Leucine and perindopril to improve physical performance in people over 70 years with sarcopenia: the LACE factorial RCT

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Scientific summary

LACE factorial RCT

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Background

Sarcopenia, defined as the age-related loss of muscle mass and strength, is a major health problem. The condition is common, affecting between 5% and 10% of community-dwelling people aged > 65 years. It is a major cause of multiple adverse outcomes for older people, including falls, fractures, hospital admission, prolonged length of stay, need for care and reduced survival.

Objectives

The primary objective of the LACE (Leucine and Angiotensin-Converting Enzyme inhibitor) trial was to determine the efficacy of leucine and perindopril in improving physical function in older people diagnosed with sarcopenia.

The secondary objectives were to:

- evaluate the effect of leucine and perindopril on muscle mass
- evaluate the ability of biomarkers to predict response to therapy in patients with sarcopenia.

In addition, the LACE programme of work sought to improve the effectiveness of screening and recruitment pathways for sarcopenia trials to facilitate the delivery of future trials in this disease area.

Methods

The LACE trial was a placebo-controlled, parallel-group, double-blind, randomised 2 × 2 factorial trial. Participants were recruited from primary care and geriatric medicine secondary care departments in 14 UK hospitals. Participants were eligible for inclusion if they were aged ≥ 70 years and had low muscle strength (handgrip of < 30 kg for men and < 20 kg for women, or a 4-metre walk speed of < 0.8 m/second) and low muscle mass as determined by bioimpedance assessment. Exclusion criteria included contraindications or existing indications to angiotensin-converting enzyme inhibitors (aortic stenosis, chronic heart failure, hypotension or symptomatic postural hypotension, hyperkalemia, hyponatraemia, serum creatinine level of > 170 µmol/l, current use of oral non-steroidal anti-inflammatory drugs, potassium supplements, aliskiren, spironolactone or other potassium-sparing diuretics); contraindications to undertaking study procedures (implantable cardioverter defibrillator or pacemaker with atrial sensing lead, peripheral oedema present above knee level, inability to mobilise without human assistance, inability to give written informed consent), other causes of myopathy (severe chronic obstructive pulmonary disease, known myositis or other established myopathy, self-reported weight loss of > 10% in the last 6 months, uncontrolled thyrotoxicosis, use of ≥ 7.5 mg/day prednisolone or equivalent), currently enrolled in a time-limited exercise-based rehabilitation programme, and presence of any progressive neurological or malignant condition with a life expectancy of < 6 months.

Eligible participants were randomised 1 : 1 to receive perindopril or a matching placebo and, separately, were randomised 1 : 1 to receive leucine or a matching placebo. A web-based randomisation system was used to conceal treatment allocation. Perindopril was commenced orally at 2 mg once daily and uptitrated to 4 mg once daily after 2 weeks if tolerated. Leucine was administered orally as 2.5 g of leucine powder three times per day with meals.

Outcomes were collected at baseline and at 6 and 12 months, with additional investigational biomarkers collected at 3 months. The primary outcome was the between-group difference in the Short Physical Performance Battery (SPPB) score by repeated measures over the 12-month follow-up period, adjusted for baseline values. The initial sample size calculation estimated that 440 participants were needed to detect a 0.5-point difference in the SPPB, assuming a power of 90%, alpha of 0.05, standard deviation of 2.7, correlation of 0.7 between time points and dropout rate of 20% at 12 months. Secondary outcome measures included appendicular muscle mass by dual X-ray absorptiometry; health-related quality of life, measured using the EQ-5D-3L (EuroQol-5 Dimensions, three-level version) measure; maximal handgrip strength; quadriceps strength; 6-minute walk distance; activities of daily living, measured using the Nottingham Extended Activities of Daily Living score; hip bone mineral density, measured by dual X-ray absorptiometry scanning; and insulin resistance, measured using HOMA-IR (HOmeostatic Model Assessment – Insulin Resistance). All adverse events were recorded, together with the number of falls. Protein-, DNA (deoxyribonucleic acid)- and RNA (ribonucleic acid)-based biomarkers were collected at baseline and at 3 and 12 months.

Analyses were prespecified in a Statistical Analysis Plan and conducted according to intention-to-treat principles. The primary outcome (the between-group difference in SPPB across the 12 months of follow-up) was analysed using repeated measures mixed models, both unadjusted and adjusted for baseline values of the variable under test, age, sex and minimisation variables. An initial test for treatment interaction showed no evidence of interaction and, thus, the comparisons of perindopril with placebo and leucine with placebo were conducted separately. Prespecified subgroup analyses for the primary outcome were conducted for the following categories: age ≤ 80 years versus > 80 years, male versus female, and above versus below the median total protein intake. Secondary outcomes were also analysed using repeated measures mixed models. Correlations between baseline biomarkers and baseline measures of physical performance and muscle mass, between baseline biomarkers and change in physical performance and muscle mass, and between short-term change in biomarkers and changes in physical performance and muscle mass were calculated.

