Section A -Research paper

Role of Vitamin D in Gastric Empting and Depression

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Abstract:

Vitamin D deficiency is recently speculated to play a role in the development of depression and affecting gastric empting. Nevertheless, few studies have explored the association between blood 25-hydroxyvitamin D [25(OH)D] concentrations, gastric empting and depression in the general population.

Keywords: Vitamin D, Gastric Empting, Depression.

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Introduction:

The term "vitamin D" refers to a group of liposoluble steroid molecules with different biological effects and comparable chemical structures. Ergocalciferol, also known as vitamin D2, and cholecalciferol, also known as vitamin D3, are the two main forms of vitamin D. Vitamin D2 is produced by the irradiation of ergosterol in yeast, whereas vitamin D3 is produced from 7-dehydrocholesterol following ultraviolet (UV)-B irradiation in human skin; this is a unique feature among vitamins**.**(1)

When the skin is exposed to sunlight, UV-B photons pass through the epidermis and the absorbed energy causes the photolysis of 7-dehydrocholesterol, which is present in the plasma membrane of keratinocytes, into previtamin D3, which is thermodynamically unstable and at 37 ℃, 80% of The formed previtamin D3 rapidly isomerizes to vitamin D3 within 8 hours. From there, it is released from the plasma membrane into the extracellular space**.**(2)

Unfortunately, there aren't many rich natural sources of vitamin D. Vitamin D2 has been detected in algae, and traces of it can also be found in plants, probably as a result of fungal contamination. Vitamin D2 is almost exclusively produced by fungus, and its synthesis from ergosterol also requires UV-B radiation. Contrarily, vitamin D3 is mostly found in animal sources, including oils from fish, such as cod liver oil, and oily fish like salmon, mackerel, and herring. Vitamin D is added to milk, some juices, some breads, yogurts, egg yolks, and cheeses. (3)

Absorption and distribution

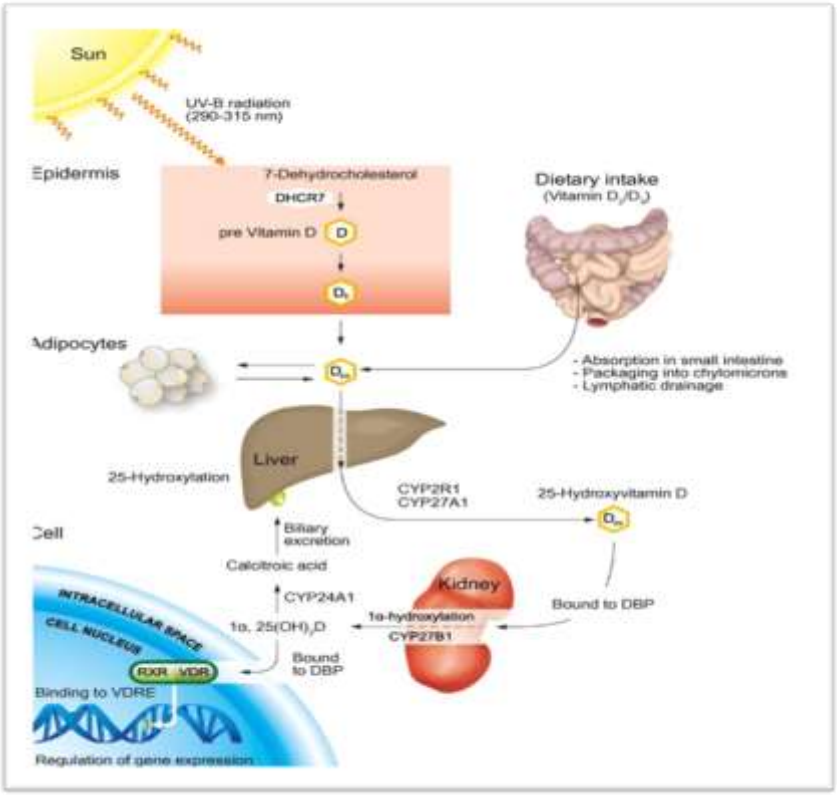
Vitamin D is liposoluble, it is assumed to share the fate of lipids, especially with its precursor cholesterol .In human git Vitamin D absorption begins in the stomach, where pepsin plays a role by releasing the associated protein fraction. In the duodenum, proteases, amylases, and lipases continue the process of vitamin D release from the food matrix, Bile acids initiate the emulsification and formation of mixed micelles containing fat-soluble substances that are then absorbed by enterocytes. (4)

