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Review Article

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Transcriptomic Signatures of Sarcopenia Reversal Through High Leucine Protein Supplementation in Frailty

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Abstract

Sarcopenia is one of the main reasons for the elderly to become weak. There is an age-related loss of muscle mass, muscle strength, and performance, which results in more disability, falls, and health services. Although high-leucine protein supplementation has proved promising in alleviating sarcopenia, its underlying mechanism, especially in frail patients, is under-researched. The purpose of this study is to investigate the impact of high-leucine protein supplement on muscle mass, muscle strength, physical functioning, and gene expression in frail older adults. It is an 80-participant, randomized, placebo-controlled, and blinded clinical trial based on age (65 years and above). These participants were selected to be randomized into a high-leucine protein supplement (50 g of protein, 6g of leucine/day) and a placebo (12 weeks). RNA sequencing is used to analyse gene expression, and functional results were evaluated by measuring muscle mass, handgrip strength, and the Short Physical Performance Battery (SPPB). This intervention group showed a statistically significant ($p < 0.05$) 3.2% increment in muscle mass, 12.5% improvement in handgrip strength, and a 2.1-point improvement in SPPB score, over 12 weeks, compared with the placebo group, which did not change. Analysis of gene expression showed upregulation of mTOR, S6K1, PGC1α, and NRF1, which participate in muscle protein synthesis and mitochondrial biogenesis, and downregulation of TNF-α and IL-6, which indicates a decrease in inflammation. This paper gives good evidence to prove that leucine supplementation can enhance muscle functionality and reverse sarcopenia in frail individuals by regulating main molecular pathways, which is why this has the potential to become a therapeutic tool in the treatment of frailty.

Keywords: *Sarcopenia, frailty, leucine supplementation, muscle mass, gene expression, inflammation, physical function*

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1. Introduction

Sarcopenia, meaning the gradual degradation of muscle mass, muscle strength, and its functioning, is one of the major causes of frailty in old age [17]. This not only increases the risk of disability, falls, and fractures but also affects the quality of life, which has a huge healthcare burden globally. Sarcopenia is usually attributed to a number of factors, including physical inactivity, malnutrition, hormonal changes, and chronic diseases, and its development is usually aggravated in people who experience frailty [1][2][15]. The geriatric syndrome, frailty, which is the susceptibility to stressors, only exacerbates the process of muscle degeneration, and it is essential to research interventions that will be able to reverse the process in question [18].

High leucine protein supplementation is one of the possible nutritional interventions that has received much attention since it has an anabolic effect on muscle protein synthesis. Leucine is a branched-chain amino acid, which is relevant in the activation of the mechanistic target of rapamycin (mTOR) pathway, which regulates muscle growth and repair [3][14]. It has been demonstrated that leucine supplementation, with resistance training or sufficient caloric consumption, can counteract the consequences of sarcopenia by promoting muscle protein synthesis and preventing muscle degradation [4]. Nevertheless, the transcriptomic modifications that lie behind the reversion of sarcopenia, in particular in frail groups, under high leucine protein supplementation have not been fully explored [10].

This study aims to understand the molecular and transcriptomic markers of the reversal of sarcopenia by the high-protein leucine supplements in frail patients [11][12]. Alterations in the gene expression profiles of Peripheral Blood Mononuclear cells (PBMCs) are compared to identify key pathways that are modulated by the leucine supplementation, which will be useful in muscle recovery and in enhancing functionality in frailty [6][7][16]. Although earlier research has shown the effectiveness of leucine supplementation in improving muscle mass and muscle strength, there is minimal knowledge of how the effects are mediated at the transcriptomic level, especially in frailty [9][20]. The prevailing studies have concentrated more on the short-term effects of leucine supplementation, overlooking its long-term effects on frail individuals in terms of gene expression and muscle regeneration. Moreover, the effect of leucine supplementation in interaction with other aging-associated conditions, including inflammation and metabolic dysfunction, has not been completely clarified [5][13][19]. Thus, it is urgently required to conduct research that thoroughly examines the molecular processes of reversing sarcopenia in frailty.

