distribution, often referred to as intramyocellular lipid, may result from net buildup of lipid due to reduced oxidative capacity of muscle fibers with aging [22, 29].

Neurologic underpinnings of muscle atrophy

The correct functioning of motor neurons is essential to the survival of muscle fibers. Age-related neurodegeneration may contribute importantly to the effects of age on muscle structure, including loss of muscle fibers, atrophy of muscle fibers, and increased clustering of muscle fibers as denervated fibers are recruited into viable motor units. Multiple levels of the nervous system are affected by age, including the motor cortex (beyond the scope of this review), the spinal cord, peripheral neurons, and the neuromuscular junction. Within the spinal cord, there is a substantial decline in the number of alpha motor neurons, and there may be a preferential loss in those motor neurons supplying fast motor units. Other reports have noted age-related losses in peripheral nerve fibers and alterations of their myelin sheaths. Finally, age-related changes have been noted in the neuromuscular junction, with reduced number [30] but increased size of terminal areas and a reduction in the number of synaptic vesicles [31]. Others have noted increases in the amount of neurotransmitters released in nerve impulses and increased sprouting and branching of terminal axons, all of which may serve as an adaptive mechanism underlying the ability of viable motor units to recruit denervated muscle fibers [32].

Key factors in age-related changes in protein balance

Skeletal muscle is characterized by a dynamic balance between the synthesis of protein from free amino acids in the cellular milieu and the dissociation of muscle protein into free amino acids. Maintenance of muscle mass requires that the rate of synthesis be in balance with the rate of degradation; over time, deficits can result in severe muscle loss. Aging is associated with decreased expression of hormonal factors that
promote protein synthesis and increased expression of both endocrine and inflammatory factors that contribute negatively to protein balance by increasing protein degradation. Figure 3 summarizes the role of endocrine, inflammatory, and other factors in protein synthesis.

**IGF-1**

Insulin-like growth factor 1 (IGF-1) is a well-known promoter of protein synthesis in skeletal muscle. Skeletal muscle fibers have a set of transmembrane receptors that bind insulin and IGF-1 to regulate proliferation, differentiation, and fusion of skeletal muscle precursor cells [33]. There are two primary sources of IGF-1. Mature IGF-1 is produced systemically by the interaction of growth hormone (GH) with the liver. The other source of IGF-1 is within the skeletal muscle itself, with two primary variants [34], including one which is produced in response to physical activity and is referred to as mechano growth factor and one which is similar to the mature IGF-1 produced within the liver [35, 36]. IGF-1 binds to receptors on skeletal muscle cell surfaces and activates a complex array of cell signaling pathways which are anabolic, anticatabolic, and antiapoptotic [37]. This age-related decline stems both from the decline of growth hormone, which results in reduced liver IGF-1 production as well as a reduction in the ability of skeletal muscle cells to produce IGF-1 locally. Therefore, the age-related decline in IGF-1 production is linked to age-related reductions in protein synthesis and muscle cell function. Finally, loss of IGF-1 may also compromise motor neuron function in aging. IGF-1 overexpression in transgenic mice has been reported to protect against age-related changes in the neuromuscular junction [38], and in other reports IGF-1 was found to be instrumental in transforming nerve action potential to the release of calcium ion from the sarcoplasmic reticulum [39].

**Age-related changes in inflammatory factors**

In chronic inflammatory diseases associated with muscle atrophy, such as cancer cachexia and autoimmune disorders, muscle cell protein degradation is accelerated, and muscle protein synthesis appears to be diminished [40, 41]. The ubiquitin–proteasome pathway is the most important mechanism for protein degradation in skeletal muscle cells. This system involves a series of enzymatic steps in which the degraded proteins are first targeted by an enzyme system that binds the target protein to the polypeptide ubiquitin. These ubiquitinized proteins are then transferred to the proteasome complex and degraded into short peptides and are finally recycled as free intracellular amino acids [42]. This pathway is promoted by inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), by hormones such as cortisol and angiotensin, as well as by reactive oxygen species.

Increased expression of these inflammatory cytokines also appears to be common in aging in skeletal muscle.

**Fig. 3** Age effects on systemic factors influencing synthesis and degradation of skeletal muscle proteins
Comparison of skeletal muscle biopsies from younger and older subjects showed increased expression of genes upregulated by inflammatory factors [43]. Levels of catabolism-inducing hormones such as cortisol have also been shown to increase with age, and cortisol is linked to increased expression of IL-6 and TNF-α. Increased TNF-α expression is also known to stimulate muscle atrophy through apoptosis. Apoptosis contributes to the loss of myonuclei in skeletal muscle cells and could theoretically result in the loss of complete fibers in sarcopenia [44].

