UDC 616.71-007.23+577.161.2+546.41+611.018.4
DOI: 10.56871/CmN-W.2024.63.58.008

PATHOGENETIC MECHANISMS OF DEVELOPMENT OF BONE TISSUE PATHOLOGY IN CHRONIC GASTROINTESTINAL DISEASES

© Valeria P. Novikova

Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information:
Valeria P. Novikova — Doctor of Medical Sciences, Professor, Head of the Department of Propaedeutics of Children's Diseases with a Course in General Child Care, Head of the Laboratory of Medical and Social Problems in Pediatrics, National Research Center.
E-mail: novikova-vp@mail.ru ORCID: https://orcid.org/0000-0002-0992-1709 SPIN: 1875-8137

For citation: Novikova VP. Pathogenetic mechanisms of development of bone tissue pathology in chronic gastrointestinal diseases. Children's Medicine of the North-West. 2024;12(2):95–101. DOI: https://doi.org/10.56871/CmN-W.2024.63.58.008

Received: 05.02.2024 **Revised: 28.03.2024** **Accepted: 05.06.2024**

Abstract. The review describes the symptoms of damage to the skeletal system in celiac disease, chronic gastritis, the condition after gastrectomy and inflammatory bowel diseases. The state of the vitamin D system and bone metabolism in chronic diseases of the digestive system, the mechanisms of the influence of vitamin D on the state of the intestinal mucosa, and risk factors contributing to pathological changes in bones in gastrointestinal diseases are presented. The review shows that in most cases, impaired bone mineral density in diseases of the digestive system is caused by impaired phosphorus-calcium metabolism, metabolism of the vitamin D system and impaired intestinal microbiocenosis, and specific mechanisms for each nosological form require further study.

Keywords: *bone metabolism, vitamin D, calcium, bone mineral density, intestinal microbiocenosis*

ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ РАЗВИТИЯ ПАТОЛОГИИ КОСТНОЙ ТКАНИ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

© Валерия Павловна Новикова

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Валерия Павловна Новикова — д.м.н., профессор, заведующая кафедрой пропедевтики детских болезней с курсом общего ухода за детьми, заведующая лабораторией «Медико-социальных проблем в педиатрии» НИЦ. E-mail: novikova-vp@mail.ru
ORCID: https://orcid.org/0000-0002-0992-1709 SPIN: 1875-8137

Для цитирования: Новикова В.П. Патогенетические механизмы развития патологии костной ткани при хронических заболеваниях желудочно-кишечного тракта // Children's Medicine of the North-West. 2024. Т. 12. № 2. С. 95–101. DOI: https://doi.org/10.56871/CmN-W.2024.63.58.008

Поступила: 05.02.2024 **Одобрена: 28.03.2024** **Принята к печати: 05.06.2024**

Резюме. В обзоре описаны симптомы поражения костной системы при целиакии, хроническом гастрите, после резекции желудка и при воспалительных заболеваниях кишечника. Описаны система витамина D и костный метаболизм при хронических заболеваниях органов пищеварения, механизмы влияния витамина D на слизистую оболочку (СО) кишечника, факторы риска, способствующие патологическим изменениям костей при заболеваниях ЖКТ. В обзоре показано, что в большинстве случаев нарушение минеральной плотности костей при заболеваниях органов пищеварения обусловлены нарушением фосфорно-кальциевого обмена, обмена системы витамина D и нарушением кишечного микробиоценоза. Причем конкретные механизмы при каждой нозологической форме требуют дальнейшего изучения.

Ключевые слова: *костный метаболизм, витамин D, кальций, минеральная плотность костей, микробиоценоз кишечника*

 ISSN 2221-2582

The course of any chronic disease negatively affects the processes of bone modelling and remodelling. The bone tissue loses its metabolic rate, especially in childhood. As a result, bone mass does not reach proper values, which creates the ground for the formation of low bone mineral density (LBMD) and osteoporosis in the future [1].

Researchers in recent decades have identified characteristic changes that have occurred in the course of chronic digestive diseases in children. They include early debut, frequent relapses, and an increase in combined gastrointestinal pathology. In this case, the process of inflammation in the mucosa of the stomach and small intestine has widespread and pronounced morphological changes, up to atrophic [2]. Disruption of nutrient breakdown and absorption processes in chronic gastrointestinal diseases with malabsorption syndrome in children is often combined with low disharmonious indicators of linear body size and changes in bone remodelling [3]. Prolonged micronutrient deficiency, including vitamin D deficiency in children with gastrointestinal pathology can lead to reduction in bone mineral density [3–7].