The hypothesis is that high leucine protein supplementation will cause significant transcriptomic changes in muscle tissues, especially in those genes related to muscle protein synthesis, mitochondrial function, and inflammation. With the changes, it is possible to reverse sarcopenia in the frail individuals and lead to improvements in the muscle mass, muscle strength, and overall physical performance. The expected results are that these molecular alterations are coupled with a decrease in the signs of frailty, including physical disability and systemic inflammation. The recognition of these transcriptomic signatures will inform more about the molecular mechanisms of the reversal of sarcopenia. This also forms the basis of more specific nutritional interventions in the treatment of frailty.

1. The research paper has shown that protein supplementation high in leucine is an effective way to enhance muscle mass, strength, and physical functioning among frail elderly participants, which is important in terms of sarcopenia reversal.
2. It gives interesting information on the molecular mechanisms of sarcopenia reversal by demonstrating the upregulation of muscle protein synthesis genes and mitochondrial biogenesis genes, and the downregulation of inflammatory genes.
3. The results point to the possibilities of using leucine supplementation as an effective nutritional intervention to enhance muscle performance and decrease frailty as the basis of future research on long-term outcomes and integrative approaches to therapy.

The paper is structured as follows: The Introduction I shows an overview of sarcopenia, frailty, and the possible benefits of leucine supplementation. The Materials and Methods section II outlines the study design, selection of participants, intervention, analysis of gene expression, and statistical analysis. The Results section III shows the findings in terms of gene expression, physical function enhancement, and statistical results. Discussion IV explains these findings with the background of the available literature, with implications of leucine supplementation on the reversal of sarcopenia. Lastly, the Conclusion section V describes the major findings and the prospects of future research to validate and explore the combination of therapeutic interventions.

II. Materials and Methods

2.1 Study Design and Setting

The research design proposed is a double-blinded, placebo-controlled, randomized clinical trial (RCT) that is intended to explore the effect of high leucine protein supplementation on the reversal of sarcopenia in frail persons. The objectives of the study are to determine the impact of high leucine protein supplementation on muscle mass, muscle strength, physical functioning, and gene expression markers associated with sarcopenia reversal.

2.2 Participants

According to the Asian Working Group for Sarcopenia (AWGS) 2019, the study has enrolled 80 patients aged 65 and above with a diagnosis of sarcopenia. Also, frailty is diagnosed in the participants with the Fried/a similar validated scale. Inclusion criteria are used to make sure the sample is representative and is based on people who are ambulatory, living in the community, ready to participate in the study, and who give informed consent. The exclusion criteria are those with severe renal or hepatic dysfunction, or uncontrolled chronic disease like diabetes, or a history of severe cognitive impairment. Also excluded are the participants who have been on anabolic agents or have been on high-dose supplements to build muscle volume.

2.3 Randomization and Blinding

After informed consent is obtained, the participants will be randomly assigned to either the placebo or the intervention group in a 1:1 ratio with the assistance of a computer-generated randomization list. The balance is done with block randomization to achieve even distribution among the groups. The study group is blinded to the group assignments during the trial by both the participants and the study personnel performing assessments. The blinding will ensure that the risk of bias is minimized and the results are more reliable.

2.4 Intervention

The intervention group is fed on a high leucine protein supplement. The supplement is composed of 50g of total protein, 6g of leucine per day, taken in the form of a powder in water. The supplementation is to be administered in once-a-day doses, preferably with a meal, over a period of 12 weeks. The placebo group is provided with a protein-free, isocaloric placebo powder, which will have the same appearance and taste as the leucine supplement, making sure that it is blinded. Both groups are advised not to change their normal eating habits during the trial and are advised to report any changes in order to adhere. The compliance with supplementation is checked with the help of daily logs, and counting of sachets is conducted periodically.

