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Summary

Cellular and molecular mechanisms underlying sarcopenia

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Sarcopenia is the degenerative loss of skeletal muscle mass and quality, as well as strength associated with aging. Sarcopenia may progress to the extent that an older person may lose his or her ability to live independently. Furthermore, sarcopenia is an important independent predictor of disability in population-based studies, linked to poor balance, gait speed, falls, and fractures. The recent elucidation of various intracellular signaling pathways and kinases involved in age-related muscle atrophy has brought a tremendously improved understanding of the pathophysiology of sarcopenia, and has heightened expectations for novel interventions. This article will focus on the cellular and molecular mechanisms responsible for sarcopenia and summarize recent advances in this field.

Key words : muscle atrophy, aging, satellite cells, atrogenes, chronic inflammation, neuromuscular junction

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特集 サルコペニアとアンチエイジング

3

サルコペニアの病因と疾患メカニズム

Investigating Mechanisms of Sarcopenia

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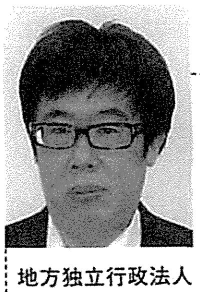
Key Words
●サルコペニア
●筋線維
●ミトコンドリア
●神経筋シナプス
●運動神経細胞

Summary

The pathological definition of sarcopenia enables us to classify the disease into subcategories and drive the development of new techniques for early diagnosis and effective medication.



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1986年 千葉大学医学部大学院修了。
サルコペニアや神経筋難病による筋萎縮のメカニズム解明と予防・治療法の研究を行っている。2006年に自己免疫性重症筋無力症の新しい発症メカニズムを解明して報告した。

はじめに

サルコペニアの臨床診断は，骨格筋量と筋力および身体運動能力（歩行速度など）の3つの定量的な指標が用いられる[1)2)]。サルコペニアの発症メカニズムの研究は認知症と比べて遅れているのが現状であるが，その理由として認知症のように病理学的な診断が確立されていないことが大きい。また，サルコペニアの成因は多様であるが，それは骨格筋の機能が運動だけでなく，体内の栄養環境の調節や体温調節など代謝機能に重要な役割を担うことに関連する。実際，サルコペニアの予防法として，現在のところ運動と栄養管理が最も有効な方法であるとされている。本稿では，サルコペニアの病因とそのメカニズムについて病理学的な観点から概説する。

加齢による骨格筋線維の変化

骨格筋は，胎児期の中胚葉細胞由来の筋前駆細胞が，細胞融合と成熟過程を経て多核の筋線維へ分化して形成される。成体の骨格筋では基底膜と筋線維の間に，単核の筋幹細胞（サテライト細胞）が存在しており，通常では細胞分裂の静止状態を維持しているが，骨格筋損傷や過負荷を受けると速やかに増殖し，筋線維へ融合されて必要な筋核数を維持する[3)]。サテライト細胞の数は加齢により減少することが観察されている。ヒトの骨格筋は，ミオシン重鎖Ⅰを発現する遅筋線維，ミオシン重鎖Ⅱa，Ⅱbを発現する速筋線維で構成される。筋線維は一度消失すると再生されない。遅筋線維はエネルギー消費に酸素消費を伴うミトコンドリアが使われるため疲労耐性が高く，

速筋線維は酸素消費を伴わない解糖系を使うため疲労耐性が低い。

ヒトやマウスを対象とした研究から，サルコペニアに伴う筋萎縮では筋線維数と筋線維の断面積の減少に加え，遅筋線維の割合が増加することがよく知られている。筆者らは，老化マウスの骨格筋を使い，ミトコンドリア機能やたんぱく質合成の低下の程度が速筋と遅筋で異なることや，骨格筋の部位によって筋線維の変化が多様であることを見出している（表１）[4]。筋線維の量的・質的な変化は生後から青年期の発達期だけでなく，中年期から超高齢期まで連続的に起きており，遺伝因子と体内外の環境因子により促進・遅延の修飾を受けると考えられる（図１）。

骨格筋はもともとミトコンドリアに富んでいるが，その機能を維持するために分裂と融合を繰り返し，品質不良のミトコンドリアはオートファジーにより除去される。オートファジーは，たんぱく質など細胞質内の成分とオルガネラなどの細胞質内の一部を無作為に分解する機構である。また，オートファジーは飢餓状態などのストレス下においては，生存に必要なエネルギーの確保とたんぱく質合成のために，細胞内成分を分解してアミノ酸を再利用する役割も担う。加齢とともに，ミトコンドリアDNA変異の蓄積，ミトコンドリア酵素たんぱく質発現の減少と活性低下，エネルギー産生効率の減弱，酸化ストレスの増大，アポトーシスの誘導，代謝機能低下および熱産生の減少などのミトコンドリア機能低下が起きることが報告されている[5]。

ミトコンドリアでは，酸化的リン酸化によるエネルギー産生の過程に副産物として活性酸素種（reactive oxygen species：ROS）が産生され，細胞内のたんぱく質，核酸，脂質などを酸化するために細胞毒性を発生させる。ROSが老化を進行させるという酸化ストレス学説の考え方は，概念として広く受け入れられている。Mn-SOD（superoxide dismutase）は，

表１．高齢マウス（生後32ヵ月）の骨格筋の変化

	ひらめ筋		長指伸筋		
	Type Ⅰ	Type Ⅱa	Type Ⅱa	Type Ⅱx	Type Ⅱb
筋線維数	変化なし	減少	変化なし	変化なし	減少
筋線維面積	変化なし	変化なし	変化なし	変化なし	減少
筋線維タイプ群化	群化	変化なし	群化	群化	脱群化
ミトコンドリア活性	低下	変化なし	変化なし	変化なし	変化なし

ひらめ筋（遅筋）と長指伸筋（速筋）では，筋線維タイプ特異的に筋萎縮の様式やミトコンドリア活性の変化が異なる。

（文献４の図より許可を得て転載）

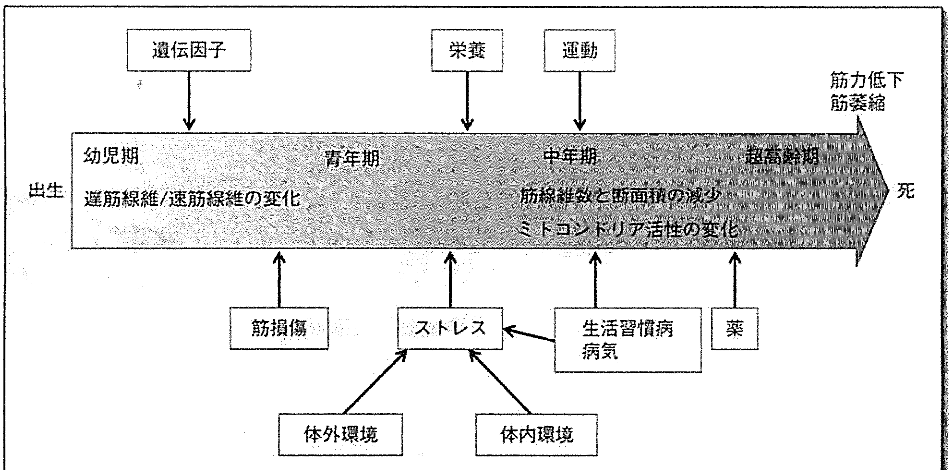

図１．筋の機能的および組織学的変化は生涯を通して起きており，遺伝因子と環境因子によりその変化が修飾される

ミトコンドリア内で酸素から生じるROSのスーパーオキサイド（$O_2^{\cdot -}$）を，過酸化水素水（H_2O_2）と酸素に変換する。Mn-SOD遺伝子を骨格筋特異的にノックアウトしたマウスを調べたところ，運動機能は著しく低下するが，筋萎縮は示さず，筋再生能もコントロールと同じであった[6]。筋線維の病理学的変化からも，サルコペニアの病態をROSによる細胞毒性の単一原因で説明することは難しい[7]。