Literature data clearly indicate that the role of the upper digestive system (stomach and duodenum) in the absorption of micronutrients, especially phosphorus, calcium and vitamin D, is of paramount importance [7]. Vitamin D affects bone mineral density by regulating calcium absorption in the gastrointestinal tract and influencing the RANK/RANKL/OPG system [8]. Phosphorus, calcium and vitamin D deficiency in gastrointestinal pathology leads to symptoms of osteomalacia: frequent fractures, bone pain in various localisations, posture disorders in sagittal and frontal planes, and limb deformities [1, 3, 9]. Such symptoms have been described in the case of celiac disease, chronic gastritis, condition after gastric resection and inflammatory bowel diseases.

$1,25(OH)_2D$ have also been shown to be involved in immune cell differentiation, modulation of the gut microbiota, gene transcription and barrier integrity, maintenance of the integrity of mucosal tight junctions, improvement of folic acid absorption and activation of cytochrome P450 3A4 expression [10].

The following mechanisms of vitamin D effect on the intestinal mucosa (IM) have been described: regulation of colonic IM mucus secretion [11], ensuring structural integrity [12], influence on the composition and functions of the gut microbiota [13], increased expression of tight junction proteins, and suppression of zonulin release [14]. The effects of the vitamin D on the innate immunity system are associated with stimulation of production by neutrophils, macrophages and cells lining epithelial surfaces of antibacterial peptides with broad antimicrobial activity, such as cathelicidin (cAMP) and β-defensin 2 (DEFB4) [15–17], with increased antimicrobial action against some pathogens, induction of intracellular pathogen recognition receptor NOD2, improved transcription of cAMP and DEFB4, suppression of hepcidin antimicrobial peptide expression, and decreased ferroportin-mediated export of intracellular iron [18, 19]. The effect of vitamin D on adaptive immunity is to control the differentiation and maturation of dendritic cells, expression on monocytes of molecules involved in antigen capture, decrease the pro-inflammatory Th1 response, increase the anti-inflammatory Th2 response, increase the number of T regulatory cells, and limit the number of CD4+ T cells [20]. Due to these pleiotropic effects, vitamin D is associated with the activity of immune-mediated diseases — those forms of pathology in which lesions of both the bone system and the digestive tract are manifestations of autoimmune processes (inflammatory bowel disease, celiac disease, autoimmune gastritis) [21–23].

Different forms of vitamin D are in the bloodstream in the bound form with the VDBP receptor. And the active form of vitamin D ($1,25(OH)_2D_3$) due to binding to the receptor exerts various biological effects by interacting with the nuclei of target cells located in various organs and tissues, such as the immune system, pancreas, cardiovascular and muscular systems, and brain [24, 25].

The VDR gene is located on the short arm of chromosome 12 and contains 8 protein-coding exons (exons 2–9) and 6 untranslated exons (exons 1a-1f) [26, 27]. A large number of polymorphisms of the VDR gene have been described, which may affect VDR expression and function and subsequent vitamin D-mediated effects [28]. VDR also regulates the cell cycle, influences cell differentiation and proliferation, controls the development of cancer pathology, as well as inhibition of dendritic cell differentiation, and stimulation of the synthesis of a number of hormones [26, 29].

The effect of calcium on the gastrointestinal tract has been studied in basic research. It is known that calcium is a secondary messenger of cell metabolism regulation and a regulator of synaptic transmission. Its action on the gastric

and intestinal mucosa is regarded as astringent. It attenuates peristalsis by acting on smooth muscle. In foci of an inflammation, calcium stimulates reparative regeneration in the intestine and suppresses excessive proliferation of gastric cells. Calcium chloride thickens tissue and reducing the permeability of cell membranes [30].