Oxidative damage

Oxidative metabolism generates reactive oxygen species (ROS), and these metabolic products are thought to accumulate over time, altering and damaging cell components, particularly mitochondria and DNA sequences [45]. Because mitochondria produce ROS, they are subject to alterations in their structure and in their DNA. Alterations to mtDNA are known to increase with age in skeletal muscle, and the frequency of abnormal mitochondrial regions is higher in those muscles which are strongly affected by sarcopenia [45–47]. The role of mitochondrial DNA alterations in age-related loss of skeletal muscle function is under intense investigation, focusing on their roles in causing skeletal muscle cell apoptosis and structural abnormalities that affect metabolic function. Structural alterations to mitochondria may affect the electron transport chain, compromising respiration. Although the loss of maximal oxygen consumption (VO2 max) with age has been primarily attributed to loss of muscle mass and reduced cardiac output, altered mitochondrial metabolism, leading to poorer muscle cell respiration, may also be involved.

Intrinsic changes to skeletal muscle

One potential mechanism for sarcopenia involves the loss of muscle regenerative capacity due to loss in the number and function of muscle satellite cells, which proliferate and differentiate into skeletal muscle fibers. Some studies have observed declines in the numbers of muscle satellite cells in both rodents and humans [48], with others reporting that this decline was larger in muscles containing primarily type II fibers than in those containing type 1 fibers [49]. However, other studies have failed to observe a change in satellite cell number with age, and others have even reported slight increases [50]. There is some evidence that failure of muscle tissue to regenerate may involve age-related changes in the molecular regulators, called myogenic regulatory factors (MRFs) of muscle satellite cell proliferation and differentiation, rather than in the number of satellite cells. In general, studies that have compared the expression of MRFs such as myogenic determination factor (myoD), myogenic regulatory factor 5, and myogenin in rats have found that expression of these factors is decreased in older compared to younger skeletal muscle [51]. Human studies have shown impaired differentiation of myoblasts, which has been associated with reduced or delayed expression of these factors [52]. Another factor in the behavior of muscle satellite cells is myostatin, which is thought to suppress differentiation and proliferation of myocytes by suppressing the expression of MRFs such as myoD and myogenin [53]. While there is considerable work which has demonstrated that myostatin suppression may have therapeutic potential for combating muscle wasting, the effect of age on myostatin expression is still under active investigation. Some investigations using rat models have found that myostatin mRNA levels have remained constant with age [54], while others observed age-related increases [55]. With respect to studies in human models of muscle wasting, there is similar variance in findings, with one cross-sectional study reporting no change in myostatin expression in the vastus lateralis muscle between young and older men [56], while a similar study in women found a 56% increase in myostatin expression in the vastus lateralis [57]. Thus, while myostatin is an important target in combating muscle wasting, the role of age-related changes in myostatin expression is still a controversial subject.

Age-related changes in the stiffness of the muscle–tendon system

When considering age-related losses in performance, it is important to take into account that muscle and tendons act as a unit. Human motion requires the transmission of contractile forces generated in skeletal muscle tissue through the tendons to the skeleton. Thus, age-related alterations in mobility are not only a function of changing skeletal muscle contractile properties but also of the mechanical properties of the tendons which operate in series with the muscle. A loss in tendon stiffness with age, for example, would reduce the rate of force development caused by skeletal muscle contraction, whereas increased tendon stiffness with age would tend to counteract the age-related decrease in skeletal muscle contractile function.

Animal studies of age effects on tendon mechanical properties have yielded variable results, with some studies showing increased stiffness with age [58], while other studies have shown decreased stiffness with age [59, 60] or little to no effect of age on tendon stiffness [61]. Narici et al. have pointed out that some of this variability may be attributable to differences in the age range between animal groups as well as due to measurement artifacts associated
Clinical manifestations of sarcopenia

With aging, multiple processes occurring within muscle tissue, such as denervation, changes in the hormonal and inflammatory environment, mitochondrial dysfunction, and changes in the expression of regulatory factors affecting the fate of satellite cells, combine to produce losses in the bulk properties of muscle tissue such as muscle mass and strength. Among the elderly, these changes may eventually result in loss of mobility and independence and increased risk of injury.