運動神経細胞と神経筋シナプスの変化

加齢に伴う運動神経細胞死が，サルコペニアの原因となる可能性が考えられるが，その病理学的根拠が乏しいのが現状である。1977年にTomlinsonらが，47人の剖検で腰仙髄の運動神経細胞数を計測すると，60歳から運動神経細胞数が減りはじめ，80歳以上になると約25％の運動神経細胞数が消失することを報告している（**図2**）[8]。加齢により運動神経細胞数が減少することは動物種を越えて報告されているが，超高齢社会を迎えた現在において，運動神経細胞死と臨床症状の因果関係に関するエビデンスがないのが現状であり，認知症との関連も含めて今後検討する必要がある。

運動神経細胞と骨格筋のつなぎ目である神経筋シナプスでは，運動刺激の神経信号を伝えて筋収縮を誘導する。加齢により神経筋シナプスの形態変化と機能低下が起き，筋力低下と筋萎縮の原因となる（**図3**）。シナプスでは神経伝達分子のアセチルコリンだけでなく，運動神経終末と筋側の双方性にさまざまな分子が分泌されて信号を交換することでシナプスが維持されており[9]，この機構が老化により障害されることが考えられる。生後22ヵ月の老化マウスを1ヵ月間運動させるとシナプスの形態変化が改善することが報告されている[10]。

ホルモン

サルコペニアの成因に関係するホルモンとして，男性ホルモン（アンドロ

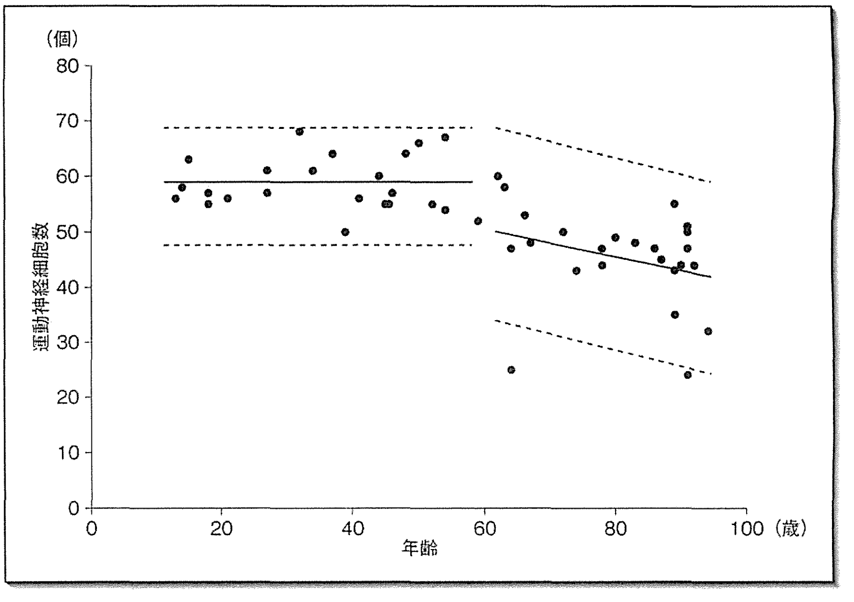

図2．ヒト仙腰髄の運動神経細胞数の加齢による減少

（文献8より引用改変）

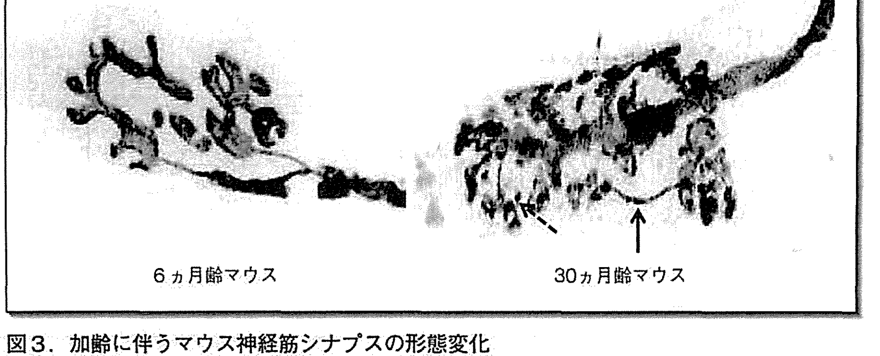

図3．加齢に伴うマウス神経筋シナプスの形態変化

点線矢印：アセチルコリン受容体凝集の散乱，実線矢印：運動神経終末のsprouting

（重本和宏，他：日本老年医学会誌 50（3），2013の図より許可を得て転載）

ゲン）とビタミンDがある。男性においては加齢に伴うアンドロゲン作用の減少と，サルコペニアと転倒の増加，生殖機能の低下，骨密度の低下などとの関連が示されている[11]。アンドロゲン低下により，筋組織のたんぱく質分解の促進，合成の低下の誘導，筋細胞のアポトーシスを亢進する。女性もアンドロゲンは微量ではあるが副腎から分泌されているが，サルコペニアとの関連について一定の見解は得られていない。

ビタミンDは骨代謝だけでなく，運動機能（転倒）との間に相関関係があることが知られている。高齢者にビタミンDを投与することで転倒防止に効果があることが報告されている。ビタミンDの作用機序として，骨格筋の細胞質内のビタミンD受容体と結合すると，たんぱく質合成や筋収縮力増強効果をもたらすことが示されている[12]。

栄養

栄養として吸収されたたんぱく質由来の分岐鎖アミノ酸（BCAA：ロイシン，バリン，イソロイシン）が，筋細胞内のたんぱく質合成を促進することがわかっている[13]。良好な栄養状態では前述のオートファジーの作用は抑制されているが，低栄養状態ではその機能が促進され，骨格筋内のたんぱく質が分解されて体内の栄養環境を維持する。サルコペニアの病態は，栄養バランスが分解側に傾いていることが考えられる。

骨格筋のたんぱく質分解はオートファジー以外に，ユビキチン－プロテオソーム系も重要な役割を担っている[14]。運動神経切断や不活動による筋萎縮の過程で誘導されるが，本来の役割は，筋のたんぱく質分解と平衡状態を保つことで骨格筋を一定の大きさに維持していると考えられる。骨格筋の肥大を抑制する機構として，ミオスタチンによる作用が知られている。ミオスタチンは，TGF-βスーパーファミリーで骨格筋により産生分泌される。高齢者の骨格筋では，マイオスタチンとユビキチン－プロテアソーム系の遺伝子発現が増加することが報告されており，サルコペニアにどの程度関与しているのか今後の解析が必要である。

マイオカイン

骨格筋は，IL-4，IL6，IL-7，LIF，FGF-21，アイリシン（irisin）などサイトカインを含むさまざまな分泌たんぱく質を産生しており，総称してマイオカイン（myokine）と総称する[15]。マイオカインは，骨格筋自体や肝臓，膵臓，脂肪細胞などへ作用し，代謝を制御していることが明らかになりつつある（図４）。サルコペニアの疫学研究から，安静時（ベースライン）の血中IL-6量と負の相関関係があることが明らかにされている。

サルコペニア肥満とは？

肥満とサルコペニアが合併した病態をサルコペニア肥満という。臨床領域で注目されているが，その診断基準は明確に定められてはいない。おそらく，単なる運動不足というだけでなく，皮下および内臓脂肪細胞，骨格筋，肝臓，膵臓などにおける代謝調節機能の加齢による変調が原因で起きる病態と考えられる（図４）。ところで，骨格筋内の脂肪細胞はサテライト細胞由来と従来考えられてきたが，最近の報告では，