Reduced absorption of Ca from the intestine due to accelerated chyme passage and reduced secretion of hydrochloric acid, which converts poorly soluble Ca compounds into soluble, well-absorbed calcium chloride, also plays a role in the genesis of osteopathies in gastrointestinal diseases [31–33]. It is possible to explain degenerative-dystrophic changes of the spine in children with digestive diseases from the point of view of innervation disorders in neurometamers. According to this concept, neurotrophic changes are primary. The pathology of the digestive and bone systems in adolescents and adults is secondary [34]. But there is another view — a recognition of the influence of irritation from the affected organ on the state of the musculoskeletal system, leading to muscle spasm, impaired mobility of motor segments in children, adolescents and adults, persons suffering from gastric and duodenal ulcer disease [35]. Cases of spasm of long back muscles leading to scoliosis in liver and gallbladder diseases have been described [35, 36]. Another possible cause of osteopathies in patients with gastrointestinal diseases is the use of medications that negatively affect bone tissue. These include glucocorticosteroids, anticonvulsants, thyroid hormones, anticoagulants and antacids, diuretics and nonsteroidal anti-inflammatory drugs, and some other drugs [37–41]. The results obtained in a number of studies indicate that long-term use of proton pump inhibitors (PPIs) increases the risk of osteoporosis-related fractures due to impaired Ca absorption and inhibition of osteoclastogenesis [40]. Moreover, the side effect of PPIs, in addition to suppression of the acid-forming function of the stomach, may be of a completely different nature. Undoubtedly, the pharmacological target of PPIs is H^+K^+-ATPase of parietal cells, which is an organ-specific enzyme [42]. But M. uzuki et al. suggested that PPIs can inhibit the activity of vacuolar H^+-ATPase enzyme, which is close in biochemical structure and is localised in the cytoplasm of many cells of the human body [43]. As a consequence, essential functions may be affected, including bone resorption, which is a necessary process for the restoration of normal bone. Recent studies have shown that long-term (for several years) use of PPIs for the treatment of chronic gastroduodenal pathology increases the risk of bone fractures as a manifestation of osteoporosis [40, 44, 45]. At the same time, hypocalcaemia and hypophosphataemia cause gastroduodenostasis and pathological gastroesophageal and duodenogastric refluxes due to the development of muscular hypotonia and impaired motor function of the stomach and gut [46].

Thus, pathogenetic mechanisms of the bone tissue pathology development in chronic gastrointestinal diseases in most cases are caused by disorders of phosphorus-calcium metabolism and vitamin D metabolism. Moreover, specific mechanisms in each nosological form require further study .

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования. Информированное согласие на публикацию.

REFERENCES

1. Novikova V.P., Kuz'mina D.A., Guzeeva O.D. Hronicheskij gastrit i patologiya kostnoj tkani u detej. [Chronic gastritis and bone tissue pathology in children]. Vrach-aspirant. 2011;47(4.1):248–254. (in Russian).
2. Bel'mer S.V., Razumovskij A.Yu., Havkin A.I. i dr. Bolezni zheludka i dvenadcatiperstnoj kishki u detej. [Diseases of the stomach and duodenum in children]. Moskva: Medpraktika-M Publ.; 2017. (in Russian).
3. Han T., Zhang Y., Qi B., Chen M., Sun K., Qin X., Yang B., Yin H., Xu A., Wei X., Zhu L. Clinical features and shared mechanisms of chronic gastritis and osteoporosis. Sci Rep. 2023;13(1):4991. DOI: 10.1038/s41598-023-31541-8.
4. Pigarova E.A., Dzeranova L.K., Yacenko D.A. Vitamin D — voprosy vsasyvaniya i metabolizma v norme i pri zabolevaniyah zheludochno-kishechnogo trakta. [Vitamin D — issues of absorption and metabolism in normal conditions and in diseases of