Loss of muscle power

Age-related loss of skeletal muscle contractile power, which is essential to human motions such as rising from a chair or climbing a flight of stairs, is one of the clinical consequences most commonly linked with sarcopenia. The decline in muscle power has been established in both genders, under multiple loading conditions, in multiple limbs, and in both cross-sectional and longitudinal studies [17]. The most important anatomic sites for muscle function measurement have primarily been in the lower body, as the muscles in these sites are critical for daily function and allow for closest comparison to biopsy data. Further, power and strength losses in the lower limbs confer the largest risk factors for falls and other sources of injury and disability [66, 67]. Lower-limb power and strength are often measured using knee extension and flexion. Measurements can be isotonic, changing the length of the muscle fibers against constant resistance, isokinetic, in which fibers are shortened or lengthened at fixed velocity, or isometric, in which fiber length remains constant in the presence of a force greater than the muscle is capable of counteracting. Isokinetic and isotonic measurements of knee extension and flexion, in that they involve translating a weight along an arc of motion within a given time interval, are measures of muscle power (although they are mostly reported as joint torques in feet pounds or Newton meters) whereas isometric measurements involve purely the ability to generate force. Because these loading conditions are more relevant to human motion, most studies have reported results of isokinetic and isometric exercise. Table 1 summarizes results of cross-sectional studies of lower-extremity muscle function [68–73]. In cross-sectional studies comparing young normal subjects in the 20–40-year age range to healthy elders in the 70–80-year age range, declines in knee extensor torque and power have ranged from 20% to 40%, with greater losses in the 50% range reported for individuals in their 1990s [74–78]. Over the lifetime, men have inherently greater knee extensor power and torque than women, but on a percentage basis, age-related losses are similar between genders, with losses in men incurring greater absolute losses because they start with higher baseline values. Compared to the abundance of cross-sectional studies, there are fewer longitudinal studies of knee extensor properties with aging. Hughes et al. examined a cohort of 52 elderly men and 68 women who had been examined 10 years earlier, finding similar declines in the knee extensors and flexors ranging from 12% to 18% per decade [79]. Longitudinal studies of smaller cohorts have shown variable results, with one study reporting losses of roughly 3% per year in 23 men aged 73–86 at baseline [80], and another study which reported no changes in strength of either men or women over an 8-year follow-up [81]. Cross-sectional studies of isometric measurements of ankle plantar flexion have shown age-related declines similar to those measured for knee extension torque and power. Studies of age-related muscle strength in the upper extremities show essentially similar results to the lower extremities, with cross-sectional studies reporting declines of 20–40% in measures such as hand-grip strength and elbow extension torque between healthy younger subjects and elderly subjects and longitudinal studies showing yearly declines ranging from 1% to 5% [17].

Loss of skeletal muscle mass

Loss of skeletal muscle mass with age has been documented by lean body mass measurements with dual X-ray absorptiometry (DXA) and with muscle cross-sectional areas quantified by three-dimensional imaging methods
such as X-ray computed tomography (CT) or with magnetic resonance imaging (MRI). Leg lean tissue mass by DXA, a marker for skeletal muscle mass, decreases by roughly 1% per year in longitudinal studies [17], a value roughly threefold smaller than the loss of skeletal muscle strength. Studies which assess muscle mass through CSA measurement have found that CSA decreases by roughly 40% between 20 and 60 years, with the reported amount varying with imaging technique, skeletal site, and gender [9, 16]. Measurements of the CSA of the quadriceps muscle using CT have shown decrements of around 25–35% between older subjects and young normal controls [82]. Large cross-sectional studies including both older men and women have found that men, on average, have larger muscle mass and cross-sectional area values than women but that the largest cross-sectional age-related changes occurred in men. This potential gender difference in age-related loss of muscle mass may reflect differences in the pattern of age-related changes in testosterone, growth hormone, and IGF-1 [17].

