

Effects of Synbiotic, Protein Supplementation Associated to Resistance Training on Inflammation, Oxidative Stress, and Muscle Strength in Older Adults with Type 2 Diabetes Mellitus: A Triple-Blinded Randomized Controlled Trial

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Background & aims: The accelerated ageing of the population represents a significant achievement of contemporary society; however, it also poses a series of challenges, particularly for developing countries, including the rise in non-communicable diseases, which can significantly increase the burden on healthcare and care services. Brazil ranks sixth globally in the number of individuals with type 2 diabetes mellitus (T2DM), with projections estimating 23.2 million cases by 2045. This places Brazil among the top ten countries with the highest prevalence of T2DM. There is an increased risk of sarcopenia with aging and T2DM, highlighting the involvement of diabetes in the pathophysiology of the musculoskeletal diseases. In addition to a low protein intake and sedentary habits, recent findings indicate that microbial dysbiosis contributes to systemic oxidative stress and the inflammaging pattern, already observed in aging process. Changes in the lifestyle of individuals with T2DM are crucial along with pharmacological interventions to improve the overall health status, since these modifications may also regulate the redox and inflammatory scenario. **Objective:** This study investigated the combined effects of Protein supplementation, Synbiotic+Protein and Resistance Training (RT) on physical performance, body composition, glycemic, inflammatory and oxidative stress parameters in older adults with T2DM. **Methods:** Randomized, triple-blinded clinical trial involving men aged over 65 with T2DM submitted to 12-week muscle-strength exercise protocol involving twice-weekly supervised sessions lasting 45-60 minutes. Participants (n=51) were allocated in three experimental groups: Control (only RT), Protein (20g of whey protein after RT) and Synbiotic+Protein (commercial capsules containing 10×10^{10} UFC/ml of *Lactobacillus acidophilus* NCFM, *Lactocaseibacillus paracasei* Lpc-37, *Bifidobacterium lactis* BI-07, *Bifidobacterium lactis* BI-04 and microcrystalline cellulose plus 20g of whey protein. **Results:** Participants showed homogeneity in bio-sociodemographic characteristics, although the SP group had lower alcohol consumption and Protein group reported higher use of sulfonylurea medication, potentially explaining the higher fat mass, body mass index and body fat percentage. All groups showed improved physical performance, and better redox balance after interventions, as indicated by higher uric acid levels (an antioxidant) and lower pro-oxidant iron concentrations in plasma. Although all groups showed higher levels of muscle injury markers (lactate dehydrogenase and creatine kinase activities), only the Protein group demonstrated strength gains, reduced insulin resistance, and oxidative insults from heme-iron species. Pro-inflammatory cytokines IFN- γ and IL-6 were also increased in the Protein group, possibly reflecting their role as mediators of integrative energy metabolism responses. The Synbiotic+Protein group exhibited reduced

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IFN- γ and increased Heme-Iron and CK concentrations. **Conclusions:** Resistance Training combined with Protein supplementation promoted strength gain and improved physical performance improvement some markers for inflammation and oxidative stress while the type and dosage used of Synbiotic combined with Protein and Resistance Training did not bring additional advantages.

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