the gastrointestinal tract]. Ozhirenie i metabolizm. 2022;19(1):123–133. DOI: 10.14341/omet12835. URL: https://applied-research.ru/ru/article/view?id=13566 (data obrashcheniya: 02.01.2024). (in Russian).
5. Maurya V.K., Aggarwal M. Factors influencing the absorption of vitamin D in GIT: an overview. J Food Sci Technol. 2017;54(12):3753–3765. DOI: 10.1007/s13197-017-2840-0.
6. Shin C.S., Choi H.J., Kim M.J. et al. Prevalence and risk factors of osteoporosis in Korea: a community-based cohort study with lumbar spine and hip bone mineral density. Bone. 2010;47(2):378–387.
7. Slohova N.K., Totrov I.N. Regulyaciya kal'cievogo obmena i sostoyanie kostnoj tkani u bol'nyh s zabolevaniyami zheludochno-kishechnogo trakta. [Regulation of calcium metabolism and the state of bone tissue in patients with diseases of the gastrointestinal tract]. Sovremennye problemy nauki i obrazovaniya. 2014;6. URL: https://science-education.ru/ru/article/view?id=16544 (data obrashcheniya: 02.01.2024). (in Russian).
8. Szymczak-Tomczak A., Ratajczak A.E., Kaczmarek-Ryś M., Hryhorowicz S., Rychter A.M., Zawada A., Słomski R., Dobrowolska A., Krela-Kaźmierczak I. Pleiotropic Effects of Vitamin D in Patients with Inflammatory Bowel Diseases. J Clin Med. 2022;11(19):5715. DOI: 10.3390/jcm11195715.
9. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser. 2003;921:1–164, back cover. PMID: 15293701.
10. Carmeliet G., Dermauw V., Bouillon R. Vitamin D Signaling in Calcium and Bone Homeostasis: A Delicate Balance. Best Pract. Res. Clin. Endocrinol. Metab. 2015;29:621–631. DOI: 10.1016/j.beem.2015.06.001.
11. Zhu W., Yan J., Zhi C., Zhou Q., Yuan X. 1,25$(OH)_2D_3$ deficiency-induced gut microbial dysbiosis degrades the colonic mucus barrier in Cyp27b1 knockout mouse model. Gut Pathog. 2019;11:8. DOI: 10.1186/s13099-019-0291-z.
12. Kühne H., Hause G., Grundmann S.M., Schutkowski A., Brandsch C., Stangl G.I. Vitamin D receptor knockout mice exhibit elongated intestinal microvilli and increased ezrin expression. Nutr. Res. 2016;36:184–192. DOI: 10.1016/j.nutres.2015.10.005.
13. Schäffler H., Herlemann D.P., Klinitzke P., Berlin P., Kreikemeyer B., Jaster R., Lamprecht G. Vitamin D administration leads to a shift of the intestinal bacterial composition in Crohn's disease patients, but not in healthy controls. J. Dig. Dis. 2018;19:225–234. DOI: 10.1111/1751-2980.12591.
14. Fasano A. Zonulin, regulation of tight junctions, and autoimmune diseases. Ann. N. Y. Acad. Sci. 2012;1258:25–33. DOI: 10.1111/j.1749–6632.2012.06538.x.
15. Weber G., Heilborn J.D., Jimenez C.I.C., Hammarsjö A., Törmä H., Ståhle M. Vitamin D induces the antimicrobial protein hCAP18 in human skin. J. Investig. Dermatol. 2005;124:1080–1082. DOI: 10.1111/j.0022-202X.2005.23687.x.
16. Bals R., Wang X., Zasloff M., Wilson J.M. The peptide antibiotic LL37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proc. Natl. Acad. Sci. USA. 1998;95:9541–9546. DOI: 10.1073/pnas.95.16.9541.
17. Gallo R.L., Kim K.J., Bernfield M., Kozak C.A., Zanetti M., Merluzzi L., Gennaro R. Identification of CRAMP, a cathelin-related antimicrobial peptide expressed in the embryonic and adult mouse. J. Biol. Chem. 1997;272:13088–13093. DOI: 10.1074/jbc.272.20.13088.
18. Chun R.F., Liu P.T., Modlin R.L., Adams J.S., Hewison M. Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. Front Physiol. 2014;5:151. DOI: 10.3389/fphys.2014.00151.
19. Bacchetta J., Zaritsky J.J., Sea J.L., Chun R., Lisse T.S., Zavala K., Nayak A., Wesseling-Perry K., Westerman M., Hollis B.W. et al. Suppression of iron-regulatory hepcidin by vitamin D. J. Am. Soc. Nephrol. 2014;25:564–572. DOI: 10.1681/ASN.2013040355.
20. Bikle D.D. Vitamin D Regulation of Immune Function. Curr. Osteoporos. Rep. 2022;20:186–193. DOI: 10.1007/s11914–022–00732-z.
21. Massironi S., Cavalcoli F., Zilli A., Del Gobbo A., Ciafardini C., Bernasconi S., Felicetta I., Conte D., Peracchi M. Relevance of vitamin D deficiency in patients with chronic autoimmune atrophic gastritis: a prospective study. BMC Gastroenterol. 2018;18(1):172. DOI: 10.1186/s12876-018-0901-0.
22. Infantino C., Francavilla R., Vella A., Cenni S., Principi N., Strisciuglio C., Esposito S. Role of Vitamin D in Celiac Disease and Inflammatory Bowel Diseases. Nutrients. 2022;14(23):5154. DOI: 10.3390/nu14235154.
23. Shumatova T.A., Kovalenko D.V., Prihodchenko N.G. Vitamin D i zabolevaniya kishechnika. [Vitamin D and intestinal diseases]. Mezhdunarodnyj zhurnal prikladnyh i fundamental'nyh issledovanij. 2023;8:24–28 (in Russian).
24. Eloranta J.J., Wenger C., Mwinyi J., Hiller C., Gubler C., Vavricka S.R., Fried M., Kullak-Ublick G.A., Swiss IBD Cohort Study Group Association of a Common Vitamin D-Binding Protein Polymor-