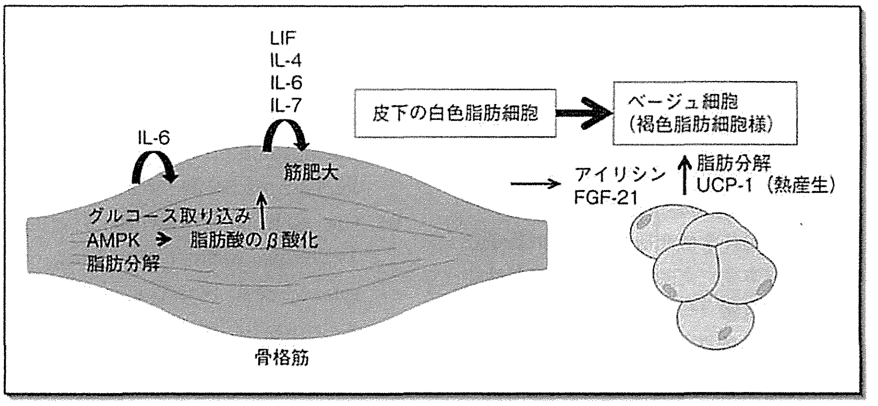

図４．筋肉から分泌されるマイオカインは筋，脂肪細胞，肝臓，骨，膵臓などのさまざまな臓器に対して代謝調節を行う

アイリシンとFGF-21は，皮下の白色脂肪細胞を褐色脂肪様の細胞（ベージュ細胞）へ変換し，熱産生や脂肪分解を誘導する。

骨格筋の間質に存在している間葉系前駆細胞が異所性脂肪細胞の起源であることが示された[16]。健康な筋では，筋線維の働きにより脂肪細胞への分化が抑制されているが，筋線維の機能が障害されると抑制シグナルが弱まり，間葉系細胞が脂肪細胞へと分化する。また，間葉系幹細胞は，サテライト細胞から筋細胞への分化を誘導する因子を分泌することが示唆されている[17]。老化による筋萎縮の病態は，何らかの原因でこのバランスが崩れて，骨格筋内の線維化や脂肪細胞が誘導されていることが考えられる。

おわりに

近年，骨格筋による全身の代謝調節の機構が次々と報告されている。加齢による全身の代謝機能の変化は，サルコペニアだけでなく認知症の両方の成因に密接な関係があるのかもしれない。

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Q.9

診断のためのバイオマーカーについて教えてください

重本 和宏

A

- バイオマーカーはサルコペニアの診断，運動や栄養補給および薬物治療の効果を評価するために有用である
- バイオマーカーは血液や尿で測定できるものが便利である
- 筋特異的に発現するマイオカイン，骨格筋の維持に必要な因子は，バイオマーカーとして有用である可能性が高い

1. バイオマーカーの意義について

超高齢社会を迎え、骨格筋量の進行的な減少にともなう機能低下、すなわちサルコペニア（加齢性筋肉減少症）は、認知症と並んで高齢者のactivity of daily living（ADL）とquality of life（QOL）を損なう主要な原因となることから，その早期診断や有効な介護予防対策が急務の課題となっている。

サルコペニアは老年症候群の主要な原因である。その定義と診断については，統一見解として，筋量，筋力と身体能力（歩行能力など）の生理学的指標を定量的に測定して評価することが、欧州の学会で発表されている(2010年)。わが国においても日本人の体格にあわせた基準作りが，厚生労働省班会議と日本老年病学会が中心となって進められている[1]。一方，この診断法に基づき臨床的にサルコペニアと診断されるケースは，筋力低下や筋萎縮だけでなく，認知症を含むほかの老年病症候群を合併しているケースが多く，病態改善の有効な治療や予防がなかなか困難である。そこで，早期にサルコペニアを診断し，運動や栄養補給による介入や薬物治療などの効果を客観的な指標で判定することで介護予防を可能にするバイオマー

カーが求められている。

2．バイオマーカーの種類

バイオマーカーは，広義には生体の生理学的状態の測定値で病態の指標になるものも含まれ，体重，筋量，筋力，身体能力などがバイオマーカーに分類されることもある（表1）。しかしながら，近年ではバイオマーカーは特定の生理メカニズムに基づく定量的変化，あるいは発症メカニズムに基づく病理学的変化の定量値などの指標を示しており，測定値の増減で病態変化を客観的に診断することができるものが対象とされている。血中に含まれる分子で病態を良く反映する分子バイオマーカーとして，たとえば前立腺がんのPSA（前立腺特異抗原）測定は，診断および治療の有効性と予後判定において，有用性が高く実用化されているよい例である。また，PET（positoron emission tomography）を使った脳イメージングによる認知症の早期診断や治療法の有効性の判定を目的に，糖代謝やアミロイド沈着を検出する方法が開発されている。サルコペニアの診断では，骨粗鬆症診断で使われている二重エネルギーX線吸収法（dual energy X-ray absorptiometry：DEXA）を使い，筋肉量について簡便で信頼性の高い測定値を得ることができる。しかし，筋肉量の測定値単独ではサルコペニアを診断することができず，前述のように筋力と身体能力の3種類の測定値による総合的評価が必要である。したがって，現時点では臨床で有用性のあるサルコペニアのバイオマーカーは，まだ開発途中と言ってよい。

3．慢性炎症とサルコペニアのバイオマーカー

これまでの疫学的研究から，サルコペニアと関連する分子バイオマーカーとしてIL-6やTNF-αがサルコペニアの指標と相関があることが報告され

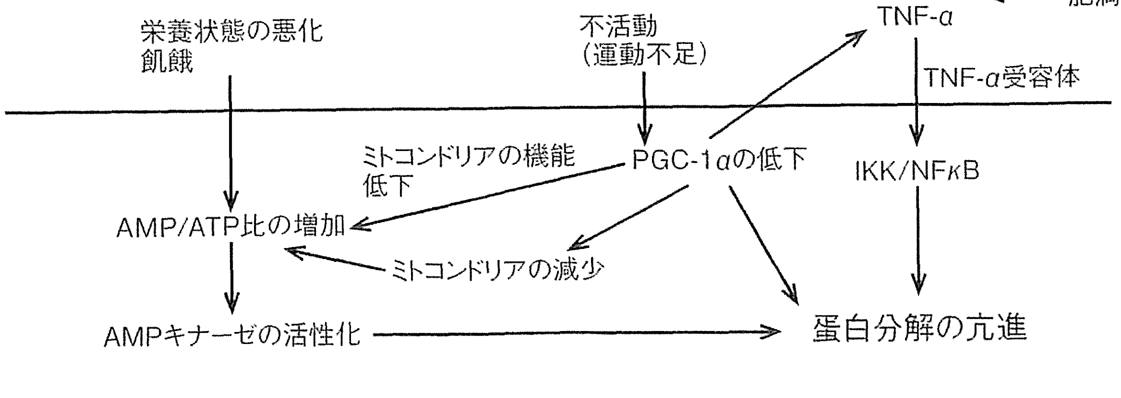
表1　サルコペニアのバイオマーカーの種類

生理学的	体重，筋量，筋力，歩行速度や持久力などの身体能力
分　子	血中，尿中，筋バイオプシーなど生体由来の検体に含まれる分子の量，ゲノムの遺伝子変異も含む
イメージング	X線，CT，MRI，PETによるイメージングで病態を反映する検出法