Hydroxylated forms of vitamin D have a different fate. They have better water-solubility not requiring bile acids for absorption. Interestingly, oral 25(OH)D3 reached 3–4 fold higher plasma levels than oral vitamin D3 within 6 h. However, the exact absorption mechanisms of hydroxylated form have yet to be discovered(5)

The small intestine is where vitamin D is absorbed, however it is unknown in humans which specific area of the gut is responsible. The ileum is the principal site of absorption in rats. After being absorbed, vitamin D is subsequently included in chylomicrons that are released into the

lymphatic capillaries, skipping the first-pass metabolic process.Due to the activity of lipoprotein lipase, a small amount of the vitamin D present in chylomicrons may be transported and quickly deposited in skeletal muscles and adipose tissues. (3)

The strong binding affinity of vitamin D and its metabolites to plasma proteins is similar to that of steroid hormones. The vitamin D binding protein (vDBP), formerly known as a group-specific component or transcalciferin, was first characterized in 1959, but it wasn't until 1975 that the transport function of the protein was discovered. The primary physiological role of vDBP is the control of total and free levels of circulating vitamin D metabolites. Dietary vitamin D is gradually transported from chylomicrons to vDBP, which serves as their circulating reservoir. However, the skin's production of vitamin D is almost totally bound to vDBP.(6).