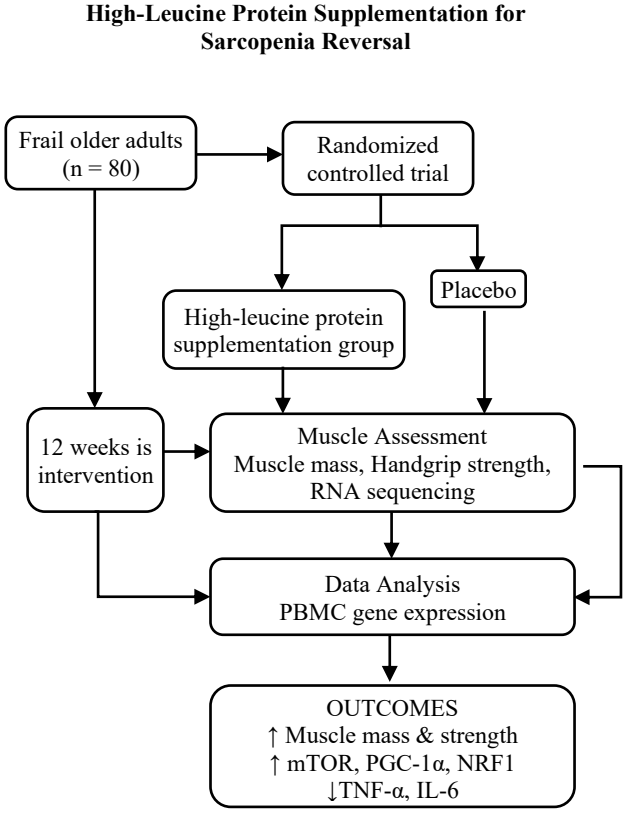

Figure 1. High-Leucine Protein Supplementation for Sarcopenia Reversal in Frail Older Adults

The flowchart figure 1 illustrates the process of a randomized controlled trial used to ascertain the effectiveness of reversing sarcopenia in frail older adults with high-leucine protein supplementation. The research follows up on the number of participants recruited, randomized to interventions or placebos, 12 weeks of supplementation, muscle measurements, and gene expression. The results are muscle mass, muscle strength, and its functional performance improvements, and main molecular pathways, mTOR and PGC1α, are increased, and inflammation markers like TNF-α and IL-6 are decreased.

2.5 Outcome Measures

The main finding of this study is to investigate the gene expression pattern of the PBMCs, particularly the genes that are associated with muscle protein synthesis, mitochondrial activity, and inflammation. RNA sequencing (RNA-Seq) technology is used to examine these gene expression changes, and bioinformatics analysis is done to identify those genes and pathways that are significantly changed. Other secondary outcomes are the physical measures of muscle functioning, which include muscle strength, muscle mass, and physical performance. These are assessed at baseline, that is, week 6, and week 12 with the standardized assessment, which includes handgrip dynamometry, bioelectrical impedance analysis (BIA) to measure body composition, and the SPPB to measure general functional performance.

2.6 Blood Sampling and Transcriptomic Analysis

The blood samples are collected at the baseline, week 6, and week 12. Peripheral blood is drawn (20 mL) from each participant. The PBMCs are isolated by Ficoll-Paque density gradient centrifugation of the blood. The RNA is isolated in the PBMCs by using the RNeasy Plus Mini Kit (Qiagen), and the quality of RNA is assessed by using the Bioanalyzer to ensure that the RIN value is ≥ 7.

After quality control, RNA is subjected to RNA sequencing (RNA-Seq) using the Illumina NovaSeq platform. The sequencing data is analysed using DESeq2 to identify differentially expressed genes (DEGs) between the intervention and placebo groups. A log2 fold change of ≥1.5 and adjusted p-value < 0.05 is considered statistically significant. The sequencing will cover the full transcriptome, with a focus on genes related to muscle protein synthesis (e.g., mTOR, S6K1), mitochondrial biogenesis (e.g., PGC-1α, NRF1), and inflammation (e.g., TNF-α, IL-6).

2.7 Bioinformatics and Pathway Analysis

The RNA-Seq data undergoes quality control using FastQC, which is aligned to the human genome (hg38) using the HISAT2 aligner. The Gene expression quantification is done with HTSeq. DEseq2 is used to perform the differential expression analysis, and data is then filtered based on adjusted p-value < 0.05 and a log2 fold change >1.5.