ていた。さらに最近の研究から，サルコペニアの病態メカニズムと慢性炎症が直接関連することが明らかにされている（**図1**）。運動不足はミトコンドリアの維持・生成に必要な転写因子共役因子のPGC1-α（peroxisome proliferator-activated receptor gamma coactivator 1）の骨格筋での発現を減少させるが，PGC1-αの減少はIL-6やTNF-αの発現に対しては増強する作用がある。肥満状態は脂肪組織からの炎症性サイトカインの分泌を増強するためにPGC1-α発現の減少による作用を増強する。TNF-αのシグナル，PGC1-αの発現低下および栄養状態の悪化は，骨格筋内のシグナルカスケードを経てどれも蛋白分解を促進する作用がある[2]。しかしながら，IL-6やTNF-αなどの炎症性サイトカインは，感染症や高齢者のさまざまな合併症でも上昇するため臨床的には特異性が低い。一方，骨格筋には，蛋白合成を促進させ筋肥大を誘導するシグナルカスケードが存在している。その代表的なシグナルがIGF-1（insulin-like growth factor 1）である。また，TGFβスーパーファミリーに属するミオスタチンは，逆に蛋白分解を誘導することで筋肥大を抑制する。正常な骨格筋においてはIGF-1とミオスタチンの作用により蛋白合成・分解の平衡状態を保っているが，老化筋での両者の発現変化に関して統一的な結果が得られていない[2]。

4．マイオカインとバイオマーカー

骨格筋は壮年期の成人男性の体重の40％（女性は35％）を占め，運動に



◆**図1　老化による骨格筋の蛋白分解のシグナル経路（想定図）**

必要な筋収縮だけでなく生体内外の環境変化にともなう代謝調節と熱産生の役割も担う。この2つの役割は，骨格筋だけでなく，骨格筋の産生するサイトカイン，いわゆるマイオカインが重要な役割を果たす。マイオカインは，IL-6，IL-8，BDNF，FGF21など多数報告されており，いずれも筋以外の脂肪組織，肝臓などの臓器に対して作用することがわかっている。2012年にハーバード大のSpiegelmanらにより，筋から分泌され脂肪細胞に作用してエネルギー消費を誘導する生体内分子のアイリシンという新しいホルモンが報告された[3]。加齢により，筋の代謝機能が変化することは古くから知られているが，筋特異的に分泌されるアイリシンが，サルコペニアのバイオマーカーとして有用かどうか今後の解析が待たれる。

5. 骨格筋の維持とバイオマーカー

骨格筋の形態・機能を維持するために，骨格筋組織幹細胞（サテライト細胞）が骨格筋の基底膜と筋線維の間に存在しており，損傷や過負荷を受けると細胞分裂と筋管細胞への分化が誘導され維持・修復を担っている。このサテライト細胞の機能を抑制する補体成分のC1qが，老化マウスの血中で増加することが報告された。C1qについてはサルコペニアの原因の1つかどうか，またバイオマーカーとして使えるかどうか興味が持たれる[4]。

骨格筋の維持には，運動神経細胞と筋のつなぎ目である神経筋シナプスが重要な役割を果たす。運動神経細胞終末から分泌されるagrinは，シナプスの維持に必須の分子である。AgrinのC末端蛋白（CAF）は，シナプスに存在するneurotrypsin（プロテアーゼ）により切断される。Neurotrypsinを運動神経細胞に過剰発現したトランスジェニックマウスは，筋萎縮の病理組織像がサルコペニアと類似する。69名の高齢者（女性47名）の血清中のCAF濃度を測定したところ，男性高齢者の筋量と有意に負の相関関係があり，ビタミンDと運動トレーニング負荷後にCAF高値の群では有意にCAFの値が下がった[5]。測定法が複雑であることが大きな欠点であるが，この着眼点のバイオマーカーの開発が今後も進むことが期待される。

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Geriatr Gerontol Int 2013; **13:** *458–465*

ORIGINAL ARTICLE: BEHAVIORAL AND SOCIAL SCIENCES

Effects of exercise and tea catechins on muscle mass, strength and walking ability in community-dwelling elderly Japanese sarcopenic women: A randomized controlled trial

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Aim: To investigate the effects of exercise and/or tea catechin supplementation on muscle mass, strength and walking ability in elderly Japanese women with sarcopenia.

Methods: A total of 128 women aged over 75 years were defined as sarcopenic and randomly assigned into four groups: exercise and tea catechin supplementation ($n = 32$), exercise ($n = 32$), tea catechin supplementation ($n = 32$) or health education ($n = 32$). The exercise group attended a 60-min comprehensive training program twice a week and the tea catechin supplementation group ingested 350 mL of a tea beverage fortified with catechin daily for 3 months. Body composition was determined by bioelectrical impedance analysis. Interview data and functional fitness measurements, such as muscle strength, balance and walking ability, were collected at baseline and after the 3-month intervention.

Results: There were significant group × time interactions observed in timed up & go ($P < 0.001$), usual walking speed ($P = 0.007$) and maximum walking speed ($P < 0.001$). The exercise + catechin group showed a significant effect (odds ratio 3.61, 95% confidence interval 1.05–13.66) for changes in the combined variables of leg muscle mass and usual walking speed compared with the health education group.

Conclusions: The combination of exercise and tea catechin supplementation had a beneficial effect on physical function measured by walking ability and muscle mass. **Geriatr Gerontol Int 2013; 13: 458–465.**

Keywords: exercise, muscle mass, physical function, sarcopenic women, tea catechin supplementation.

Introduction

It is generally accepted that aging is associated with a progressive decline of lean body mass, and muscle mass in particular. This involuntary loss of skeletal muscle mass and strength, defined as sarcopenia, has been associated with loss of independence, diminished quality of life, physical disability, increased risk for falls, mobility impairments, high healthcare burden and medical needs, and mortality in the elderly.[1,2] Hence, prevention and treatment of sarcopenia is very important and necessary for the well-being of the growing elderly population. Although there are several methods of treatment that have being researched, skeletal muscle disuse or inactivity has been considered potentially preventable with targeted interventions.[3,4] Resistance exercise is considered the cornerstone of sarcopenia[5] management, as its beneficial effects in increasing muscle mass and strength have been confirmed in previous studies.[6–8]

Furthermore, several studies have investigated the treatment effects of green tea beverages abundant in tea catechins (TC), a chemical anti-oxidant,[9–11] as a potential nutritional supplementation for elderly adults; however, the results are controversial. Previous studies have suggested that TC have many health benefits for different disorders varying from cancer to weight loss.[9,11] Research on TC, and its effects on age-related declines in functional fitness and muscle mass in humans are scarce, and the mice studies available show inconsistent evidence. One study investigated the combined effects of exercise and TC ingestion in mice, and found that concomitant TC ingestion with habitual exercise is beneficial for suppressing age-related declines in physical

Accepted for publication 2 July 2012.

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 doi: 10.1111/j.1447-0594.2012.00923.x

performance,[10] focusing on endurance exercise. Nevertheless, there are few, if any, randomized controlled trials on the effects of exercise and TC supplementation on basic physical function in elderly people.

The purpose of the present study was to investigate the effects of exercise and/or TC ingestion on muscle mass, strength and walking ability in sarcopenic women.

Methods

Study population

Invitation letters were mailed to 1472 people aged 75 years and older who were randomly selected from the Basic Resident Register of elderly people residing in the Itabashi ward of Tokyo, Japan. There were 1355 responses to the invitation letters, where 1094 people agreed to participate and 261 people refused or did not respond. The baseline assessment was carried out at the Tokyo Metropolitan Institute of Gerontology (TMIG) between October and November 2009, where 974 participated and 120 who had initially agreed to participate were absent.