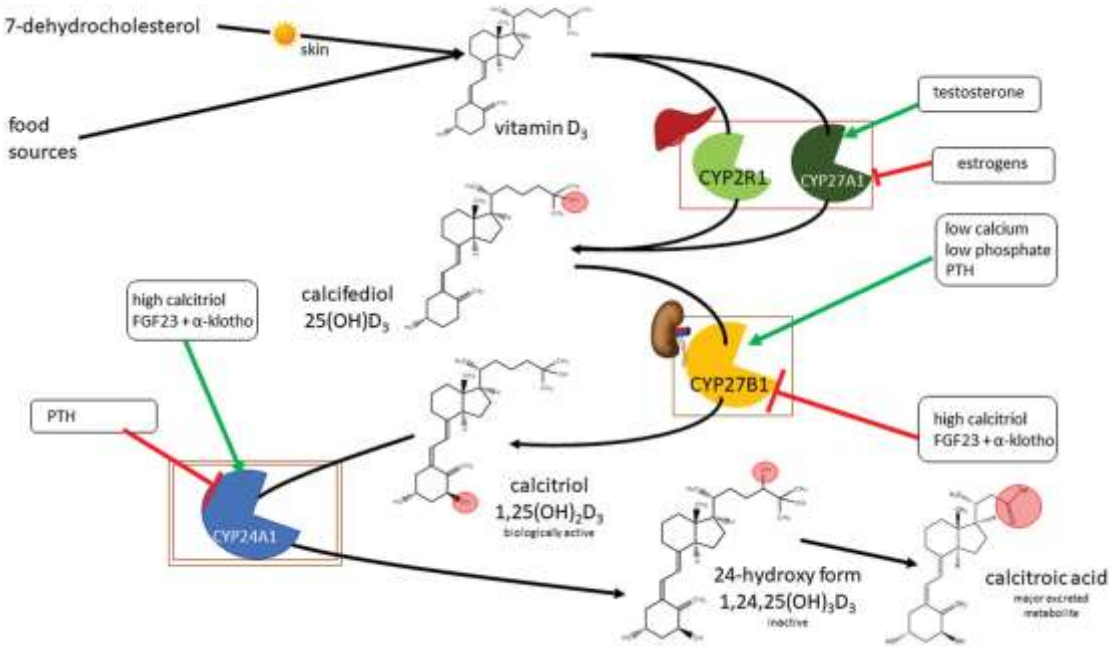


FIGURE(1): Vitamin D synthesis and metabolism CYP2R1, microsomal Cytochrome P450 Family 2 Subfamily R Member 1**; CYP27A1,** mitochondrial Cytochrome P450 Family 27 Subfamily A Member 1**; DHCR7,**7-dehydrocholesterol reductase**; CYP24A1,** Cytochrome P450 Family 24 Subfamily A Member 1**; CYP27B1 ,**cytochrome P450 family 27 subfamily B member 1**; RXP,**retinoid x receptor; **VDRE,** vitamin D response elements**; DBP,** vitamin D binding protein. (7)

Metabolism

Both dietary and endogenously formed vitamin D2/3 are two steps away from their active forms. The first activation step is the conversion of vitamin D2/3 to its 25- hydroxylated form in the liver There are many enzymes with 25- hydroxylase activity, but evidence indicates that microsomal cytochrome P450 2R1 (CYP2R1) is the principal vitamin D hydroxylase in humans. Mitochondrial CYP27A1 can also carry out this reaction but only in the case of vitamin D3.(8)

The second step in the activation of vitamin D is the conversion of 25(OH)D2/3 to its biologically active form calcitriol [1,25(OH)2D2/3] by the CYP27B1. This conversion takes place either in the kidneys or in a number of extrarenal tissues. Inactivation of calcitriol is ensured by the 24-hydroxylation, promoted by CYP24A1 which expressed in most cells and is induced by elevation in calcitriol plasma concentrations, representing negative feedback protection against hypercalcemia The formed 1,24,25(OH)3D has low biological activity and is further metabolized in the liver and kidneys into calcitroic acid into calcitroic acid, the major inactive vitamin D metabolite, which is excreted into the bile.(9)



FIGURE(2). Systemic vitamin D3 metabolism and its regulation. FGF23: fibroblast growth factor 23; PTH: parathyroid hormone(3)

Mechanism of action

From a molecular perspective, the effects of vitamin D are mediated by VDR, a nuclear receptor. After entering the cell, calcitriol triggers heterodimerization of VDR with retinoid X receptor (RXR) and recruits other necessary regulatory molecules. The formed VDR/RXR dimer interacts with specific DNA sequences, known as vitamin D response elements (VDREs), in regulated genes and either activates or represses DNA transcription.(10)

Research has discovered that VDREs are present not only at proximal promoters of the target gene but can also be situated within introns or intergenic regions with many kilobases in front or behind the regulated gene.(11)