Risk factors conferred by decrements in muscle power and mass

Prospective cohort studies have demonstrated the association of age-related loss of muscle strength and mass with adverse clinical outcomes in the older population, including falls, mobility limitations, incident disability, and fractures [66, 67, 83]. Moreland et al. have carried out a meta-analysis summarizing the relation of upper- and lower-body weakness to falls [67]. Measures of lower-body weakness, defined as increased chair stand time and reduced knee extension strength, have been correlated to incidence of any fall with odds ratios ranging from 1.2 to 2.5, to injurious falls with odds ratios around 1.5, and to recurrent falls with much higher odds ratios, ranging from 2.2 to 9.9. Upper-body weakness, which is typically assessed using hand-grip strength or manual muscle testing, is also correlated to fall incidence, with odds ratios for incident falls ranging from 1.2 to 2.3 and for recurrent falls with odds ratios of 1.4–1.7. Clearly, lower-extremity weakness is a better predictor of falls than weakness of the upper body. Other studies have explored the mechanisms by which impaired muscle strength relates to falls by analyzing the effect of muscle strength in single-step recovery from a forward fall [84–87]. This may be simulated by leaning subjects forward and then releasing them, measuring muscle activation, joint kinetics, and other characteristics as the subjects step forward after release. Multiple studies have found that older individuals have discernible differences in these measurements. Thelen et al. compared muscle activities in young and elderly subjects and found that the latter showed delays in activating the hip flexors and knee extensors during the period in which the stepping leg is swung into position [84, 85]. Wojcik et al. found that elderly adults generate lower hip flexion and extension torques than young adults during single-step recoveries after being placed at a forward lean angle [86, 87]. Thus, there is evidence that reduced strength of the hip and other lower-leg muscles, in addition to impaired neuromuscular activation, may be implicated in poor recovery from falls. In addition to falls, muscle weakness and reduced muscle mass have been associated with incident disability. The Health, Aging, and Body Composition Study investigators carried out studies of body composition, muscle strength, and other risk factors on incident mobility limitation, defined as inability to walk a quarter mile or climb a flight of ten stairs. Visser et al. observed that low-thigh muscle CSA measured at baseline resulted in a 45% and 34% increased risk of mobility limitations 5 years later in men and women, respectively [88]. For low-knee extensor power and torque, the risk of incident mobility limitation was even higher, at 66% and 69% for men and women, respectively [88]. The same study found that men and women in the lowest quartile of thigh muscle cross-sectional area and leg muscle mass had a 30–40% increase of risk for the inability to carry out the activities of daily living. For major disability, which includes inability to carry out activities of daily living, inability to walk a

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Measurement/joint/movement</th>
<th>Age range (years)</th>
<th>Study design</th>
<th>Changes with aging&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean et al. 2004 [73]</td>
<td>F</td>
<td>IK/hip/FLX, EXT</td>
<td>21–82</td>
<td>CS</td>
<td>22–33%</td>
</tr>
<tr>
<td>Johnson et al. 2004 [72]</td>
<td>F</td>
<td>IK, IM/hip/AD, AB</td>
<td>21–91</td>
<td>CS</td>
<td>24–34% IK, 144–56% IM</td>
</tr>
<tr>
<td>Kubo et al. 2007 [71]</td>
<td>M</td>
<td>IM/ankle/PF</td>
<td>20–77</td>
<td>CS</td>
<td>140%</td>
</tr>
<tr>
<td>Morse et al. 2005 [70]</td>
<td>M</td>
<td>IM/ankle/PF</td>
<td>25.3±3.5–73.8±3.5</td>
<td>CS</td>
<td>47%</td>
</tr>
<tr>
<td>Lanza et al. 2003 [68]</td>
<td>M</td>
<td>IT, IM/knee, ankle/EXT, DF</td>
<td>20–85</td>
<td>CS</td>
<td>26–32%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Expressed as percent change with aging

K isokinetic, IM isometric, IT isotonic, FLX flexion, EXT extension, AD adduction, AB abduction, PF plantar flexion; DF dorsiflexion, CS cross-sectional

Table 1: Age-related changes in muscle power and muscle strength
quarter mile, or climb ten steps, low-thigh CSA increased risk by 40% whereas low-knee extensor strength resulted in over a doubling of the risk. These subjects were also followed up for incident hospitalizations, and low-thigh CSA and muscle strength showed a similar predictive power for this outcome. Thigh muscle cross-sectional area and knee extension torque have also been shown to correlate to incident hip fracture in the Health ABC study [89]. Lang et al. observed that knee extension torque and low cross-sectional area individually resulted in increased risk of incident hip fracture by 50–60%, independent of bone mineral density (BMD).

The increased risk of mobility loss and injury resulting from loss of muscle mass and power are part of a vicious cycle which is amplified with age. In addition to reductions in performance, the intermediate consequences of muscle loss include reductions in metabolic rate and aerobic capacity. The loss of power and endurance increase the difficulties associated with procuring adequate nutrition and increase the effort required to undertake exercise. The combination of nutritional loss and reduced physical activity levels results in further loss of muscle mass and power, exacerbating the process of sarcopenia. The resulting decrements in power, endurance, and physical performance, if unchecked, then lead to a loss of independence which may or may not be preceded by injury or illness, for example a fall and/or fracture.