We operationally defined sarcopenic women based on categorization into at least one of the following inclusion criteria: (i) appendicular skeletal muscle mass/height^2 less than 6.42 kg/m^2 and knee extension strength less than 1.01 Nm/kg ($n = 99$);[12,13] (ii) appendicular skeletal muscle mass/height^2 less than 6.42 kg/m^2 and usual walking speed less than 1.10 m/sec ($n = 21$);[14] (iii) body mass index (BMI) less than 22 and knee extension strength less than 1.10 Nm/kg ($n = 130$); and (iv) BMI less than 22 and usual walking speed less than 1.10 m/sec ($n = 16$). Out of 974 people, 266 (27.3 %) participants were operationally defined as sarcopenic (Fig. 1).

Participants for the interventions were recruited from 266 sarcopenic women. Exclusion criteria included: (i) severe knee or back pain; (ii) severely impaired mobility; (iii) impaired cognition (Mini-Mental State Examination [MMSE] score <24);[15] (iv) missing baseline data; and (v) unstable cardiac conditions. A total of 138 participants (51.9%) were excluded from the study based on the exclusion criteria, or declined participation. The present study protocol was approved by the Clinical Research Ethics Committee of TMIG. The intervention procedures were fully explained to all participants and written informed consent was obtained.

Randomized group assignment

After the baseline assessment, computer-generated random numbers were assigned to 128 participants, who were then sorted and equally divided into four groups, and any variable that identified individual information was not included in the randomization process. The groups were randomly assigned to one of the four interventions: exercise and tea catechin supplementation (Ex + TC; $n = 32$), exercise (Ex; $n = 32$), tea catechin supplementation (TC; $n = 32$) or health education (HE; $n = 32$) groups. The allocation sequence was concealed from the study coordinator, and data collection was carried out by separate physical therapy staff members who were also blind to the allocation of treatments.

Outcome measures

Data were collected at baseline and after the 3-month intervention. Measures included interview surveys, body composition assessments and physical function tests. Measurements of height and weight were used to calculate BMI (kg/m^2).

Interview survey

Each participant was interviewed face-to-face to assess the individual's history of falls, fear of falling, pain, exercise habits, urinary incontinence, frequency of going out, self-rated health and so on.

Body composition assessment

Percent body fat, lean body mass, and total and segmental muscle mass were measured using a multifrequency bioelectrical impedance analysis (BIA) instrument that operated at frequencies of 5, 50, 250 and 550 kHz (Well-Scan 500; Elk, Tokyo, Japan). The participants stood on two metallic electrodes on the scales of the BIA instrument barefoot, holding two metallic grip electrodes placed in the palm of each hand with the fingers wrapped around the handrails. Segmental muscle mass values of each leg, arm and the trunk were measured and added to obtain appendicular skeletal muscle mass and leg muscle mass.

Performance measures

The performance measures included muscular strength (grip strength, knee extension strength), walking ability (usual and maximum walking speed, and timed up & go [TUG]) and balance ability (one leg standing time with eyes open). For the TUG test, time was measured in seconds from the time the participants stood up from a straight-backed chair placed against a wall, walked 3 m toward a cone as quickly and safely as possible, walked around the cone, and sat down on the chair again.[16] Assistive walking devices were allowed in measures of walking speed and TUG only if they expressed concerns about walking without a device, or if the investigators believed there was a danger of falling. Knee extension strength was measured twice, and the higher value

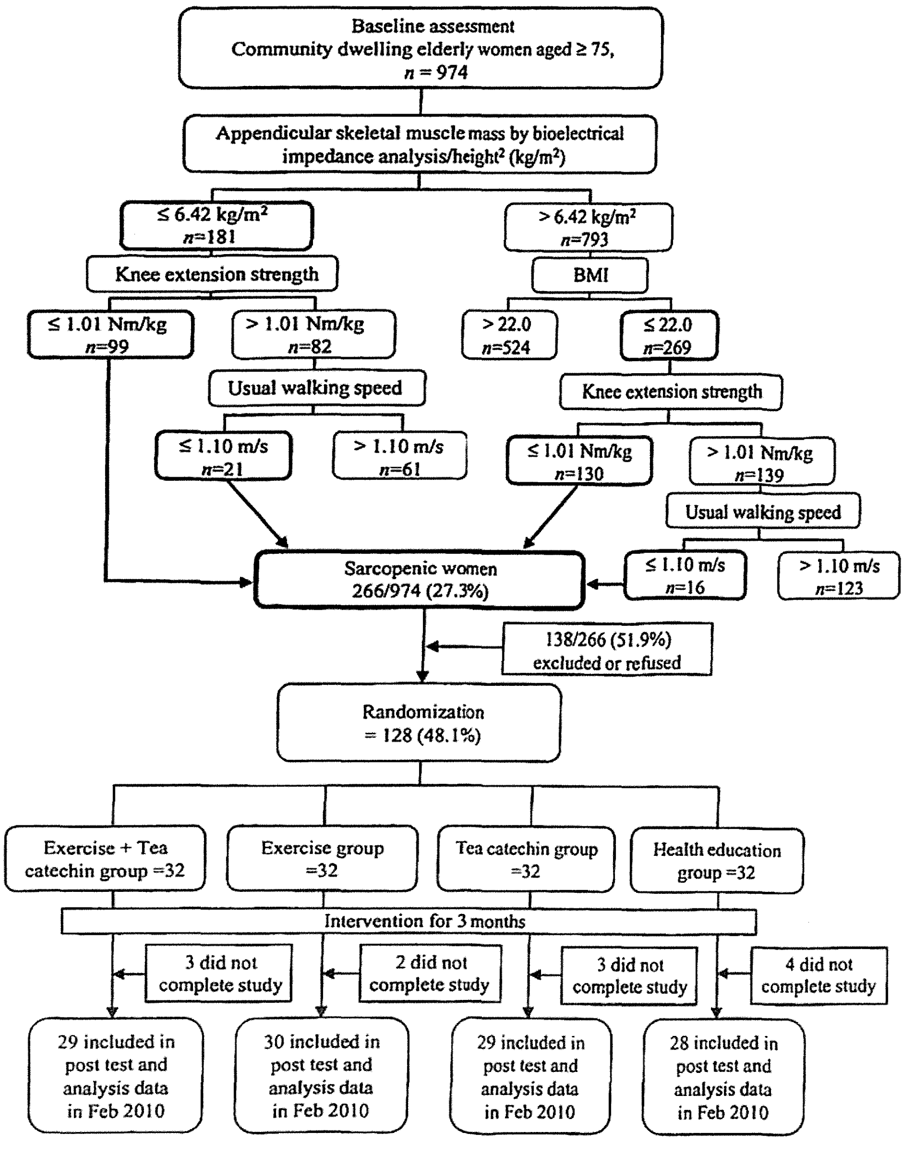

Figure 1 Algorithm for the selection of women operationally defined as sarcopenic, and flowchart of participants in the randomized controlled trial of exercise and tea catechin supplementation. BMI, body mass index.

divided by bodyweight (Nm/kg) was analyzed. Detailed procedures for the performance measures have been described previously.[17]

Intervention

Exercise

The exercise consisted of stretching, muscle strengthening, balance and gait training of moderate intensity maintained at approximately 12–14 on the Borg Rate of Perceived Exertion scale.[18] Each class was 60 min, held at the TMIG twice per week for 3-months. To ensure proper instruction to all participants, the two exercise intervention groups were divided into four subgroups, where the participants exercised together within their assigned subgroup in one of four exercise sessions offered per day.

The exercise session included a 5-min stretching warm-up of the neck, shoulders, lower back, hips, knees and ankles, 30-min of strengthening exercises, 20 min of balance and gait training, followed by a 5-min cool-down.