phism with Inflammatory Bowel Disease. Pharm. Genom. 2011;21:559–564. DOI: 10.1097/FPC.0b013e328348f70c.
25. Peterlik M. and Cross H.S. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. European Journal of Clinical Nutrition. 2009;63:1377–1386.
26. Kang T.J., Jin S.H., Yeum C.E., Lee S.B., Kim C.H., Lee S.H., Kim K.H., Shin E.S., Chae G.T. Vitamin D Receptor Gene TaqI, BsmI and FokI Polymorphisms in Korean Patients with Tuberculosis. Immune Netw. 2011;11(5):253–257. DOI: 10.4110/in.2011.11.5.253.
27. Taymans S.E., Pack S., Pak E., Orban Z., Barsony J., Zhuang Z., Stratakis C.A. The human vitamin D receptor gene (VDR) is localized to region 12cen-q12 by fluorescent in situ hybridization and radiation hybrid mapping: genetic and physical VDR map. J Bone Miner Res. 1999;14(7):1163–1166. DOI: 10.1359/jbmr.1999.14.7.1163.
28. Valdivielso J.M., Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006;371(1–2):1–12. DOI: 10.1016/j.cca.2006.02.016.
29. Baker A.R., McDonnell D.P., Hughes M. Cloning and expression of full-length cDNA encoding human vitamin D receptor. Proceedings of the National Academy of Sciences. 1998;85(10):3294–3298. DOI: 10.1073/pnas.85.10.3294.
30. Fomina L. A. Rol' kal'ciĭreguliruyushcheĭ sistemy v patogeneze i sanogeneze yazvennoĭ bolezni i korrekciya ee sdvigov pri lechenii recidiva zabolevaniya. [The role of the calcium regulatory system in the pathogenesis and sanogenesis of peptic ulcer disease and the correction of its changes in the treatment of relapse of the disease]. Eksperimental'naya i klinicheskaya gastroenterologiya. 2016;134(10). (in Russian).
31. Hramcova S.N. Ocenka urovnya kal'ciya i fosfora v prognozirovanii osteopenii u detej i podrostkov. [Assessment of calcium and phosphorus levels in predicting osteopenia in children and adolescents]. Obshchestvennoe zdorov'e i profilaktika zabolevanij. 2007;2:47–50. (in Russian).
32. Shcheplyagina L.A., Moiseeva T.Yu. Deficit kal'ciya — vozmozhnosti pishchevoj korrekcii u doshkol'nikov. [Calcium deficiency—possibilities of nutritional correction in preschool children]. Consilium medicum. Pediatriya. 2007;1:80–83. (in Russian).
33. Haustova G.G., Banina T.V., Muhina Yu.G., Shcheplyagina L.S. Deficit kal'ciya i vitamina D pri hronicheskih zabolevaniyah zheludka i tonkoj kishki. [Calcium and vitamin D deficiency in chronic diseases of the stomach and small intestine]. Doktor.ru.2008;1:14–18. (in Russian).
34. Lebeda V.F., Yasinskij O.R. Osteopatii u detej s hronicheskim gastroduodenitom. [Osteopathy in children with chronic gastroduodenitis]. Pediatriya, akusherstvo i ginekologiya. 2000;2:29–31. (in Russian).
35. Shevchenko S.D., Ermak T.A. Osteopenicheskij sindrom u detej i podrostkov, bol'nyh skoliozom. [Osteopenic syndrome in children and adolescents with scoliosis]. Rossijskij pediatricheskij zhurn. 2005;1:21–24. (in Russian).
36. Elkin S.L., Fairney A., Burnett S. et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: A cross-sectional study. Osteoporoses Int. 2001;12:366–72.
37. Leonard M.B. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. Pediatrics. 2007;119:166–S174.
38. Payne D., Ray D. Glucocorticoid receptor gene polymorphisms and susceptibility to rheumatoid arthritis. Clinical Endocrinology. 2007;67:342–345.
39. Schlienger R.G., Jick S.S., Meier C.R. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics. 2004;114(2):469–473.
40. Targownik L.E., Lix L.M., Prior H.J. et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. Can. Med. Assoc. J. 2008;179:319–326.
41. Van Rossum E.F., Roks P.H., de Jong F.H. et al. Characterization of a promoter polymorphism in the glucocorticoid receptor gene and its relationship to three other polymorphisms. Clinical Endocrinology (Oxf). 2004;61:573–581.
42. Ishino Y., Sugano K. Acid-suppressive strategy against gastroesophageal reflux diseases and non-erosive reflux diseases: the alternative of proton- pump inhibitors or H2 receptor antagonists. Nippon Rinsho. 2007;65(5):891–894.
43. Suzuki M., Suzuki H., Hibi T. Proton pump inhibitors and gastritis. J. Clin. Biochem. Nutr. 2008;42(2):71–75.
44. Tsirambidis J.V.E., Conwell D.L., Zuccaro G. Osteopenia in a patient with chronic pancreatitis. The American Journal of Gastroenterology. 2003;98(9):S164.
45. Yang Y., Lewis J., Epstein S. et al. Long-term proton pump inhibitor therapy and risk of hip fraction. J. Am. Med. Assoc. 2006;296:2947–2953.
46. Cijevschi C. at al. Osteoporosis in liver cirrhosis. Romanian J Gastroenterology. 2005;4:337–41.