Treatments for sarcopenia

Exercise

Many studies have documented that exercise provides benefits extending across multiple physiological systems in the aged population. Resistive training, also known as weight or strength training, can be used to counteract age-related muscle loss by increasing the number and cross-sectional areas of skeletal muscle fibers. Increases of 11.4% in mid thigh muscle CSA and greater than 100% in knee extensor torque were reported by Frontera et al. in a cohort of elderly men who had undergone 12 weeks of high-intensity resistance exercise training [90], with similar changes observed in a subsequent study in women by Charette and colleagues [91]. Moreover, resistance exercise even has benefits when it is not routinely performed. A recent study by Henwood and Taaffe documented that resistive exercise can produce sustained increases in knee extensor torque even after periods of deconditioning following cessation of exercise [92]. The benefits of resistive exercise have been shown to extend even to frail populations. Increases of 3–9% in muscle CSA, doubling of muscle strength, and improvement in functional performance indices have been reported in nursing home populations after bouts of progressive resistance training [93, 94]. Resistive exercise has been shown to be well tolerated in the elderly and is of value in the prevention of falls and loss of mobility. The time and equipment requirements to undertake a program of resistive exercise are modest, with sessions of 30 min, twice per week, using either exercise machines or body weight and elastic bands. Finally, resistive exercise has been shown to result in improvement in a range of different clinical conditions common in elderly people, including osteoporosis, osteoarthritis, heart disease, diabetes, and depression. A summary of relevant literature on exercise and pharmacologic intervention in the elderly is presented in Table 2.

Hormone replacement

In elderly men, epidemiologic studies generally support a relationship between declines in testosterone levels with age and loss of muscle strength and functional status [95]. Menopause and age-related reduction of estrogen levels in

Table 2  Studies examining various interventions for age-related muscle loss

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Gender</th>
<th>Age</th>
<th>N</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solerte et al. (2008) [149]</td>
<td>S</td>
<td>M, F</td>
<td>66–84</td>
<td>41</td>
<td>AA supp.</td>
<td>↑Lean mass, ↓IGF-1, ↓TNF-α</td>
</tr>
<tr>
<td>Trappe et al. (2000) [150]</td>
<td>E</td>
<td>M</td>
<td>74±2</td>
<td>7</td>
<td>RT</td>
<td>↑S; ↑MHC I</td>
</tr>
<tr>
<td>Trappe et al. (2001) [151]</td>
<td>E</td>
<td>F</td>
<td>74±2</td>
<td>7</td>
<td>RT</td>
<td>↑S</td>
</tr>
<tr>
<td>Slivka et al. (2008) [152]</td>
<td>E</td>
<td>M</td>
<td>80–86</td>
<td>6</td>
<td>RT</td>
<td>↑S, ↓CSA</td>
</tr>
<tr>
<td>Fiatarone et al. (1990) [93]</td>
<td>E</td>
<td>M</td>
<td>90±3</td>
<td>10</td>
<td>HIRT</td>
<td>↑S, ↑CSA</td>
</tr>
<tr>
<td>Frontera et al. (2003) [154]</td>
<td>E</td>
<td>F</td>
<td>68–79</td>
<td>14</td>
<td>RT</td>
<td>↑S, ↑CSA</td>
</tr>
<tr>
<td>Wittert et al. (2003) [155]</td>
<td>E</td>
<td>M</td>
<td>60–86</td>
<td>76</td>
<td>TE</td>
<td>↔S, ↑CSA</td>
</tr>
</tbody>
</table>

S sarcopenia, E elderly, Myo-29 a myostatin inhibiting drug, AA Supp amino acid supplement, RT resistance training, HIRT high-intensity resistance training, TE testosterone, S strength, CSA muscle cross-sectional area, IGF-1 insulin-like growth factor 1, TNF-α tumor necrosis factor alpha, MHC I, myosin heavy chain type I isoform
women may also impact muscle strength because estrogen is converted to testosterone, which has an anabolic effect on muscle protein synthesis. Further, both sex hormones may suppress inflammatory cytokines that exert catabolic effects on muscle. Thus, hormone replacement has always received considerable interest as a therapy for sarcopenia. In women, trials of estrogen and testosterone therapy have failed to yield any meaningful increases of muscle strength [96]. Studies of testosterone replacement therapy in men has had mixed results, depending on age of the subjects. Several studies have shown that administration of testosterone in hypogonadal younger men produced significant increases in lean body mass and muscle strength [97–99]. Strength increases ranged from 20% to 60% but tended to be smaller than the increases produced by resistive exercise training. Anabolic effects of testosterone therapy on older hypogonadal men tend to be weaker, with most studies reporting minimal changes in body composition and no increases in muscle strength [96]. However, some studies have reported moderate strength improvements ranging from 10% to 25%, but unlike the negative results, all of these trials lacked control groups. However, it should be noted that testosterone is administered to older men in much lower doses than to younger men because of increased risk of prostate cancer and other side effects [96].