Muscle strength training

Strengthening exercises were carried out in a progressive sequence from the seated position, which initially provided a secure and stable position, to the standing position. Other resistance was applied through use of resistance bands for upper body strengthening and ankle weights for the lower body, as well as increasing the repetitions and sets of the exercises. Participants were initially instructed to complete up to one eight-repetition set of each type of exercise, which gradually increased to 10 repetitions, and up to two sets.

Resistance was increased on a group basis when the participants were able to execute each exercise without loss of proper execution. Each individual's ability to increase intensity was assessed by the principal investigator, the exercise instructor and assistant trainers.

To strengthen lower extremities, a fixed weight was placed on the ankle during the exercises. Weights of 0.50 kg, 0.75 kg, 1.00 kg, and 1.50 kg were prepared and used in accordance with each participant's strength level as the resistance progressively increased. Strengthening of the leg muscles focused on hip extensors and adductors, knee flexors and extensors, and ankle dorsi- and plantarflexors.

Gait and balance training

The participants practiced various walking patterns, focusing on stability maintenance during walking. Participants were taught to focus their attention on increasing toe elevation of the forward leg, heel elevation of the rear limb, and stride length through gait exercises including walking with directional changes and weight shifting. The balance training contained exercises, such as one-leg stands, tandem stand and tandem walking, for each participant to train their static, dynamic and lateral balancing ability.

Tea catechin supplementation

Bottles containing 350 mL of tea fortified with 540 mg of catechin were provided for the participants in the TC supplementation group every 2 weeks. The participants were instructed to drink one bottle per day, every day for 3 months. To monitor their TC intake accurately, the participants were asked to record the volume of tea consumed (the whole bottle, half the bottle, or about one-quarter) on record sheets that were collected every 2 weeks, along with the bottle caps of finished bottles. Participants who drank at least 54 bottles or more out of the 90 bottles (60%) were considered to have completed the supplementation intervention.

Health education

The HE group served as the control group, and the participants took a class once a month for 3 months, a total of three times. Health professionals taught topics such as cognitive function, the long-term care system and oral hygiene. No specific instructions on diet or physical activity were given, and the participants were asked to continue their regular lifestyle habits.

Data analysis

Differences in baseline measures between the groups were measured using a one-way analysis of variance (ANOVA), and χ^2-tests were carried out on categorical variables. Two-way repeated-measures ANOVA was used to analyze differences in the effect of the intervention on outcome measures between groups, and a post-hoc test was carried out where significant P-values (<0.05) were found to determine which groups were significantly different. Percentage changes in leg muscle mass and strength, and walking ability postintervention were calculated using the formula: % change = ((postintervention value − baseline value) / baseline value) × 100. To compare the effects of the four intervention groups on combined variables of leg muscle mass and functional fitness after 3 months of intervention, multiple logistic regressions were carried out. All analyses were carried out using SPSS software, Windows version 19.0 (SPSS, Tokyo, Japan) and SAS, version 9.2 for Windows (SAS Institute Japan, Tokyo, Japan).

Results

All of the baseline characteristics including age, percent body fat, muscle mass, walking speed, urinary incontinence and falls were similar between the groups (Table 1).

In comparing the pre- and postintervention changes in performance measures and body composition by two-way repeated-measures ANOVA (Table 2), there were significant group × time interactions in TUG ($F = 15.408$, $P = 0.005$), usual walking speed ($F = 4.327$, $P = 0.007$) and maximum walking speed ($F = 15.161$, $P < 0.001$), where the changes in the Ex + TC group were greater than the HE group.

Figure 2 shows the within group analyses of percent changes from pre- to postintervention. Leg muscle mass significantly increased in the Ex + TC group (2.21%, $P = 0.016$), whereas only small changes in the other groups were observed. Usual walking significantly increased in the Ex + TC group (11.36%, $P = 0.010$), a modest increase was seen in the Ex group (4.84%, $P = 0.020$), and slight decreases were observed in the TC and HE groups.

The multiple logistic regression analysis showed that the Ex + TC group had a significant effect on the combined variables of increased leg muscle mass and improved usual walking speed (OR 3.61, 95% CI 1.05–13.66; Table 3). The OR for increased leg muscle mass and knee extension strength in the Ex + TC group, although statistically non-significant, were more than twofold as great as the Ex or TC only groups.

Discussion

Although sarcopenia was originally defined as the age-related loss of muscle mass,[19] muscle strength does not depend solely on muscle mass, and the relationship

Table 1 Selected variable characteristics of participants at baseline by study group

Variables†	Ex + TC (n = 32)	Ex (n = 32)	TC (n = 32)	HE (n = 32)	ANOVA P-value
Age (years)	81.1 ± 3.7	79.6 ± 4.2	80.0 ± 4.0	80.2 ± 5.6	0.525
Height (cm)	145.0 ± 5.5	145.9 ± 5.8	145.6 ± 4.9	145.9 ± 5.4	0.892
Bodyweight (kg)	43.7 ± 4.1	41.5 ± 4.5	42.4 ± 5.7	42.7 ± 5.0	0.413
Percent body fat (%)	29.0 ± 3.7	28.1 ± 4.2	27.8 ± 4.8	30.3 ± 3.6	0.110
Lean body mass (kg)	30.2 ± 3.2	30.4 ± 3.6	29.9 ± 3.1	30.5 ± 2.8	0.894
Muscle mass (kg)	27.8 ± 3.0	28.0 ± 3.3	27.5 ± 2.9	28.1 ± 2.6	0.917
Legs muscle mass (kg)	10.2 ± 1.2	10.2 ± 1.3	10.2 ± 1.2	10.3 ± 1.0	0.992
Grip strength (kg)	18.5 ± 3.5	18.2 ± 4.9	16.1 ± 3.4	17.2 ± 4.0	0.078
Usual walking speed (m/sec)	1.3 ± 0.2	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.2	0.677
Maximal walking speed (m/sec)	1.7 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	0.235
Timed up & go	6.61 ± 1.63	7.13 ± 1.68	7.07 ± 1.96	6.82 ± 1.21	0.597
One leg standing time with eyes open	27.1 ± 23.5	24.8 ± 21.8	32.1 ± 24.5	34.5 ± 24.4	0.375
Knee extension strength (Nm)	50.4 ± 10.7	44.5 ± 14.8	46.4 ± 9.7	47.0 ± 10.7	0.242
Exercise habit, yes (%)	48.4	40.7	37.5	19.2	0.144
Urinary incontinence, yes (%)	45.2	40.6	40.6	38.5	0.962
Frequency of outings, >once per day (%)	22.6	31.3	34.4	42.3	0.455
Fear of falling, yes (%)	71.0	84.4	68.8	73.1	0.489
Falls, yes (%)	25.8	31.3	21.9	11.5	0.347
Self-rated health, unhealthy (%)	12.9	34.4	25.0	15.4	0.163

†Data are presented as mean and standard deviation for continuous variables, and percentage for categorical variables. ANOVA (one-way analysis of variance) for continuous variables and χ^2-test for categorical variables. Ex, exercise group; HE, health education group; TC, tea catechin group.

between strength and mass is not linear. Recently, the European Working Group on Sarcopenia in Older People recommended using both low muscle mass and muscle strength or low physical performance as indicators for sarcopenia.[20] In the present study, sarcopenic women were operationally defined based on the declines in muscle strength or walking speed that accompany the loss of skeletal muscle mass or low BMI. The results of the present study showed that the combination of exercise and TC can effectively improve muscle mass and walking speed in sarcopenic elderly women; however, the present results could not confirm the efficacy of the combined intervention on both muscle mass and strength.

