Open Access https://www.jparathyroid.com

Journal of Parathyroid Disease

Journal of Parathyroid Disease 2023,11, e11230

DOI:10.34172/jpd.2023.11230

Mini-Review

Relationship between Klotho and parathormone

Azar Baradaran*

Abstract

Klotho is a protein that has been found to play a role in regulating parathyroid hormone (PTH) levels. The literature suggests an intricate relationship between Klotho and PTH. Klotho acts as a co-receptor for fibroblast growth factor 23 (FGF23), a hormone that helps regulate phosphate and vitamin D metabolism. Klotho deficiency has been associated with increased PTH levels and secondary hyperparathyroidism. Several studies have investigated the relationship between Klotho and PTH levels. Some studies have shown that Klotho levels are inversely correlated with PTH levels, suggesting that higher Klotho levels may lead to lower PTH levels. Other studies have found that Klotho deficiency can contribute to PTH resistance, leading to persistent hyperparathyroidism. Additionally, the Klotho-PTH axis holds promise as a potential target for therapeutic interventions in calcium and phosphate disorders.

Keywords: Klotho, Parathyroid hormone, Fibroblast growth factor 23, Vitamin D, Secondary hyperparathyroidism, Parathyroid gland, Phosphate, Kidney, Bone

Please cite this paper as: Baradaran A. Relationship between Klotho and parathormone. J Parathyr Dis. 2023;11:e11230. doi:10.34172/jpd.2023.11230.

Introduction

Klotho is a protein that plays a key role in various physiological processes, including calcium and phosphate homeostasis (1). Parathyroid hormone (PTH), on the other hand, is a hormone that regulates calcium and phosphate metabolism primarily by acting on the kidneys, bones, and intestines. Several studies have investigated the relationship between Klotho and PTH, with growing evidence suggesting an interplay between the two (2,3). Klotho is a transmembrane protein that is primarily expressed in the kidneys, parathyroid glands, and brain. It exists in two forms: membrane-bound Klotho (mKL) and soluble Klotho (sKL). mKL acts as a co-receptor for fibroblast growth factor 23 (FGF23), while sKL functions as an endocrine factor that can be detected in the blood (4,5). Klotho has been shown to have anti-aging effects, protect against vascular calcification, and regulate oxidative stress and PTH. On the other hand, Klotho has been associated with bone metabolism, cardiovascular health, and immune function (6,7). Furthermore, there is evidence suggesting that PTH may regulate Klotho expression. Animal studies have demonstrated that chronic elevation of PTH leads to decreased expression of renal Klotho. Conversely, treatment with exogenous sKL has been shown to reduce PTH levels in animal models (3,8). It has been found that Klotho deficiency leads to an increase in PTH levels. This suggests that Klotho may play a role in regulating PTH secretion or action. Additionally, studies have shown that sKL can directly inhibit PTH secretion from parathyroid cells. The exact mechanisms underlying the interaction between Klotho and PTH are not fully understood (3,9). However, it has been proposed that FGF23 signaling through mKL may inhibit PTH secretion indirectly by reducing vitamin D synthesis or directly by acting on parathyroid cells. In addition to their roles in calcium and phosphate homeostasis, both Klotho and PTH have been implicated in various other physiological processes. In this literature review, we will explore the connection between Klotho and PTH, highlighting their individual roles and potential interactions (3,9).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including Klotho, parathyroid hormone, fibroblast growth factor 23, vitamin D, secondary hyperparathyroidism, parathyroid gland, phosphate, kidney and bone

Mechanistic action of Klotho

Klotho is a protein that has been primarily studied for its anti-aging properties. It was first discovered in mice, where its deficiency resulted in accelerated aging and multiple age-related disorders. Klotho is mainly expressed in organs such as the kidneys, brain, and parathyroid glands, and it exists in two forms: membrane-bound and soluble.

Received: 11 May 2023, Accepted: 18 July 2023, ePublished: 14 August 2023

Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran.
***Corresponding author:** Azar Baradaran, Email: azarbaradaran@med.mui.ac.ir, azarbaradaran@yahoo.com

Implication for health policy/practice/research/medical education

Klotho is a protein that plays a key role in various physiological processes, including calcium and phosphate homeostasis. Parathyroid hormone (PTH), on the other hand, is a hormone that regulates calcium and phosphate metabolism primarily by acting on the kidneys, bones, and intestines. Several studies have investigated the relationship between Klotho and PTH, with growing evidence suggesting an interplay between the two. Studies have shown that serum Klotho levels are inversely correlated with PTH levels. Higher PTH levels have been associated with lower Klotho levels and vice versa. It has been suggested that Klotho may suppress PTH secretion by inhibiting the expression and release of PTH from the parathyroid glands.