Considerable interest has also been devoted to testing the effect of GH on sarcopenia. Growth hormone exerts an indirect anabolic effect on muscle by stimulating production of IGF-1 in the liver. Levels of growth hormone are systematically lower in the elderly, and thus it was hypothesized that GH would be effective in combating muscle loss in elderly subjects. However, most studies have shown that GH treatment is ineffective in the elderly, both from the standpoint of muscle mass and muscle strength. The failure of GH treatment to augment muscle strength in elderly subjects has led to other approaches, such as treatment with growth-hormone-releasing hormone, which was found to increase GH production and produce moderate increases in muscle strength [96–100]. Additionally, others have tried direct administration of IGF-1. By complexing IGF-1 to its primary circulating binding protein IGFBP-3, it is possible to significantly increase the IGF-1 dose while eliminating the side effect of hypoglycemia that occurs with IGF-1 alone [101]. Boonen et al. reported that administration of IGF-1/IGFBP-3 to elderly women with recent hip fracture was well tolerated and resulted in increased grip strength [102].

Newer pharmacologic approaches

Among the newer approaches evolving towards treatment of muscle wasting is inhibition of myostatin, which counteracts the myogenic regulatory factors which promote the differentiation and proliferation of myocytes. In animal studies, myostatin blockade using experimental agents and other approaches appears to produce increases in muscle mass and strength in rodent models [103–105]. Another approach involves administration of selective androgen receptor modulators (SARMs). These nonsteroidal agents target the androgen receptor, which is found in sexual organs, skeletal muscle, and bone but have less of a stimulative effect on prostate and other sexual organs, making them a candidate for treatment of frailty in older subjects. These agents have been shown to improve lean body mass in rodent models [106] and are currently in early clinical trials.

Skeletal muscle and bone strength

Maintenance of muscle mass and strength is critical for preservation of physical activity in older age and important for reducing the risks of falls and their most serious consequence, skeletal fractures. However, muscles exert powerful loads on the skeleton, and there is considerable interest in reducing fracture risk by using exercise strategies to increase or at least protect against loss of skeletal mass and strength with age [107]. The use of exercise strategies to strengthen the skeleton is based on the adaptive response of bone to varying mechanical loads as described by Frost, who proposed a homeostatic process governing the balance between bone remodeling, modeling, and repair as a function of varying strains imposed by inputs such as impacts and muscle forces [108]. The relationship between mechanical strains and skeletal tissue responses vary with the skeletal site, but the “set points” that trigger remodeling and modeling responses and thus the overall responsiveness of bone tissue to mechanical loading are modulated by the overall hormonal milieu.

A series of animal experiments have studied the relationships between mechanical strain and bone geometry and strength [109]. These studies have demonstrated the responsiveness of skeletal tissue to dynamic changes in mechanical loading and have shown the importance of the timing as well as the magnitudes of applied loads [110]. Recent studies have also indicated that mechanical loading has an effect on other properties of bone such as fatigue resistance and second moment of inertia that are significantly larger than effects on bone density and mass [111].

However, studies examining the effect of exercise regimes on bone in elderly subjects have indicated relatively modest effects. An excellent review of various exercise strategies on bone health has been published by Suominen [107]. Impact exercise such as walking and aerobic training has a pronounced benefit on overall health, and a small but positive effect on bone mass. However, from an anabolic point of view, resistive exercise seems to
exert more favorable effects for potential improvements of bone strength. High-intensity and progressive trials of resistance exercise have shown significant effects on BMD at vertebral and hip sites. Studies in general have shown that the exercise must be continued to maintain the benefit that the additional gain is lost within a few years of the program if the protocol is not continued.

Assessment of skeletal muscle using imaging

Imaging offers the potential for an anatomic site-specific assessment of multiple targets related to skeletal muscle physiology. Imaging has an important role in research studies of sarcopenia etiology and response to intervention. The primary imaging target in skeletal muscle mass assessment is lean body mass assessment by DXA, which involves use of standard clinical bone densitometers to decompose nonbone tissue into lean and fat body mass components. Measurements may be obtained of total body lean and fat mass as well as regional measures in the central and appendicular skeleton. As this is an extremely widespread and well-known technology, which is commonly used in clinical studies in both bone and muscle research, we will refer the readers to several reviews that lay out the technical considerations for DXA soft tissue assessment [112–116].