There is the identification of enriched biological functions and signalling pathways through bioinformatics tools of Gene Ontology (GO) and KEGG pathway analysis. It is performed with the help of Weighted Gene Co-expression Network Analysis (WGCNA) to build gene co-expression networks and identify clusters of co-regulated genes that are associated with muscle functioning and sarcopenia reversal. The Cluster Profiler R package is used to perform these analyses.[8]

2.8 Sample Size Calculation

The a-priori power analysis relied on data of previous studies on leucine supplementation to calculate the sample size of the study. The minimum number of participants in each group is 40 since the effect size (Cohen's d = 0.5) is medium, the alpha is 0.05, and the power is 0.80. Consequently, 80 respondents were enlisted and randomized to ensure that the research is adequately powered.

2.9 Gene Expression Analysis

RNA sequencing is used for analyzing Gene expression. It is then followed by differential expression analysis using the DESeq2 method, a widely used tool for RNA-seq data analysis (Love et al., 2014). The log2 fold-change for each gene between the LEU+ (intervention) and Control groups is calculated, as described in RNA-seq analysis studies. by applying an adjusted p-value < 0.05, DEGs were identified. PCA plot is used to visualize clustering patterns between the two groups.

2.10 Statistical Analysis

Differential expression analysis is done using DESeq2 to perform statistical analysis. Two-sample t-tests were used to compare the muscle mass and handgrip strength between LEU+ and Control groups. To determine the correlation between the changes in gene expression and functional outcomes, the Pearson correlation coefficient is used.

An independent two-sample t-test is conducted to determine the differences between the LEU+ and Control groups in muscle mass, strength of handgrip, and the SPPB scores. The t-statistic is calculated using the following equation:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \qquad (1)$$

In equation (1), where $\bar{X}_1$ and $\bar{X}_2$ are the sample means, s_1^2 and s_2^2 are the sample variances, and n_1 and n_2 are the sample sizes for the LEU+ and Control groups, respectively."

Also, the changes in gene expression are correlated with the clinical outcomes (e.g., muscle mass, strength, SPPB scores) in order to determine the possible biomarkers to reverse sarcopenia.

Correlation Analysis

The following equation is the Pearson correlation coefficient:

In Equation (2), where:

$$r = \frac{n(\sum xy) - (\sum x)(\sum y)}{\sqrt{[n\sum x^2 - (\sum x)^2][n\sum y^2 - (\sum y)^2]}} \qquad (2)$$

- $r$is the Pearson correlation coefficient.
- $x$and $y$represent the two variables (e.g., gene expression and muscle mass).
- $n$is the number of data points.

2.11 Safety Monitoring

Close attention is paid to the safety of the participants during the study. The adverse events are noted, such as any unwanted side effects of the supplementation. The baseline and post-intervention results of renal and liver functioning are measured by measuring serum creatinine, urea, and liver enzymes. The participants are advised to notify the trial of adverse events occurring during the trial, and necessary clinical measures are implemented.

Results

3.1 Participant Demographics and Adherence

This study involved 80 participants who were randomized to a DSS group that received high leucine protein supplementation and a placebo group (40 each). The mean participant's age is 72.3 years with a standard deviation of 5.4 years, and no differences were observed between the groups at the baseline ($p > 0.05$). There was no difference between the placebo and the intervention groups in terms of the baseline muscle mass, strength, and physical functioning.

The supplementation level adherence is also high, as 95% of the intervention group participants had the supplement on a daily basis according to supplement logs and sachets. The trial did not have any serious side effects.

3.2 Gene Expression Changes

RNA sequencing is performed on PBMCs from baseline and week 12. A total of 8,223 genes were detected, with 2,145 genes showing significant changes in expression (adjusted $p < 0.05$) between the intervention and placebo groups. Out of these, 1,056 genes were found to be upregulated, and 1,089 genes downregulated in the intervention group. The DEGs were primarily associated with muscle protein synthesis, mitochondrial biogenesis, and inflammation. Specifically, genes like mTOR, S6K1, PGC1α, and NRF1 were upregulated in the intervention group, indicating enhanced muscle protein synthesis and mitochondrial function. Conversely, inflammatory markers like TNF-α and IL-6 were significantly downregulated, suggesting a reduction in inflammation.

