Enhancing Klotho Levels

Klotho levels can be increased through either exercise (showing increases up to 88.5%) or supplementation approaches (including vitamin D and direct Klotho protein supplementation).

Abstract

Evidence indicates that both exercise and supplementation protocols yield significant increases in Klotho levels. Aerobic, resistance, and high-intensity interval training regimens have produced increases ranging from approximately 8.4% to 88.5% over 12-week periods, with one study suggesting that about 150 minutes of activity per week affords the greatest benefit. In trials of vitamin D supplementation using 50,000 IU weekly, levels either rose or were maintained (with statistical support at P 0.035 and P $<$ 0.001). Direct Klotho protein supplementation at 20 g/kg/day in rat models increased renal expression by 148% (P $<$ 0.05), while gene delivery and senolytic interventions restored levels and mitigated indicators of renal stress.

Interventions varied by population, design, and duration, with exercise studies conducted in sedentary or middle-aged adults and supplementation approaches applied to both human and animal models. Although head-to-head comparisons are not available, the data support physical exercise and select supplementation protocols as effective means for enhancing Klotho.

Paper search

Using your research question "What are the most effective ways to increase Klotho levels?", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 99 papers most relevant to the query.

Screening

We screened in papers that met these criteria:

- **Intervention Focus**: Does the study investigate interventions specifically aimed at increasing Klotho levels (-Klotho and/or s-Klotho)?
- **Study Design**: Is the study either an experimental study (RCT or controlled trial) OR a systematic review/meta-analysis of Klotho-increasing interventions?
- **Measurement Quality**: Does the study measure Klotho levels using validated biochemical methods AND include both baseline and post-intervention measurements?
- **Intervention Type**: Does the study examine a pharmacological, lifestyle, dietary, or exercise intervention?
- **Study Population**: Is the study conducted in either human or animal subjects?
- **Protocol Clarity**: Does the study provide a clearly defined and detailed intervention protocol?
- **Research Focus**: Does the study go beyond merely examining Klotho genetics, biomarkers, or effects by including an active intervention component?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

  Identify the type of study design used. Look in the methods section for specific details about:

- Randomized controlled trial
- Experimental study
- Observational study
- Crossover design
- Parallel group design

If multiple design elements are present, list all. If unclear, note "design not clearly specified". Prioritize the most specific design description found in the text.

- **Participant Characteristics**:

  Extract the following details about participants:

- Total number of participants
- Age range or mean age
- Gender distribution (% male/female)
- Health status/inclusion criteria
- Exclusion criteria

If ranges or means are provided, record both. If percentages are given, convert to actual numbers if possible. If any participant characteristics are missing or unclear, note "insufficient information".

- **Intervention Type and Modalities**:

  List all specific intervention types used in the study, including:

- Type of exercise (e.g., aerobic, high-intensity interval training, electromyostimulation)
- Duration of intervention
- Frequency of intervention
- Intensity of intervention

Be precise about specific details. If multiple intervention groups exist, list details for each group separately. If quantitative details are provided (e.g., 4 or 8 weeks), include those specific numbers.

- **Klotho Measurement Methods**:

  Identify and record:

- Type of Klotho measured (e.g., plasma levels, serum levels)
- Specific measurement technique
- Timing of measurements (baseline, post-intervention)
- Units of measurement

If multiple measurement points exist, list all. If measurement method is technical or complex, quote directly from methods section.

- **Primary Outcomes Related to Klotho**:

  Extract:

- Specific changes in Klotho levels
- Statistical significance of changes
- Magnitude of change (absolute or percentage)
- Any correlations with other physiological markers

Prioritize statistically significant results. If multiple outcomes are reported, list all. Use exact p-values and numerical changes when available.

- **Study Limitations and Potential Biases**:

  Identify:

- Limitations explicitly mentioned by authors
- Potential sources of bias
- Generalizability of results
- Funding sources or conflicts of interest

If no limitations are explicitly stated, note "no limitations reported by authors". Look in discussion or limitations sections for this information.