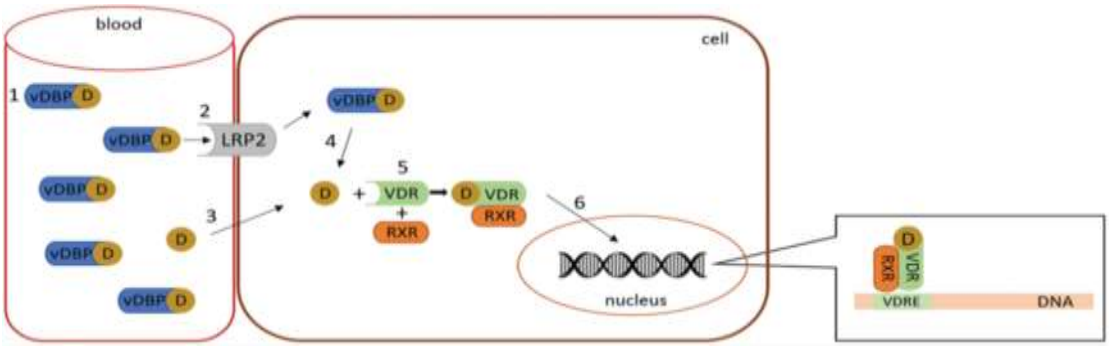


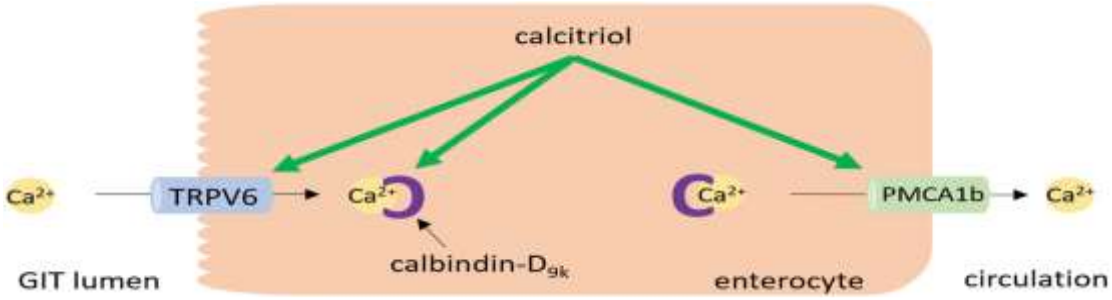
FIGURE (3) Mechanism of vitamin D (calcitriol) action. In this figure vitamin D should be understood as its active form - calcitriol. The majority of circulating vitamin D is bound to vitamin D binding protein (vDBP) (1). This complex may only enter cells with the megalin/cubulin system (LRP2) (2). Free vitamin D can enter any cell through passive diffusion (3). vDBP-bound vitamin D is released inside the cells (4). In the cytoplasm, vitamin D interacts with its receptor (VDR) and creates a heterodimer with retinoid X receptor (RXR) (5). The active VDR complex enters the nucleus (6) and binds to the responsive elements (VDRE) of regulated genes.(3)

Biological effects of vitamin D

The most well-known physiological role of vitamin D is the control of calcium homeostasis. In the intestine the increased absorption of calcium is crucially dependent on vitamin D. With low levels of vitamin D, the small intestine absorbs only 10–15% of dietary calcium. When vitamin D levels are adequate, the absorption rises to 30–40%, Calcitriol stimulates the synthesis of transient receptor potential vanilloid channel6 (TRPV6), an apical epithelial calcium channel that facilitates calcium entry into the enterocyte, and calbindin-D9k, an intracellular calcium-binding protein that

buffers potentially toxic levels of calcium in the enterocytes In the final step, the plasma membrane calcium pump(PMCA), whose isoform PMCA1b in the intestine is upregulated by calcitriol, transports calcium from enterocytes into the circulation.(3)

In addition to other neuroprotective benefits like anti-inflammatory and anti-oxidative effects, studies have shown that 1,25(OH)2 vitamin D3 or vitamin D has important effects on brain development and function. Additionally, studies have demonstrated that vitamin D has a modulatory influence on the generation and action of glucocorticoids. This includes the expression of neurotrophic factors such as glial-derived neurotrophic factor (GDNF) and neurotrophic factor-3 (NT3), particularly in the hippocampus. (12)



FIGURE(4). Calcium absorption in the enterocyte. In hypocalcemia, calcitriol upregulates calcium transient receptor potential vanilloid channel 6 (TRPV6) and calbindin-D9k in the enterocyte, thus stimulating the calcium absorption in the intestine. Also, the expression of plasma membrane calcium pump type 1b (PMCA1b) is increased by calcitriol. GIT: gastrointestinal tract. (3)

Vitamin D deficiency causes

Vitamin D deficiency is the most common nutritional deficiency worldwide in both children and adults **(13).**

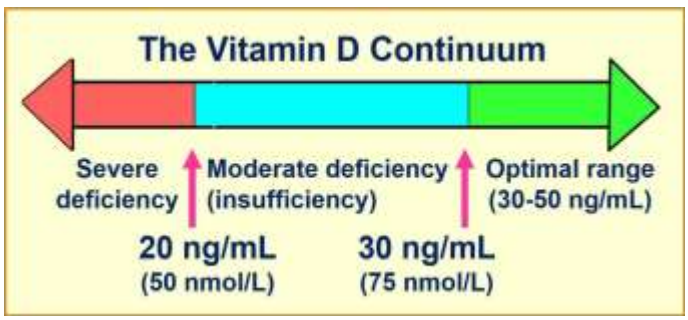


FIGURE (5): Vitamin D level changes (14).