CT imaging may be employed to quantify bulk characteristics of muscle and body composition that are highly related to muscle strength and to overall functional ability in the elderly. In particular, CT imaging is widely used to study muscle and fat in epidemiologic studies of body composition. Typically, acquisitions have included single cross sections at the L1/2 or L4/5 intervertebral space to image body fat or volumetric measurements obtained in the abdomen and in the thigh, usually relating to the mid thigh or to a bony landmark [23, 83, 88, 117–121]. As shown in Fig. 4, the key variables quantified include the total muscle CSA of the mid thigh, the CSA values of the quadriceps and hamstrings, the total CSA of subcutaneous fat, and the attenuation coefficients of the total thigh muscle and the hamstrings and quadriceps separately. The CSA values of the total thigh muscle and quadriceps muscle are positively associated with increasing knee extensor strength [118]. The CSA declines with age, as does the muscle strength, and is smaller in females than in males [117–119]. Another property of great interest to the study of sarcopenia is the mean attenuation coefficient [23, 117–119], which is computed within all of the muscle regions after a threshold is applied to exclude depots of fat embedded within each muscle group. In elderly subjects, the mean attenuation coefficient, when calculated in this manner, has been shown histologically to correspond to fat accumulation within and between the muscle cells. The increasing fat infiltration into the muscle with aging may be an important, if not central, aspect of sarcopenia. Lower values of the mean thigh muscle attenuation coefficient correspond to increasing fattiness of muscle tissue. Decreasing thigh muscle attenuation is correlated to decreasing muscle strength, a relationship which is independent of the muscle CSA and the total amount of adipose tissue in the thigh.

Measures of CSA and muscle attenuation assessed at multiple skeletal sites are associated with indices of functional capacity in elderly adults, including chair stand and leg strength measurements which have been shown to be strongly predictive of falls [83, 88, 121]. Several studies based on the Health, Aging, and Body Composition Study, a large NIH-funded population study, have related measures of body composition derived by CT to indices of functional ability and quality of life in the independently living elderly. Visser et al. examined the relationship between measures of thigh composition and lower-extremity perfor-
mance (LEP), assessed by two timed tests: a series of five chair stands without use of arms and a 6-m walk [83]. Reduced thigh CSA was associated with poorer LEP, as was reduced thigh muscle attenuation coefficient, even after the adjustment for muscle area. The attenuation coefficient of thigh muscle is not only related to current physical performance but is also related to incident functional decline. Analyzing longitudinal data from the Health ABC study, Visser et al. observed that low baseline values of thigh muscle attenuation predicted incident mobility limitation, defined as inability to walk one-quarter mile or climb ten steps [88]. Reduced thigh muscle attenuation coefficient is also associated with increased insulin resistance and the presence of metabolic syndrome in the elderly. Diabetes and other weight-related health conditions are associated with poor vision, musculoskeletal pain, and other conditions which are themselves indicators of increased fall risk [23].

Magnetic resonance imaging

MRI is an imaging technique that is based on using radio waves to excite protons in the presence of an external magnetic field. The resonance frequency at which protons maximally absorb the radioenergy is based on their local chemical environment. Because musculoskeletal tissues are rich in proton-containing molecules such as muscle proteins and lipids, MRI is an inherently powerful tool at depicting the anatomy of muscle tissues, particularly in the delineation of lean and adipose components of muscles. While some investigators have used 3D MRI acquisitions to determine lean tissue and intermuscular fat volumes in a range of applications, the true advantage of MRI is the ability to obtain spectroscopic data that can probe in vivo the ATP-generating functions within skeletal muscle and the storage of important nutrients such as lipid and glycogen.

Proton magnetic resonance spectroscopy (1H-MRS) is a technique that can differentiate lipids stored within adipocytes (extramyocellular lipid, EMCL) from intramyocellular lipid (IMCL) stored as droplets on the border of the myoplasm [122–127]. This differentiation is based on the variance in resonance frequency between protons contained in relatively cylindrical deposits of EMCL in adipocytes and protons contained in IMCL deposits which are spherical in shape. These resonances show up as different peaks on the proton spectrum of skeletal muscle (Fig. 5). Probing IMCL is of clinical importance because IMCL stores represent lipid which borders mitochondria and which represent an energy supply of free fatty acids for oxidation. IMCL intensity determined by 1H-MRS has been found to correlate with insulin resistance and obesity. The risk of insulin resistance is known to increase with age, and aging skeletal muscle is characterized by decreasing oxidative capacity that may lead to increased IMCL.