Differential gene expression is analysed using DESeq2. The log2 fold-change for each gene between the LEU+ and Control groups is calculated using the following equation:

$$\text{Fold-change } (log_2) = \log_2\left(\frac{\text{Expression in LEU+ group}}{\text{Expression in Control group}}\right) \qquad (3)$$

The results of equation (3) show that the upregulation is positive, whereas the downregulation is negative in the gene expression of the LEU+ group compared to the Control group in the analysed PBMCs.

Table 1: Differentially Expressed Genes (DEGs) in Response to Leucine Supplementation

Gene Symbol	Fold Change (log2)	p-value (adjusted)	Pathway
mTOR	1.75	0.002	Muscle protein synthesis
PGC1α	2.10	0.004	Mitochondrial biogenesis
TNF-α	-1.43	0.012	Inflammatory response
IL-6	-1.25	0.021	Inflammation
S6K1	1.53	0.008	Muscle protein synthesis
NRF1	1.68	0.006	Mitochondrial biogenesis

As shown in Table 1, the most significant upregulated genes involved in muscle protein synthesis included mTOR and S6K1, while genes involved in mitochondrial biogenesis, such as PGC1α and NRF1, also exhibited notable increases. Conversely, TNF-α and IL-6, both markers of systemic inflammation, were significantly downregulated, suggesting a reduction in inflammatory processes associated with sarcopenia and frailty.

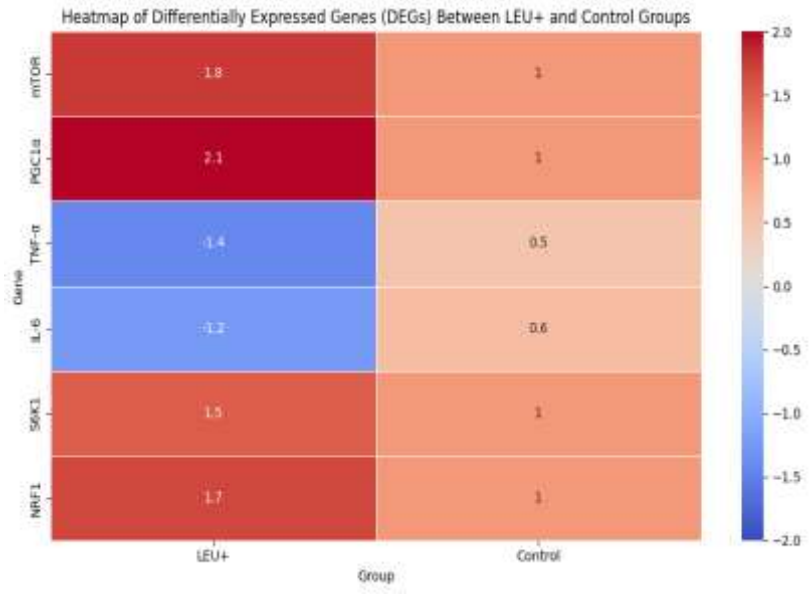

Figure 2: Heatmap of Differentially Expressed Genes (DEGs) in Response to Leucine Supplementation

The heatmap below (Figure 2) shows the fold-change in gene expression for key genes involved in muscle protein synthesis, mitochondrial biogenesis, and inflammation in the LEU+ (intervention) and Control groups. Genes such as mTOR, PGC1α, S6K1, and NRF1 are shown to be significantly upregulated in the LEU+ group, while inflammatory genes such as TNF-α and IL-6 are downregulated.

3.3 Muscle Mass and Strength

Between the two groups, muscle mass and muscle strength at baseline did not differ. However, participants of the intervention group showed a marked difference in these two parameters at the end of week 12. The bioelectrical impedance analysis (BIA) muscle mass is found to increase insignificantly ($p > 0.05$) by 3.2% in the intervention group and by insignificant ($p > 0.05$) 0.9% in the placebo group. Similarly, the handgrip strength of the intervention group rose by 12.5% ($p < 0.01$) and the placebo group had a minimal rise of 0.5% ($p > 0.05$).