Although vitamin D3 can be endogenously synthesized in the human body, there are many factors that could impair the synthesis of the vitamin D.The major cause of vitamin D deficiency is insufficient sun exposure Additionally, aging decreases the concentration of 7-dehydrocholesterol, the vitamin D3 precursor in human skin, individuals on a vegetarian and/or vegan diet may be at higher risk of vitamin D deficiency, Other causes of vitamin D deficiency include various gastrointestinal and renal disorders genetic mutations of involved enzymes, vDBP polymorphisms, tumors, pregnancy and therapeutic drug interactions.(3)

Vitamin D deficiency symptoms

Lack of vitamin D reduces the body's ability to absorb dietary calcium and phosphate, which compromises the strength of bones. Rickets is one of the effects of vitamin D insufficiency in children.Also it causes osteomalacia and osteoporosis, conditions that lead to the demineralization of bones and a higher risk of fractures as well as localized or generalized bone pain and bone deformities. (15)

There is increased susceptibility to viral infections, muscle weakness, slower healing of epidermal wounds and even associated with the atrophy of type II muscle fibers. Localized hair loss (i.e. alopecia areata) has also been reported.it also may be involved in neurological disorders such as multiple sclerosis.(3)

Vitamin D in specific health conditions

Cardiovascular diseases

Despite progress in the prevention of cardiovascular diseases, a significant proportion of first cardiovascular events occur among individuals without traditional risk factors. The advancement of pathophysiology of atherosclerotic vascular diseases has brought new insight regarding potential indicators of underlying hidden atherosclerosis and cardiovascular risk. (16)

The attention has been focused on various inflammatory markers, especially vitamin D. As a growing body of evidence has identified vitamin D deficiency as a potential risk factor for acute coronary syndrome**.** (17)

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a multifactorial disease and vitamin D deficiency is considered a risk factor.The prevalence of vitamin D deficiency in IBD is about 30–40%. Although vitamin D supplementation significantly increased 25(OH)D levels in patients with IBD,the

impact of this adjuvant treatment on inflammation and the course of IBD is not yet clearly proven, nor is the target level of vitamin D known. (18)

COVID-19

The immunopathology of COVID-19 calls for unusual therapeutic choices, such as vitamin D, which could be an efficient and secure method for managing this disease. The COVID-19 pandemic has enormous health and socioeconomic effects. (19)

Acute kidney injury:

AKI affects more than 50% of critically ill patients worldwide and is independently associated with higher mortality, a longer length of hospital stay, and an increased risk of long term complications including bone fractures**.** (20)

Vitamin D and depression

Vitamin D is a special neurosteroid hormone that may have a significant influence in the development of depression. The cingulate cortex and hippocampus are two brain regions that have been linked to the pathophysiology of depression and have vitamin D receptors on neurons and glia. Because vitamin D is involved in so many different aspects of brain function, such as neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity, and brain development, it is biologically probable that this vitamin may be linked to depression and that its supplementation may be a key component of treating depression .(3)

Currently, there are at least three lines of evidence to support this association: first, an increased region-specific expression of vitamin D receptors in brain areas (such as prefrontal and cingulate cortices) known to play a key role in mood regulation; second, the modulatory role proposed for vitamin D in the association between depression and inflammation (through a possible immune-modulatory mechanisms) last, the emerging insights about the neuroprotective properties of vitamin D (by virtue of its anti-inflammatory effects).(21)

Clinical studies that assess the efficacy of vitamin D supplementation in the treatment of depression and anxiety are still scarce and their results are, at times, controversial.(21)

Vitamin D and gastric emptying

Degenerative processes of the enteric nervous system and the dorsal vagal nucleus correlate with delayed gastric emptying, it is postulated that the vitamin D status may also be associated with gastric dysmotility.(23)

Interestingly, Vitamin D defficiency is found to be strongly related with functional problems in intestinal neuromotility apart from psychiatric disorders like anxiety and depression With the weak pyloric sphincter, food from the small intestines will tend to flow back into the stomach.(24)

findings indicate that injectable vitamin D therapy for delayed gastric emptying in diabetic patient is effective for the vast majority of individuals who have vitamin D insufficiency.(25).