Results

A total of 320 potential participants from 14 UK centres were screened between June 2016 and December 2018, and 145 participants were randomised: 73 were allocated to perindopril and 72 to the perindopril placebo; 72 were allocated to leucine and 73 to the leucine placebo. The mean age of participants was 79 years and 78 out of the 145 (54%) were women. The mean SPPB was 7.0 points (where best function is 12 points), denoting significantly impaired physical performance. A total of 96% of participants fulfilled the current European Working Group criteria for probable sarcopenia, although only 31% fulfilled the criteria for confirmed sarcopenia that includes low muscle mass. The median adherence rate was lower for perindopril than for the perindopril placebo (76% vs. 96%; $p = 0.99$). The median adherence rate was the same in the leucine and the leucine placebo groups (76% vs. 76%; $p < 0.001$).

Perindopril had no significant effect on the primary outcome [adjusted treatment effect −0.1 points, 95% confidence interval (CI) −1.2 to 1.0 points]. Treatment effects across prespecified subgroups were similar, and treatment effect did not correlate significantly with adherence. No significant treatment effect was seen for any secondary outcome, except worse EQ-5D-3L thermometer scores for the perindopril group than for the perindopril placebo (treatment effect −12 points, 95% CI −21 to −3 points). More adverse events were seen in the perindopril group ($n = 218$ vs. $n = 165$), but falls rates were similar. Combining these results with those of previous trials of angiotensin-converting enzyme inhibitor inhibitors (ACEi) and angiotensin receptor blockers in a meta-analysis excluded a minimally clinically important benefit on SPPB, handgrip strength or leg strength.

Leucine had no significant effect on the primary outcome (adjusted treatment effect 0.1 points, 95% CI −1.0 to 1.1 points). Treatment effects did not differ by age or sex, and treatment effect did not correlate significantly with adherence. A greater increase in the SPPB was noted in participants with protein intake below the median than in those with protein intake above the median (2.6, 95% CI 0.6 to 4.5, vs. −0.1, 95% CI −0.8 to 0.6), although this was not significant on formal interaction testing ($p = 0.70$). A greater increase in the SPPB was also noted in those with confirmed sarcopenia (low muscle mass and strength) than in those with low strength alone (1.7, 95% CI 0.7 to 2.7, vs. −0.5, 95% CI −1.4 to 0.3), although again this was not significant on formal interaction testing ($p = 0.06$). No significant treatment effect was seen for any secondary outcome. There were similar numbers of adverse events (187 in the leucine group, 196 in the placebo group) and similar rates of falls in both groups. Combining these results with those of previous trials of leucine in a meta-analysis did not show evidence of a clinically important benefit on measures of physical performance or lean body mass.

Analysis of screening and recruitment metrics showed higher response rates and higher overall numbers randomised through primary care recruitment than through secondary care recruitment [138/13,808 (1.0% of total invited) vs. 7/1202 (0.6% of total notes screened)]. At 10 sites where it was possible to compare central and local prescreening strategies, the conversion rate from prescreening to randomisation was 18 out of 588 (3.1%) for centralised calls compared with 73 out of 1814 (4.0%) for local prescreening calls ($p = 0.29$). Only a weak relationship was seen between higher (worse) Strength Assistance Rise Climb – Falls score at screening and lower likelihood of progression to randomisation ($r = -0.08$; $p = 0.03$). Muscle mass estimates generated using the Sergi equation were systematically biased, tending to underestimate dual-energy X-ray absorptiometry-measured muscle mass in people with low muscle mass.

None of the biomarkers tested showed consistent or strong associations with either baseline muscle mass or physical performance, either in cross-sectional analyses at baseline, using baseline biomarkers to predict change in mass and performance over time, or using change in biomarkers to predict longer-term change in mass and performance.

Conclusions: implications for health care

The results from this randomised controlled trial do not support the use of either 4 mg of perindopril once daily or 2.5 g of leucine three times per day as standalone interventions to treat sarcopenia in older people. We did not find any biomarker able to predict change in muscle mass or physical performance in this study population.

Suggestions for further research

Further trials are needed to test whether leucine could benefit subgroups of patients with low muscle mass and/or low protein intake. In addition, trials comparing the effect of leucine as an adjunct to resistance training and trials comparing protein supplementation plus leucine with protein supplementation alone would help to delineate the role (if any) of leucine as a treatment for sarcopenia. It is unlikely that conducting further trials of ACEi will lead to clinically significant benefits, and interventions exploiting alternative pathophysiological mechanisms should be prioritised. Further exploration of the LACE trial data set will yield information on clusters of biomarkers that may predict disease trajectory and identify mechanistic subgroups for future intervention studies. Blood-borne biomarkers that can be used to easily confirm a diagnosis of sarcopenia should be sought, particularly biomarkers that can replace the need to measure muscle mass, as this requirement remains an impediment to the widespread diagnosis of sarcopenia in clinical practice.

There is a need to develop novel approaches to sarcopenia trials' platforms to accelerate progress in this field. The development of these approaches should build on the knowledge gained in the LACE trial on how to more efficiently find and recruit people with sarcopenia and can utilise the network of UK centres that have gained experience recruiting patients with sarcopenia in the LACE trial.

Study registration

This trial is registered as ISRCTN90094835 and EudraCT 2014-003455-61. The systematic review is registered as PROSPERO CRD42014013398.

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