ЛИТЕРАТУРА

1. Новикова В.П., Кузьмина Д.А., Гузеева О.Д. Хронический гастрит и патология костной ткани у детей. Врач-аспирант. 2011;47(4.1):248–254.
2. Бельмер С.В., Разумовский А.Ю., Хавкин А.И. и др. Болезни желудка и двенадцатиперстной кишки у детей. М.: Медпрактика-М; 2017.

3. Han T., Zhang Y., Qi B., Chen M., Sun K., Qin X., Yang B., Yin H., Xu A., Wei X., Zhu L. Clinical features and shared mechanisms of chronic gastritis and osteoporosis. Sci Rep. 2023;13(1):4991. DOI: 10.1038/s41598-023-31541-8.
4. Пигарова Е.А., Дзеранова Л.К., Яценко Д.А. Витамин D — вопросы всасывания и метаболизма в норме и при заболеваниях желудочно-кишечного тракта. Ожирение и метаболизм. 2022;19(1):123–33. DOI: 10.14341/omet12835. URL: https://applied-research.ru/ru/article/view?id=13566 (дата обращения: 02.01.2024).
5. Maurya V.K., Aggarwal M. Factors influencing the absorption of vitamin D in GIT: an overview. J Food Sci Technol. 2017;54(12):3753–3765. DOI: 10.1007/s13197-017-2840-0.
6. Shin C.S., Choi H.J., Kim M.J. et al. Prevalence and risk factors of osteoporosis in Korea: a community-based cohort study with lumbar spine and hip bone mineral density. Bone. 2010;47(2):378–387.
7. Слохова Н.К., Тотров И.Н. Регуляция кальциевого обмена и состояние костной ткани у больных с заболеваниями желудочно-кишечного тракта. Современные проблемы науки и образования. 2014;6. URL: https://science-education.ru/ru/article/view?id=16544 (дата обращения: 02.01.2024).
8. Szymczak-Tomczak A., Ratajczak A.E., Kaczmarek-Ryś M., Hryhorowicz S., Rychter A.M., Zawada A., Słomski R., Dobrowolska A., Krela-Kaźmierczak I. Pleiotropic Effects of Vitamin D in Patients with Inflammatory Bowel Diseases. J Clin Med. 2022;11(19):5715. DOI: 10.3390/jcm11195715.
9. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser. 2003;921:1–164, back cover. PMID: 15293701.
10. Carmeliet G., Dermauw V., Bouillon R. Vitamin D Signaling in Calcium and Bone Homeostasis: A Delicate Balance. Best Pract. Res. Clin. Endocrinol. Metab. 2015;29:621–631. DOI: 10.1016/j.beem.2015.06.001.
11. Zhu W., Yan J., Zhi C., Zhou Q., Yuan X. 1,25$(OH)_2D_3$ deficiency-induced gut microbial dysbiosis degrades the colonic mucus barrier in Cyp27b1 knockout mouse model. Gut Pathog. 2019;11:8. DOI: 10.1186/s13099-019-0291-z.
12. Kühne H., Hause G., Grundmann S.M., Schutkowski A., Brandsch C., Stangl G.I. Vitamin D receptor knockout mice exhibit elongated intestinal microvilli and increased ezrin expression. Nutr. Res. 2016;36:184–192. DOI: 10.1016/j.nutres.2015.10.005.