References:

1. Armas, L. A. G., Hollis, B. W., & Heaney, R. P. (2004). Vitamin D2 is much less effective than vitamin D3 in humans. Journal of Clinical Endocrinology and Metabolism, 89(11), 5387–5391. https://doi.org/10.1210/jc.2004-0360
2. Holick, M. F., Chen, T. C., Lu, Z., & Sauter, E. (2007). Vitamin D and skin physiology: A D-lightful story. Journal of Bone and Mineral Research, 22(SUPPL. 2), 28–33. https://doi.org/10.1359/jbmr.07s211
3. Janoušek, J., Pilařová, V., Macáková, K., Nomura, A., Veiga-Matos, J., Silva, D. D. da, Remião, F., Saso, L., Malá-Ládová, K., Malý, J., Nováková, L., & Mladěnka, P. (2022). Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. Critical Reviews in Clinical Laboratory Sciences, 59(8), 517–554. https://doi.org/10.1080/10408363.2022.2070595
4. Borel, P., Caillaud, D., & Cano, N. J. (2015). Vitamin D bioavailability: state of the art. Critical reviews in food science and nutrition, 55(9), 1193–1205. https://doi.org/10.1080/10408398.2012.688897
5. Farraye, F. A., Nimitphong, H., Stucchi, A., Dendrinos, K., Boulanger, A. B., Vijjeswarapu, A., Tanennbaum, A., Biancuzzo, R., Chen, T. C., & Holick, M. F. (2011). Use of a novel vitamin D bioavailability test demonstrates that vitamin D absorption is decreased in patients with quiescent crohn's disease. Inflammatory Bowel Diseases, 17(10), 2116–2121. https://doi.org/10.1002/ibd.21595
6. Bouillon, R., Schuit, F., Antonio, L., & Rastinejad, F. (2020). Vitamin D Binding Protein: A Historic Overview. *Frontiers in Endocrinology*, *10*(January), 1–21. https://doi.org/10.3389/fendo.2019.00910

7. Kitson, M. T., & Roberts, S. K. (2012). D-livering the message: The importance of vitamin D status in chronic liver disease. *Journal of Hepatology*, *57*(4), 897–909. https://doi.org/10.1016/j.jhep.2012.04.033
8. Thacher, T. D., Fischer, P. R., Singh, R. J., Roizen, J., & Levine, M. A. (2015). CYP2R1 mutations impair generation of 25-hydroxyvitamin D and cause an atypical form of vitamin D deficiency. *Journal of Clinical Endocrinology and Metabolism*, *100*(7), E1005–E1013. https://doi.org/10.1210/jc.2015-1746
9. Tong, B. C.-K., & Benjamin Chun-Kit Tong. (2017). 乳鼠心肌提取 HHS Public Access. *Physiology & Behavior*, *176*(5), 139–148. https://doi.org/10.1021/acschembio.6b00569.Calcitroic
10. Christakos, S., Li, S., De La Cruz, J., & Bikle, D. D. (2019). New developments in our understanding of vitamin metabolism, action and treatment. Metabolism: clinical and experimental, 98, 112–120. https://doi.org/10.1016/j.metabol.2019.06.010
11. Lee, S. M., Meyer, M. B., Benkusky, N. A., O'Brien, C. A., & Pike, J. W. (2015). Mechanisms of enhancer-mediated hormonal control of Vitamin D receptor gene expression in target cells. Journal of Biological Chemistry, 290(51), 30573–30586. https://doi.org/10.1074/jbc.M115.693614
12. Anglin, R., Samaan, Z., Walter, S., & McDonald, S. (2013). Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. The British Journal of Psychiatry, 202(2), 100-107. doi:10.1192/bjp.bp.111.106666
13. Hossein-nezhad, A., & Holick, M. F. (2013, July). Vitamin D for health: a global perspective. In Mayo clinic proceedings (Vol. 88, No. 7, pp. 720-755). Elsevier.
14. Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., ... & Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology & metabolism, 96(7), 1911-1930.
15. Sahay, M., & Sahay, R. (2012). Rickets-vitamin D deficiency and dependency. Indian journal of endocrinology and metabolism, 16(2), 164–176. https://doi.org/10.4103/2230-8210.93732