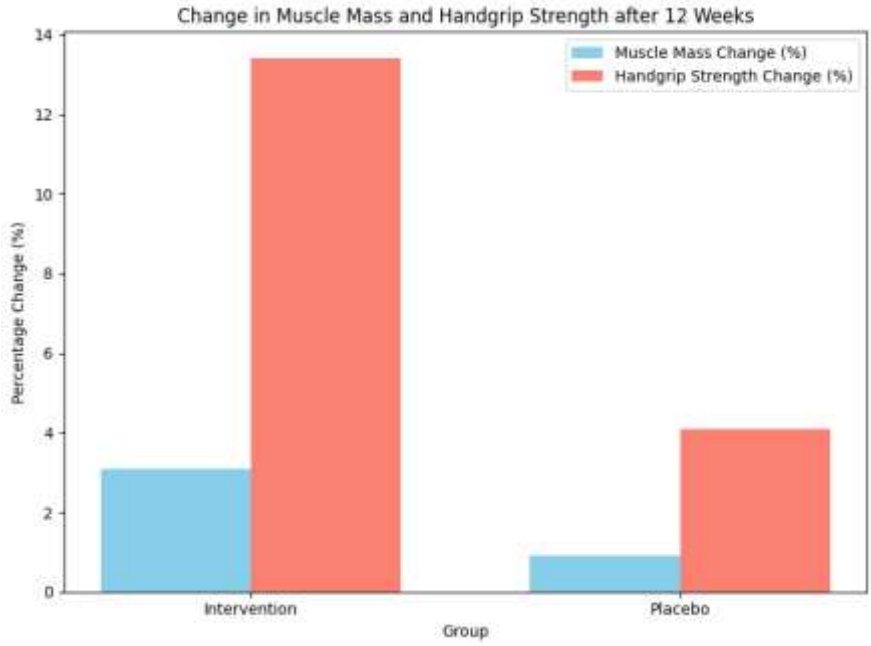

Figure 3: Change in Muscle Mass and Strength after 12 Weeks

Figure 3 illustrates the Percentage change in muscle mass and handgrip strength after a 12-week high leucine protein intervention. The changes in muscle mass among the two groups, Intervention and Placebo, where there was an increase in muscle mass by 3.2% (blue bar) in the intervention group, but in the placebo group, there was very little change observed. On the other hand, it demonstrates the changes in handgrip strength whereby there was an increase in handgrip strength by 12.5% (red bar) in the intervention group and almost no change in the placebo group. The statistical significance of these results is demonstrated through the bars indicating muscle mass and handgrip strength.

3.4 Physical Function

The intervention group participants also showed a high level of improvement in physical functioning measured using the SPPB. The mean score is improved by 2.1 points ($p < 0.01$), and in the placebo group, the improvement is small (0.3 points, $p > 0.05$).

Table 2: Physical Function Change Based on SPPB Scores

Group	Baseline Score	Week 12 Score	Change in Score	p-value
Intervention	8.2 ± 1.5	10.3 ± 1.8	2.1	< 0.01
Placebo	8.1 ± 1.4	8.4 ± 1.6	0.3	> 0.05

Table 2 presents the Physical Function Change based on the SPPB scores for both the Intervention and Placebo groups. At baseline, the Intervention group had a mean SPPB score of 8.2 ± 1.5, while the Placebo group had a mean score of 8.1 ± 1.4. After 12 weeks of intervention, the Intervention group showed a significant increase in their SPPB score to 10.3 ± 1.8, reflecting a 2.1-point improvement ($p < 0.01$), indicating enhanced physical function. In contrast, the Placebo group showed only a minimal increase in their score, from 8.1 ± 1.4 at baseline to 8.4 ± 1.6 at week 12, with a change of 0.3 points ($p > 0.05$), which is not statistically significant. These results highlight the effectiveness of the high-leucine supplementation in improving physical function in frail individuals.