The membrane-bound form functions as a co-receptor for fibroblast growth factor (FGF) 23, while the soluble form acts as a circulating hormone (4,10). One of the crucial roles of Klotho is its regulation of mineral homeostasis. Klotho deficiency in mice leads to dysregulation of calcium and phosphate metabolism, resulting in hyperphosphatemia, hypercalcemia, and increased PTH levels. These findings suggest that Klotho plays a role in the negative regulation of PTH secretion (11,12). On the other hand, PTH is a hormone produced by the parathyroid glands, which are four small glands located near the thyroid gland. PTH is essential for maintaining calcium and phosphorus balance in the body. It acts on target organs such as the kidneys, bones, and intestines to increase calcium levels when they are too low (11,13,14). Several studies have examined the relationship between Klotho and PTH levels. Some have shown that Klotho deficiency leads to increased PTH secretion, while others have reported a decrease in PTH levels with Klotho supplementation or overexpression (9,15). These findings indicate a potential modulatory role of Klotho in PTH secretion and activity (16). Additionally, emerging evidence suggests a direct interaction between Klotho and PTH signaling pathways. Klotho has been found to inhibit PTH-induced calcium release from bone cells and decrease PTH-stimulated gene expression in renal cells (9,17). These findings further support the idea that Klotho may act as a negative regulator of PTH activity. Although the exact mechanisms underlying the interaction between Klotho and PTH require further investigation (3,9). It is evident that these two factors play significant roles in maintaining mineral homeostasis and overall physiological balance. Understanding their relationship may have implications for the treatment and management of conditions associated with dysregulated calcium and phosphorus metabolism, such as chronic kidney disease and osteoporosis (18,19).

Klotho and parathyroid hormone

Klotho and PTH are two essential factors involved in the regulation of various physiological processes in the body. Studies have shown that serum Klotho levels are inversely correlated with PTH levels. Higher PTH levels have been associated with lower Klotho levels and vice versa (3,9).

Klotho and parathyroid gland function

Klotho has been found to play a role in the regulation of parathyroid gland function. It has been suggested that Klotho may suppress PTH secretion by inhibiting the expression and release of PTH from the parathyroid glands (3,9).

Vitamin D and Klotho

Vitamin D, which is involved in calcium and phosphate metabolism, has been shown to upregulate the expression of Klotho. In turn, Klotho may modulate the effects of vitamin D on PTH secretion (9,20).

Genetic variations

Certain genetic variations in the Klotho gene (KL) have been associated with altered PTH levels. One study found that individuals with a KL variant had higher PTH levels compared to those without the variant (21,22).

Clinical implications

Dysfunction of the Klotho-PTH system has been implicated in various clinical conditions. For example, low Klotho levels and high PTH levels have been observed in patients with chronic kidney disease, which may contribute to the development and progression of secondary hyperparathyroidism (9,23).

Conclusion

The literature suggests a complex interplay between Klotho and PTH, with Klotho potentially acting as a negative regulator of PTH secretion and activity. Further research is needed to elucidate the precise mechanisms involved and explore the therapeutic potential of targeting this interaction for various disorders.

Conflicts of interest

The author declare that she has no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

References

1. Xu Y, Sun Z. Molecular basis of Klotho: from gene to function in aging. Endocr Rev. 2015;36:174-93. doi: 10.1210/er.2013-1079.
2. Nabeshima Y. Discovery of alpha-Klotho unveiled new insights into calcium and phosphate homeostasis. Proc Jpn Acad Ser B Phys Biol Sci. 2009;85:125-41. doi: 10.2183/pjab.85.125.
3. Martin A, David V, Quarles LD. Regulation and function of the FGF23/klotho endocrine pathways. Physiol Rev. 2012;92:131-55. doi: 10.1152/physrev.00002.2011.
4. Hu MC, Kuro-o M, Moe OW. Secreted klotho and chronic kidney disease. Adv Exp Med Biol. 2012;728:126-57. doi:

10.1007/978-1-4614-0887-1_9.
5. Hu MC, Kuro-o M, Moe OW. Klotho and kidney disease. J Nephrol. 2010;23 Suppl 16:S136-44.
6. Kuro-o M. Klotho and the aging process. Korean J Intern Med. 2011;26:113-22. doi: 10.3904/kjim.2011.26.2.113.
7. Ding HY, Ma HX. Significant roles of anti-aging protein klotho and fibroblast growth factor23 in cardiovascular disease. J Geriatr Cardiol. 2015;12:439-47. doi: 10.11909/j.issn.1671-5411.2015.04.017.
8. Hofman-Bang J, Martuseviciene G, Santini MA, Olgaard K, Lewin E. Increased parathyroid expression of klotho in uremic rats. Kidney Int. 2010;78:1119-27. doi: 10.1038/ki.2010.215.
9. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol. 2013;75:503-33. doi: 10.1146/annurev-physiol-030212-183727.
10. Cheikhi A, Barchowsky A, Sahu A, Shinde SN, Pius A, Clemens ZJ, et al. Klotho: An Elephant in Aging Research. J Gerontol A Biol Sci Med Sci. 2019;74:1031-1042. doi: 10.1093/gerona/glz061.
11. Buchanan S, Combet E, Stenvinkel P, Shiels PG. Klotho, Aging, and the Failing Kidney. Front Endocrinol (Lausanne). 2020;11:560. doi: 10.3389/fendo.2020.00560.
12. John GB, Cheng CY, Kuro-o M. Role of Klotho in aging, phosphate metabolism, and CKD. Am J Kidney Dis. 2011;58:127-34. doi: 10.1053/j.ajkd.2010.12.027.
13. Khan M, Jose A, Sharma S. Physiology, Parathyroid Hormone. [Updated 2022 Oct 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 . Available from: https://www.ncbi.nlm.nih.gov/books/NBK499940/.
14. Nussey S, Whitehead S. Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers; 2001. Chapter 5, The parathyroid glands and vitamin D. Available from: https://www.ncbi.nlm.nih.gov/books/NBK24/
15. Hu MC, Kuro-o M, Moe OW. Renal and extrarenal actions of Klotho. Semin Nephrol. 2013;33:118-29. doi: 10.1016/j.semnephrol.2012.12.013.
16. Fan Y, Liu W, Bi R, Densmore MJ, Sato T, Mannstadt M, et al. Interrelated role of Klotho and calcium-sensing receptor in parathyroid hormone synthesis and parathyroid hyperplasia. Proc Natl Acad Sci U S A. 2018;115:E3749-E3758. doi: 10.1073/pnas.1717754115.
17. Lanske B, Razzaque MS. Molecular interactions of FGF23 and PTH in phosphate regulation. Kidney Int. 2014;86:1072-4. doi: 10.1038/ki.2014.316.
18. Patel DD, Vachhani U, Rajput A, Raghavani P, Parchwani DN, Dholariya S. Analysis of the Prevalence and Severity of Dysregulated Bone Mineral Homeostasis in Nondialyzed Chronic Kidney Disease Patients. J Lab Physicians. 2021;14:144-150. doi: 10.1055/s-0041-1732495.
19. Sun M, Wu X, Yu Y, Wang L, Xie D, Zhang Z, et al. Disorders of Calcium and Phosphorus Metabolism and the Proteomics/Metabolomics-Based Research. Front Cell Dev Biol. 2020;8:576110. doi: 10.3389/fcell.2020.576110.
20. Haussler MR, Whitfield GK, Kaneko I, Forster R, Saini R, Hsieh JC, et al. The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. Rev Endocr Metab Disord. 2012;13:57-69. doi: 10.1007/s11154-011-9199-8.
21. Martín-Núñez E, Donate-Correa J, Kannengiesser C, De Brauwere DP, Leroy C, Oudin C, et al. A Novel Heterozygous Deletion Variant in KLOTHO Gene Leading to Haploinsufficiency and Impairment of Fibroblast Growth Factor 23 Signaling Pathway. J Clin Med. 2019;8:500. doi: 10.3390/jcm8040500.
22. Ide N, Ye R, Courbebaisse M, Olauson H, Densmore MJ, Larsson TE, et al. In vivo evidence for an interplay of FGF23/Klotho/PTH axis on the phosphate handling in renal proximal tubules. Am J Physiol Renal Physiol. 2018;315:F1261-F1270. doi: 10.1152/ajprenal.00650.2017.
23. Hu MC, Kuro-o M, Moe OW. Klotho and chronic kidney disease. Contrib Nephrol. 2013;180:47-63. doi: 10.1159/000346778.