16. Murray, C. J., & Lopez, A. D. (2013). Measuring the global burden of disease. The New England journal of medicine, 369(5), 448–457. https://doi.org/10.1056/NEJMra1201534
17. Parker, S. K., Bindl, U. K., & Strauss, K. (2010). Making things happen: A model of proactive motivation. Journal of management, 36(4), 827-856.
18. Lamb, C. A., Kennedy, N. A., Raine, T., Hendy, P. A., Smith, P. J., Limdi, J. K., ... & IBD Guidelines eDelphi Consensus Group. (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut, 68(Suppl 3), s1-s106.
19. Banerjee, A., Ganguly, U., Saha, S., Chakrabarti, S., Saini, R. V., Rawal, R. K., Saso, L., & Chakrabarti, S. (2021). Vitamin D and immuno-pathology of COVID-19: many interactions but uncertain therapeutic benefits. Expert review of anti-infective therapy, 19(10), 1245–1258. https://doi.org/10.1080/14787210.2021.1905519
20. Hoste, E. A., Bagshaw, S. M., Bellomo, R., Cely, C. M., Colman, R., Cruz, D. N., Edipidis, K., Forni, L. G., Gomersall, C. D., Govil, D., Honoré, P. M., Joannes-Boyau, O., Joannidis, M., Korhonen, A. M., Lavrentieva, A., Mehta, R. L., Palevsky, P., Roessler, E., Ronco, C., Uchino, S., … Kellum, J. A. (2015). Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive care medicine, 41(8), 1411–1423.
21. Gowda, U., Mutowo, M. P., Smith, B. J., Wluka, A. E., & Renzaho, A. M. (2015). Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition (Burbank, Los Angeles County, Calif.), 31(3), 421–429. https://doi.org/10.1016/j.nut.2014.06.017
22. Kouba, B. R., Camargo, A., Gil-Mohapel, J., & Rodrigues, A. L. S. (2022). Molecular Basis Underlying the Therapeutic Potential of Vitamin D for the Treatment of Depression and Anxiety. International journal of molecular sciences, 23(13), 7077. https://doi.org/10.3390/ijms23137077
23. Kwon, K. Y., Jo, K. D., Lee, M. K., Oh, M., Kim, E. N., Park, J., Kim, J. S., Youn, J., Oh, E., Kim, H. T., Oh, M. Y., & Jang, W. (2016). Low serum Vitamin D levels may contribute to gastric dysmotility in de novo Parkinson's disease. Neurodegenerative Diseases, 16(3–4), 199–205.

24. Das, D. S., Saharia, G. K., Panigrahi, M. K., & Sahoo, D. (2023). Association of vitamin D and functional dyspepsia: a case-control study. Annals of Medicine & Surgery, 85(10), 4667–4673. https://doi.org/10.1097/ms9.0000000000001204
25. Talreja, K. L., Bhatti, H. A., Siddiqui, H., Kumari, S., Panjwani, R., Mesud, M., Rao, M. F. S., Bangash, S. A., & Batool, M. (2022). Association of vitamin D deficiency with diabetic gastroparesis and its intramuscular vitamin D treatment. International Journal of Health Sciences, 6, 6394–6404. https://doi.org/10.53730/ijhs.v6ns8.13799