The benefits of resistance training in increasing muscle mass and strength for older people have been made quite clear throughout the literature.[6–8] According to a recent review, resistance exercise has been shown to increase muscle protein synthesis, and evidence suggests increases in size of both type 1 and type 2 muscle fibers, leading to overall improvement in muscle power and physical functioning.[5] However, our data did not show beneficial effects of exercise alone on measures of muscle mass or strength. This might be because of the intensity the participants in this intervention exercised at, as some studies showed that higher intensity and volume training were associated with greater strength improvements among older populations, compared with low- and moderate-intensity training.[7,21] Nevertheless, high-intensity exercise for frail elderly people is difficult and might lead to negative or adverse outcomes. Exercise at high intensities might aggravate previously mild discomforts of the lower back or knee, potentially causing mild, moderate or even severe pain. Furthermore, motivating frail elderly people to properly carry out high-intensity exercise is very challenging. Even though exercise of high intensity and volume can increase muscle mass and strength effectively, Taaffe[22] has suggested that training once or twice a week at moderate intensity is sufficient for improvement; therefore, the use of such training on frail elderly people should be reconsidered.

The role of anti-oxidants in aging has recently been a topic of interest. Studies have reported that aging skeletal muscle has been associated with decreased oxidative capacity, which might be linked to mitochondrial dysfunction.[23–25] One previous study suggested that TC might prevent decreases in muscle force production in mice.[26] Another mice study indicated that TC can effectively decrease oxidative stress, which might contribute, to a certain extent, to the maintenance of skeletal muscle mitochondrial function and energy metabolism; therefore, the concomitant intake of TC and regular exercise might suppress age-related declines in physical function.[10]

Table 2 Comparison of muscle mass and functional fitness variables among groups after 3-month interventions

Variables†	Group	Baseline	After 3-month intervention	ANOVA (G × T); *P*-value
Muscle mass (kg)	Ex + TC	28.38 ± 2.46	28.33 ± 2.69	*F* = 0.323 *(0.809)*
	Ex	29.09 ± 2.85	28.92 ± 2.98	
	TC	27.47 ± 3.02	27.28 ± 2.83	
	HE	28.23 ± 2.40	28.35 ± 2.33	
Appendicular skeletal muscle mass (kg)	Ex + TC	14.31 ± 1.30	14.18 ± 1.41	*F* = 1.280 *(0.286)*
	Ex	14.79 ± 1.45	14.45 ± 1.57	
	TC	13.66 ± 1.66	13.58 ± 1.51	
	HE	13.96 ± 1.21	14.11 ± 1.23	
Legs muscle mass (kg)	Ex + TC	10.45 ± 0.98	10.57 ± 1.08	*F* = 0.524 *(0.667)*
	Ex	10.59 ± 1.23	10.73 ± 1.22	
	TC	10.14 ± 1.29	10.12 ± 1.14	
	HE	10.30 ± 0.92	10.50 ± 0.94	
Grip strength (kg)	Ex + TC	18.63 ± 3.39	19.33 ± 4.71	*F* = 0.519 *(0.670)*
	Ex	19.11 ± 4.67	19.26 ± 4.54	
	TC	16.41 ± 3.34	17.11 ± 2.81	
	HE	17.84 ± 4.03	17.74 ± 3.59	
Timed up & go (s)	Ex + TC	8.68 ± 1.99	7.37 ± 1.64	*F* = 15.408 *(<0.001)*
	Ex	8.81 ± 1.60	7.03 ± 1.34	
	TC	8.89 ± 2.20	8.44 ± 2.15	
	HE	8.43 ± 1.70	8.88 ± 2.09	
Usual walking speed (m/s)	Ex + TC	1.25 ± 0.21	1.37 ± 0.24	*F* = 4.327 *(0.007)*
	Ex	1.26 ± 0.22	1.36 ± 0.30	
	TC	1.25 ± 0.24	1.24 ± 0.19	
	HE	1.27 ± 0.18	1.26 ± 0.20	
Maximum walking speed (m/s)	Ex + TC	1.74 ± 0.30	2.01 ± 0.39	*F* = 15.161 *(<0.001)*
	Ex	1.73 ± 0.23	2.06 ± 0.32	
	TC	1.78 ± 0.27	1.71 ± 0.23	
	HE	1.79 ± 0.33	1.71 ± 0.30	
Knee extension strength (Nm)	Ex + TC	52.81 ± 9.39	49.85 ± 8.97	*F* = 2.556 *(0.061)*
	Ex	51.39 ± 13.01	49.73 ± 13.38	
	TC	47.34 ± 9.56	39.42 ± 8.29	
	HE	47.54 ± 11.28	43.13 ± 10.93	

†Data are presented as mean and standard deviation. A post-hoc analysis was carried out using the Scheffe method. ANOVA two-way repeated-measure analysis of variance. Ex, exercise group; G, group; HE, health education group; T, time; TC, tea catechin.

Table 3 Adjusted odds ratio for changes in leg muscle mass and functional fitness after intervention according to study group

Dependent variable†	Type of intervention						
	HE	TC		Ex		Ex + TC	
	Reference	OR	95% CI	OR	95% CI	OR	95% CI
Leg muscle mass and usual walking speed	1.00	1.32	0.40–4.70	1.99	0.57–7.38	3.61	1.05–13.66
Leg muscle mass and knee extension strength	1.00	0.40	0.07–2.08	0.82	0.16–4.06	2.25	0.58–9.93

†Dependent variable; change of muscle mass and functional fitness: 1 = improve, 0 = no change or decrease. Ex, exercise; HE, health education; OR, adjusted odd ratio; TC, tea catechin.

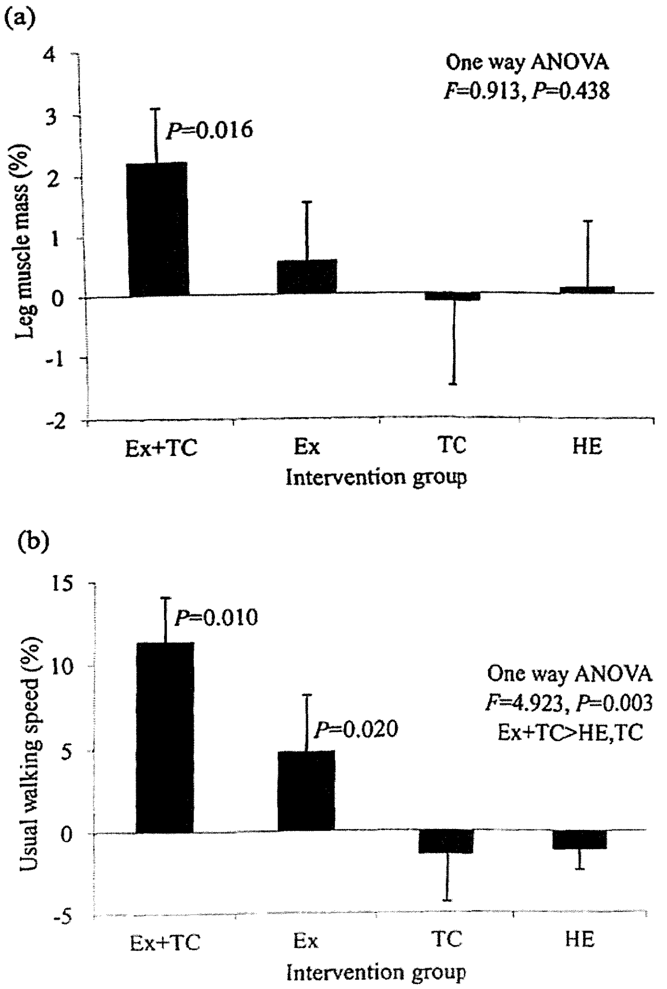

Figure 2 Mean (± SE) changes in (a) leg muscle mass and (b) usual walking speed after exercise (Ex), tea catechin supplementation (TC), usual walking speed after exercise and tea catechin supplementation (Ex + TC), or health education (HE). Bars indicate the average changes from baseline to after the 3-month interventions. A post-hoc analysis was carried out using the Scheffe method.