Results

Characteristics of Included Studies

Study	Study Design	Population Characteristics	Intervention Type	Duration	Full text retrieved
Amaro-Gahete et al., 2018	Randomized controlled trial, parallel group design	80 sedentary, healthy adults aged 45-65 years	Physical activity recommendation, high-intensity interval training, whole-body electromyostimulation	12 weeks	No

Study	Study Design	Population Characteristics	Intervention Type	Duration	Full text retrieved
Amaro-Gahete et al., 2019	Randomized controlled trial, parallel group design	74 sedentary middle-aged adults (mean age 53.4 ± 5.0 years)	Physical activity recommendation, high-intensity interval training, high-intensity interval training with whole-body electromyostimulation	12 weeks	No
Baghaiee et al., 2018	Experimental study with elements of randomized controlled trial and parallel group design	40 Wistar rats (young: 4 months; middle-aged: 11-15 months)	Aerobic exercise training	4 or 8 weeks	Yes
Corrêa et al., "Klotho, much more than an anti-aging protein"	Systematic review and meta-analysis	621 participants aged 30 to 65 years	Various exercise training protocols	Minimum of 12 weeks	No
Corrêa et al., 2022	Systematic review and meta-analysis	621 participants aged 30 to 65 years, healthy or with specific diseases	Aerobic training, resistance training, combined training	Minimum of 12 weeks	Yes
Etemadi et al., 2021	Randomized controlled trial, parallel group design	86 patients with hypovitaminosis D requiring hemodialysis	Cholecalciferol supplementation	12 weeks	No
Norman et al., 2007	Randomized controlled trial, experimental study	90 participants aged over 60 years with vitamin D deficiency	Vitamin D supplementation	12 weeks	Yes
Takenaka et al., 2023	Experimental study, parallel group design	Rats with subtotal nephrectomy	Subcutaneous klotho protein supplementation	No mention found	No

Study	Study Design	Population Characteristics	Intervention Type	Duration	Full text retrieved
Wang and Tsun, 2009	Experimental study, parallel group design	Spontaneously hypertensive rats (SHR) and matched Wistar Kyoto rats	Gene delivery using adeno-associated virus carrying mouse klotho full-length cDNA	No mention found	No
Zhu et al., 2022	Experimental study	Mice, human cell cultures, and patients with idiopathic pulmonary fibrosis (IPF)	Orally-active, clinically-translatable senolytics (Dasatinib plus Quercetin)	No mention found	No

Based on the information provided in the table, we identified:

- Study Design :
  - 4 randomized controlled trials
  - 5 experimental studies
  - 2 systematic reviews and meta-analyses
- Population Characteristics :
  - 6 studies focused on adult human participants
  - 3 studies used rat models
  - 1 study included a mix of human and animal subjects
  - 2 studies specifically mentioned sedentary participants
  - 5 studies included participants with specific health conditions
- Intervention Type :
  - Exercise interventions were most common, found in 5 studies
  - 3 studies used supplementation approaches
  - 2 studies incorporated whole-body electromyostimulation
  - 1 study each used gene therapy and drug interventions
- Duration :
  - 4 studies lasted 12 weeks
  - 2 studies had a minimum duration of 12 weeks
  - 1 study had a duration of 4-8 weeks
  - We didn't find duration information for 3 studies
- Intervention Categories :
  1. Exercise interventions (various modalities)
  2. Vitamin D supplementation

3. Direct Klotho supplementation or gene delivery
4. Senolytic treatments

- Study Duration :
  - Most human studies lasted for 12 weeks
  - Animal studies had varying durations

Effects of Interventions on Klotho Levels

Exercise Interventions

Study	Intervention Protocol	Baseline Klotho	Final Klotho	Percent Change
Amaro-Gahete et al., 2018	Physical activity recommendation, high-intensity interval training, whole-body electromyostimulation	No mention found	No mention found	No mention found
Amaro-Gahete et al., 2019	Physical activity recommendation, high-intensity interval training, high-intensity interval training with whole-body electromyostimulation	No mention found	No mention found	Increase reported (P 0.019)
Baghaiee et al., 2018	Moderate aerobic training	No mention found	No mention found	Significant increase (P=0.011)
Corrêa et al., "Klotho, much more than an anti-aging protein"	Various exercise training protocols	No mention found	No mention found	Significant increase ($P < 0.0001$)
Corrêa et al., 2022	Aerobic training, resistance training, combined training	No mention found	No mention found	8.39% to 88.51% increase

Based on the information provided in the table:

- Intervention Protocols :
  - 2 studies included physical activity recommendations
  - 2 studies included high-intensity interval training (HIIT)
  - 2 studies included whole-body electromyostimulation
  - 2 studies included aerobic training

  - 1 study each included resistance training and combined training
  - 1 study mentioned various exercise training protocols

- Percent Change :
  - All 4 studies that reported changes showed an increase in Klotho levels
  - 3 studies reported statistical significance:
    * 1 study with P 0.019
    * 1 study with P = 0.011
    * 1 study with P < 0.0001
  - 1 study reported a specific range of increase from 8.39% to 88.51%

- We didn't find intervention protocol or percent change information in the provided data for 5 and 6 studies, respectively.

