MelaOstrong: Study Protocol with Statistical Analysis Plan

Title: Pilot Study Assessing the Efficacy of Melatonin and Osteogenic Loading on Bone Health in a Postmenopausal Population with Osteopenia: MelaOstrong Randomized Controlled Trial

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Study Objective: The purpose of this study was to assess whether melatonin (MEL), osteogenic loading (OL), or their combination improved bone health and quality of life (QOL) in osteopenic adults. The central hypothesis was that melatonin combined with OL would improve objective and subjective measures of bone health compared with placebo groups (mock loading plus placebo and osteogenic loading plus placebo). The main outcomes include DXA-based bone density measures (BMD and T-scores), functional outcomes (Timed Up & Go, sit-to-stand), bone turnover markers (CTX, P1NP), inflammatory markers (CRP), melatonin, cortisol, and QOL measures (PSS, STAI, CES-D, and QualiOst).

Study Design: This was a 12-month randomized controlled clinical trial in osteopenic adults. Participants were randomized into four groups:

1. Mock loading (ML) plus placebo
2. Mock loading (ML) plus melatonin
3. Osteogenic loading (OL) plus placebo
4. Osteogenic loading (OL) plus melatonin

The study aimed to enroll 40 participants, with 10 per group. Participants received the assigned intervention for 12 months.

Interventions: Participants were assigned to take either melatonin 5 mg capsules by mouth nightly before bed for 12 months or a placebo containing plant fiber, with matching size, color, and shape. Participants were assigned to osteogenic loading (OL) and attended once-weekly loading sessions for 12 months. The loading protocol used four devices targeting the upper body, lower body, core, and postural regions. Participants assigned to mock loading exerted approximately one multiple of body weight or less on each device.

Study Population: Eligible participants were aged 18 years or older with osteopenia, defined as a DXA T-score between −1.0 and −2.5. Participants had to be willing to complete the 12-month study, undergo DXA testing, provide urine samples, complete questionnaires, attend study visits, and follow the assigned capsule (Placebo or 5 mg Melatonin/nightly) and/or loading intervention (Once every week).

Key Exclusion Criteria: Women or men with osteoporosis; women or men with osteopenia due to hyperparathyroidism, multiple myeloma, metastatic bone disease, chronic steroid use including corticosteroids; women or men who are on any bone therapies (i.e. bisphosphonates, SERMs, hormone therapy, teriparatide, and denosumab); women with COPD; women or men who smoke; pregnant women; and men or women with muscular dystrophy, unmedicated hypertension, or unrepaired hernia, regular use of proton pump inhibitor medication, or any thyroid/parathyroid dysfunctions.

Outcome Measures: The primary outcome assessed was change in bone health assessed by BMD and T-scores. Secondary outcomes included urinary P1NP, CTX, melatonin, cortisol, CRP, FRAX, Timed Up and Go, Sit-to-Stand, PSS, CES-D, STAI, and QualiOst.

Data Collection: Data were collected at baseline, month 3, and month 12. DXA scans were performed at baseline and month 12. Urine samples, blood pressure, functional assessments, and questionnaires were collected at baseline, month 3, and month 12. Data and samples were coded to protect participant confidentiality.

Statistical Analysis Plan: Descriptive statistics were calculated for baseline participant characteristics and each study outcome. Baseline differences across groups were assessed using one-way ANOVA. For the primary outcomes, changes in BMD and T-scores over 12 months were assessed within groups using paired t-tests and across groups using one-way ANOVA. For secondary outcomes, including urinary P1NP, CTX, melatonin, cortisol, CRP, PSS, CES-D, STAI, and QualiOst, mixed-effects analyses with interaction terms were used to assess changes within and between groups over time. Tukey's multiple comparison tests were performed as post hoc analyses. For FRAX outcomes, paired t-tests were used to assess within-group changes over time. Pearson correlation coefficients were used to assess relationships between variables. A three-way repeated-measures ANOVA was performed to evaluate the effects of melatonin, time, and loading. All analyses were conducted using GraphPad Prism version 10. Statistical significance was defined as $p < 0.05$