The data in the present study showed leg muscle mass improvements of 2.21% in the combined exercise and TC group, but the changes in muscle strength were not significant. These results are inconsistent with previous research showing strong associations between increases in muscle mass and increases in strength;[4] hence, further research is necessary.

The improvements observed in walking speed is an important finding, as studies have reported that walking speed is an indicator of vitality and a predictor of functional decline,[27] subsequent disability,[28] survival[29] and other adverse outcomes.[30] A recent statement from the Society on Sarcopenia, Cachexia and Wasting Disease stated that an improvement in gait speed of at least 0.1 m/s can be considered clinically significant.[31] The results of the current study showed that walking speed increased in the Ex group by 0.10 m/s and in the Ex + TC group by 0.12 m/s after the 3-month intervention. Exercise alone or combined exercise and TC supplementation might be effective for improving walking ability in sarcopenic women.

As sarcopenia is a multifactorial condition involving age-related declines in muscle mass, strength or function, effective treatments should target improvements in muscle mass and physical function. In the current study, the OR for muscle mass and usual walking speed improvement was more than threefold as great in the Ex + TC group compared with the HE group. Although investigation into mechanisms of the anti-oxidant capacities of TC together with exercise was beyond the scope of the present study, our results show that the combination of exercise and TC effectively enhanced muscle mass and walking ability.

The present study had several limitations. First, investigation into the mechanisms of the anti-oxidative effects of TC was not explored. Future studies should investigate TC effects on reactive oxygen species and oxidative stress markers in order to provide further understanding and insight into the treatment of sarcopenia. Second, muscle mass was measured using BIA. Other methods of measuring muscle mass, such as magnetic resonance imaging (MRI), computerized tomography and dual-energy X-ray absorptiometry, are typically considered more accurate.[32] Previous studies have reported strong correlations between MRI and BIA measurements for muscle mass in older adults.[12,33,34] Hence, the validity of the BIA measurements has little influence on the interpretation of the results in the present study. Third, 51.9% (138 sarcopenic women) were excluded from the present study based on the exclusion criteria or refused participation, and were not included in this intervention trial. Future research should consider the external validity of the populations included in randomized controlled trials, and perhaps shift the focus to community-dwelling older adults often excluded from intervention studies.

Acknowledgments

This research was supported by a Grant-in-Aid for Scientific Research B from the Japanese Society for the Promotion of Science (22300243). The authors have no financial or any other kind of personal conflicts with this trial. The sponsor had no role in the design and conduct of the study; subject recruitment; collection, management, analysis and interpretation of data; or preparation of the manuscript. M S, Y Y and I T are researchers with Kao Corp., and their contributions limited to providing the tea catechin supplementation. E Hosoi assisted in the revision of manuscript.

Disclosure statement

The authors declare no conflict of interest.

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European Journal of Clinical Nutrition (2013) 67, 395–400

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ORIGINAL ARTICLE

Accuracy of segmental multi-frequency bioelectrical impedance analysis for assessing whole-body and appendicular fat mass and lean soft tissue mass in frail women aged 75 years and older

M Kim and H Kim

BACKGROUND/OBJECTIVE: We aimed to examine the accuracy of segmental multi-frequency bioelectrical impedance analysis (SMF-BIA) for the assessment of whole-body and appendicular fat mass (FM) and lean soft tissue mass (LM) in frail older women, using dual-energy X-ray absorptiometry (DXA) as a reference method.
SUBJECTS/METHODS: All 129 community-dwelling Japanese frail older women with a mean age of 80.9 years (range, 75–89 years) from the Frailty Intervention Trial were recruited. The agreements between SMF-BIA and DXA for whole-body and appendicular body composition were assessed using simple linear regression and Bland–Altman analysis.
RESULTS: High coefficients of determination (R^2) for whole-body FM ($R^2 = 0.94$, s.e. of estimate (SEE) = 1.2 kg), whole-body LM ($R^2 = 0.85$, SEE = 1.4 kg), and appendicular FM ($R^2 = 0.82$, SEE = 1.1 kg) were observed between SMF-BIA and DXA. The R^2 coefficient for appendicular LM was moderate ($R^2 = 0.76$, SEE = 0.8 kg). Bland–Altman plots demonstrated that there was systematic (constant) bias (that is, DXA minus SMF-BIA) with overestimation of whole-body FM (bias = − 1.2 kg, 95% confidence interval (CI) = − 1.5 to − 0.1) and underestimation of whole-body LM (bias = 2.1 kg, 95% CI = 1.8–2.3) by SMF-BIA. Similar, the appendicular measurements also demonstrated systematic bias with overestimation of appendicular FM (bias = − 0.3 kg, 95% CI = − 0.5 to − 0.1) and underestimation of whole-body LM (bias = 1.5 kg, 95% CI = 1.4–1.7) by SMF-BIA. In addition, the individual level accuracy demonstrated a non-proportional bias for whole-body LM ($r = 0.08$, $P = 0.338$) and appendicular FM ($r = 0.07$, $P = 0.413$).
CONCLUSIONS: SMF-BIA had acceptable accuracy for the estimation of whole-body and appendicular FM and LM in frail older women, although SMF-BIA underestimated LM and overestimated FM relative to DXA.

European Journal of Clinical Nutrition (2013) **67**, 395–400; doi:10.1038/ejcn.2013.9; published online 6 February 2013

Keywords: body composition; bioelectrical impedance analysis; sarcopenia; frailty

INTRODUCTION

Frailty is an important and common geriatric syndrome that is described as a status of increased vulnerability resulting from the loss of complexity in resting dynamics involving multiple physiological systems with advancing age.[1] The prevalence of frailty increases with age, from 3.9% at 65–74 years to 11.6% at 75–84 years and to 25% in people older than 85 years. In addition, frailty is more prevalent in women than in men.[1] Sarcopenia is a loss of skeletal muscle mass and size that occurs with aging.[2] Although many definitions of sarcopenia have been reported,[3–5] current definitions focus on loss of appendicular skeletal muscle mass as well as low muscle strength and low physical performance.[6] The European Working Group on Sarcopenia in Older People consensus definition of sarcopenia is based on three stages: the presarcopenia stage involves low muscle mass with normal muscle strength and physical performance; the sarcopenia stage involves low muscle mass and either diminished muscle strength or physical performance; and severe sarcopenia combines all three factors.[6] Several pathophysiological overlaps between sarcopenia and frailty have been observed.[7] Thus, age-related loss in muscle mass and strength are a major component in the development of frailty in the elderly.[8,9] Moreover, frailty is associated with a decline in muscle mass and quality and a parallel increase in fat mass (FM).[10] Measurement of body composition, including FM and muscle mass in older populations provide important information about their nutritional status. Therefore, the understanding of the body composition of frail elderly populations is an important part of clinical assessment with a goal of optimal prevention and treatment strategies.

Dual-energy X-ray absorptiometry (DXA) is an accepted method for the estimation of whole-body and segmental body fat and fat-free mass (FFM), which includes lean soft tissues and bone minerals.[11–13] However, DXA has disadvantages for use in clinical settings, such as the high cost of equipment, risk of radiation exposure and lack of access to instruments. For clinical use, bioelectrical impedance analysis (BIA) has been used as an attractive alternative method.[4,14,15] BIA is a portable, non-invasive, easy to use and convenient method for the patient, and it is also relatively inexpensive compared with other methods.[16] Of the BIA devices developed over the years, segmental multi-frequency (SMF)-BIA devices have advantages

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Received 17 September 2012; revised 19 December 2012; accepted 21 December 2012; published online 6 February 2013