MRS may also be used to detect resonances of 31P and 13C nuclei contained in ATP, ADP inorganic phosphate, glycogen, and other chemical forms in skeletal muscle cells, shedding important light on muscle metabolism. 31P-MRS can be used to directly analyze relative abundances of 31P contained in compounds of interest to energetics of skeletal muscle, including ATP, inorganic phosphate, and phosphocreatine [128–134]. Based on these primary measurements, it is also possible to use 31P-MRS to indirectly...
estimate the intracellular pH, as well as the free concentrations of ADP and Mg$^{2+}$ ions. These measurements allow the technique to be used to estimate rates of ATP synthesis under ischemic (glycogenolytic) conditions or aerobic (oxidative) conditions. Other applications in skeletal muscle studies include estimates of the oxidative capacity of skeletal muscle, as well as the proton efflux and buffer capacity, which provide insight into the recovery of skeletal muscle from exercise.

The wide chemical shift of the $^{13}$C resonance allows $^{13}$C-MRS to assess the relative abundances of a wide range of molecules related to glycogen synthesis and glycogenolysis [129, 135–143]. Using the natural abundance (1.1%) of $^{13}$C, it is possible to detect resonances of $^{13}$C in glycogen and triglyceride. This allows for estimates of glycogen turnover in skeletal muscle and for studies of insulin resistance and type 2 diabetes. By administration of $^{13}$C glucose, it is possible to enrich $^{13}$C, allowing for more advanced determinations, such as examining glycogen synthesis rate and quantifying organelle and mitochondrial activity during the TCA cycle.

Positron emission tomography

Positron emission tomography (PET) is an imaging technique which is employed to image the biodistribution of a compound of interest labeled with a positron-emitting atom, for example an $^{18}$F or $^{13}$C. The most commonly employed PET imaging agent is $^{18}$F-fluorodeoxyglucose (FDG), a glucose analog which is widely employed to study glucose metabolism across multiple tissue types. $^{18}$F-FDG penetrates the cell membrane and is phosphorylated to FDG-6-phosphate and is no longer metabolized and thus is trapped within the cell. It builds up in the cell in proportion to the rate of glucose transport across the cell membrane and also in relation to the activities of hexokinase and glucose-6-phosphotase within the cell. In skeletal muscle, FDG imaging has been employed to study glucose utilization. When used in conjunction with compartmental modeling, this approach has been employed to dissect the rate of glucose utilization in terms of the components of cell membrane transport and phosphorylative activity in insulin resistance associated with both obesity and diabetes [144, 145]. Another application of PET which is relevant to skeletal muscle is the use of $^{11}$C-methyl-methionine to estimate the rate of protein synthesis. This agent accumulates in skeletal muscle as $^{11}$C-labeled protein, and the use of this methylated agent has advantages over radiolabeled leucine in that the latter accumulates in the blood as $^{13}$C-labeled CO$_2$. Fischmann and others have validated this technique against skeletal muscle biopsy and have used it to outline the rate of skeletal muscle protein synthesis in healthy young volunteers [146–148].

Conclusions

Sarcopenia represents a set of outcomes, including the primary outcomes of loss of skeletal muscle strength and endurance, and secondary outcomes which include loss of mobility and increased risk of disability and mortality. The bulk changes of muscle tissue which lead to these outcomes result from multiple processes occurring at the cellular level. These processes impact the performance of muscle by reducing the number of fibers and the performance of individual fibers. Age-related loss of motor neurons results in denervation of entire fibers, with a concomitant adaptive process that recruits some but not all of these of these fibers into surviving motor units. Changes in the hormonal and inflammatory milieu result in impairment of protein synthesis and increased protein degradation. Buildup or ROS may result in mitochondrial dysfunction which impairs muscle respiration and may result in fiber deterioration through loss of myonuclei. Alterations in expression of myogenic regulatory factors may impair the ability of aged muscle to repair damage. Fortunately, despite this wide range of deleterious age-related changes, there are promising interventions. Multiple studies have shown that resistive exercise among the elderly of both genders can result in substantial improvements in muscle strength and in overall functional status, where increases in muscle strength indices can exceed 50–100%. For subjects who cannot tolerate or are unwilling to undertake exercise, pharmacologic interventions, such as GH or IGF-1 interventions, are under investigation. These have had mixed results, and newer approaches, such as myostatin inhibition and selective androgen receptor modulators, are also in the early stages of investigation. Noninvasive imaging approaches such as CT, MRI, and PET are showing promise as clinical tools that may yield important basic information regarding the mechanisms of sarcopenia and the modes of action of multiple interventions.

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References