Supplementation Interventions

Study	Supplement Type	Dosage	Klotho Change	Additional Effects
Etemadi et al., 2021	Cholecalciferol	50,000 IU weekly	Significant increase (P = .035)	No mention found
Norman et al., 2007	Vitamin D (cholecalciferol)	50,000 IU weekly	Prevented reduction (P < 0.001)	No mention found
Takenaka et al., 2023	Klotho protein	20 g/kg/day	+148% increase in renal expressions (p < 0.05)	Decreased albuminuria, blood pressure, FGF23, serum phosphate
Wang and Tsun, 2009	Klotho gene delivery	No mention found	Increased to control levels	Reduced oxidative stress, ameliorated kidney damage
Zhu et al., 2022	Senolytics (Dasatinib plus Quercetin)	No mention found	Increase reported	No mention found

Based on the information provided in the table:

- Supplement Types :
  - 2 studies used Vitamin D (cholecalciferol)
  - 1 study used Klotho protein
  - 1 study used Klotho gene delivery
  - 1 study used Senolytics (Dasatinib plus Quercetin)

- Dosage :
  - 2 studies used 50,000 IU weekly of Vitamin D
  - 1 study used 20 g/kg/day of Klotho protein
  - We didn't find dosage information for 2 studies

- Klotho Change :
  - 4 studies reported an increase in Klotho levels
  - 1 study reported prevention of Klotho reduction
- Additional Effects :
  - 1 study reported decreased albuminuria, blood pressure, FGF23, and serum phosphate
  - 1 study reported reduced oxidative stress and ameliorated kidney damage
- We didn't find any information for 5 studies across all categories in the provided data.

Comparative Effectiveness

Given the heterogeneity of the interventions and the lack of head-to-head comparisons, it is challenging to definitively state which approach is most effective in increasing Klotho levels. However, based on the studies we reviewed:

- Exercise Interventions : The studies we reviewed reported that exercise interventions showed significant increases in Klotho levels, with effects ranging from 8.39% to 88.51% according to Corrêa et al. (2022).
- Direct Klotho Supplementation : Takenaka et al. (2023) reported a 148% increase in renal Klotho expression with direct Klotho protein supplementation.
- Vitamin D Supplementation : The studies we reviewed indicated that Vitamin D supplementation shows promise in either increasing Klotho levels or preventing their reduction.
- Gene Therapy and Senolytic Approaches : The studies we reviewed demonstrated potential for these approaches, but more research may be needed to quantify their effectiveness relative to other interventions.

It's important to note that these interventions may have different mechanisms of action and could potentially be complementary.

Factors Influencing Intervention Effectiveness

Duration and Intensity

- Exercise Interventions :
  - Corrêa et al. (2022) reported that protocol duration and volume influenced S-Klotho concentration.
  - They suggested an optimal volume of around 150 minutes per week for the highest change in Klotho levels.
  - Both high-intensity interval training and moderate aerobic training showed significant increases in Klotho levels.
- Supplementation Interventions :
  - The studies on vitamin D used a consistent dosage of 50,000 IU weekly for 12 weeks.

Population-Specific Responses

The studies we reviewed included diverse populations:

- Exercise interventions were primarily studied in sedentary, healthy adults or middle-aged individuals.
- Vitamin D supplementation was investigated in patients with hypovitaminosis D requiring hemodialysis and in older adults with vitamin D deficiency.
- Klotho supplementation and gene delivery were studied in animal models with specific conditions (subtotal nephrectomy, hypertension).
- Senolytic treatments were tested in mice, human cell cultures, and patients with idiopathic pulmonary fibrosis.

Combined Interventions

- Most studies focused on single intervention approaches.
- Corrêa et al. (2022) noted that combined aerobic and resistance training did not show significant changes in Klotho levels, unlike individual training modalities.
- This unexpected finding highlights the complexity of Klotho regulation and the need for careful consideration when designing combined interventions.

References

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