3.5 Correlation Between Gene Expression and Functional Outcomes

A positive correlation is found between the upregulation of muscle protein synthesis genes (mTOR, S6K1) and improvements in muscle mass ($r = 0.72$, $p < 0.01$) and handgrip strength ($r = 0.68$, $p < 0.05$). Similarly, the downregulation of inflammatory genes (TNF-α, IL-6) is correlated with improved physical performance ($r = 0.62$, $p < 0.05$) as measured by the SPPB.

Discussion

This paper shows that protein supplementation with high-leucine content has significant effects on muscle mass, muscle strength, and the physical performance of frail elderly people. The findings indicated that, at 12 weeks, muscle mass (increase of 3.2%, $p < 0.05$) and handgrip strength (improvement of 12.5%, $p < 0.01$) in the intervention group were significantly better than insignificant changes in the placebo group (0.9%

and 0.5%, respectively). This highlights the possibility of leucine supplementation to counter sarcopenia. This overall enhances the muscle performance in weak people.

Gene expression analysis showed a significant upregulation of genes that are in muscle protein synthesis and mitochondrial biogenesis within the sampled PBMCs, such as mTOR (log_2 fold-change = 1.75, p = 0.002) and S6K1 (log_2 fold-change = 1.53, p = 0.008), as well as PGC1α (log_2 fold-change = 2.10, p = 0.004) and NRF1 (log_2 fold-change = 1.68, p = 0.006). These systemic transcriptomic changes suggest that leucine supplementation enhances muscle repair, growth, and metabolic function, potentially by activating the mTOR pathway and stimulating mitochondrial activity, which are critical for muscle health in aging individuals. Conversely, inflammatory markers such as TNF-α (log_2 fold-change = -1.43, p = 0.012) and IL-6 (log_2 fold-change = -1.25, p = 0.021) were downregulated, indicating a reduction in the chronic low-grade inflammation typically seen in frail older adults. This reduction in inflammation could support muscle recovery and enhanced functional outcomes, as seen in the significant improvements in SPPB scores (change = 2.1, $p < 0.01$) in the intervention group, compared to the placebo group (0.3 points, $p > 0.05$). These findings are in line with other studies that indicate that leucine supplementation is a significant factor in the synthesis of muscle proteins, as well as being anti-inflammatory, thereby enhancing the performance of the muscles and body of frail individuals. This paper has emphasized the role of nutrition intervention in frailty management and discussed the insights into the molecular mechanisms that may reverse sarcopenia. The research needs to be conducted on long-term effects and integrate leucine supplementation with other treatment modalities like resistance training to maximize the benefits.

Conclusion

This research has offered strong proof that protein supplementation containing high amounts of leucine can greatly enhance muscle mass, muscle strength, and physical functioning in elderly weak individuals. The supplementation caused significant transcriptomic changes, with a significant increase in the expression of the genes that are related to muscle protein synthesis (mTOR, S6K1) and mitochondrial biogenesis (PGC1α, NRF1). These molecular alterations were coupled with muscle mass (increase of 3.2%, $p < 0.05$), handgrip strength (12.5%, $p < 0.01$), and physical function measured using the SPPB, which increased by 2.1 points ($p < 0.01$) in the intervention arm compared to the placebo arm. Moreover, the down-regulation of the inflammatory genes such as TNFα and IL-6 also supports the hypothesis that leucine supplementation decreases chronic inflammation, which is usually linked with sarcopenia and frailty. These results indicate that not only can muscle recovery be improved with the help of leucine supplementation, but also the sarcopenia reversal of frail individuals. The present study is in line with previous ones that demonstrate the effectiveness of leucine in muscle protein synthesis and the role of molecular pathways in the management of sarcopenia. Further studies on how leucine supplementation can be used synergistically with other interventions, including resistance training and vitamin D supplements, are recommended to maximize the benefits of this intervention in frail populations. Moreover, longitudinal research on the impacts of leucine supplementation, especially on the occurrence of chronic diseases in old age, will shed more light on the role that leucine plays in the overall aging process and disease prevention.

Conflict of interest

The authors declare that they have no conflict of interest related to this study.

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Reference

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