13. Schäffler H., Herlemann D.P., Klinitzke P., Berlin P., Kreikemeyer B., Jaster R., Lamprecht G. Vitamin D administration leads to a shift of the intestinal bacterial composition in Crohn's disease patients, but not in healthy controls. J. Dig. Dis. 2018;19:225–234. DOI: 10.1111/1751-2980.12591.
14. Fasano A. Zonulin, regulation of tight junctions, and autoimmune diseases. Ann. N.Y. Acad. Sci. 2012;1258:25–33. DOI: 10.1111/j.1749-6632.2012.06538.x.
15. Weber G., Heilborn J.D., Jimenez C.I.C., Hammarsjö A., Törmä H., Ståhle M. Vitamin D induces the antimicrobial protein hCAP18 in human skin. J. Investig. Dermatol. 2005;124:1080–1082. DOI: 10.1111/j.0022-202X.2005.23687.x.
16. Bals R., Wang X., Zasloff M., Wilson J.M. The peptide antibiotic LL37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proc. Natl. Acad. Sci. USA. 1998;95:9541–9546. DOI: 10.1073/pnas.95.16.9541.
17. Gallo R.L., Kim K.J., Bernfield M., Kozak C.A., Zanetti M., Merluzzi L., Gennaro R. Identification of CRAMP, a cathelin-related antimicrobial peptide expressed in the embryonic and adult mouse. J. Biol. Chem. 1997;272:13088–13093. DOI: 10.1074/jbc.272.20.13088.
18. Chun R.F., Liu P.T., Modlin R.L., Adams J.S., Hewison M. Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. Front Physiol. 2014;5:151. DOI: 10.3389/fphys.2014.00151.
19. Bacchetta J., Zaritsky J.J., Sea J.L., Chun R., Lisse T.S., Zavala K., Nayak A., Wesseling-Perry K., Westerman M., Hollis B.W. et al. Suppression of iron-regulatory hepcidin by vitamin D. J. Am. Soc. Nephrol. 2014;25:564–572. DOI: 10.1681/ASN.2013040355.
20. Bikle D.D. Vitamin D Regulation of Immune Function. Curr. Osteoporos. Rep. 2022;20:186–193. DOI: 10.1007/s11914–022–00732-z.
21. Massironi S., Cavalcoli F., Zilli A., Del Gobbo A., Ciafardini C., Bernasconi S., Felicetta I., Conte D., Peracchi M. Relevance of vitamin D deficiency in patients with chronic autoimmune atrophic gastritis: a prospective study. BMC Gastroenterol. 2018;18(1):172. DOI: 10.1186/s12876-018-0901-0.
22. Infantino C., Francavilla R., Vella A., Cenni S., Principi N., Strisciuglio C., Esposito S. Role of Vitamin D in Celiac Disease and Inflammatory Bowel Diseases. Nutrients. 2022;14(23):5154. DOI: 10.3390/nu14235154.
23. Шуматова Т.А., Коваленко Д.В., Приходченко Н.Г. Витамин D и заболевания кишечника. Международный журнал прикладных и фундаментальных исследований. 2023;8:24–28.
24. Eloranta J.J., Wenger C., Mwinyi J., Hiller C., Gubler C., Vavricka S.R., Fried M., Kullak-Ublick G.A., Swiss IBD

Cohort Study Group Association of a Common Vitamin D-Binding Protein Polymorphism with Inflammatory Bowel Disease. Pharm. Genom. 2011;21:559–564. DOI: 10.1097/FPC.0b013e328348f70c.
25. Peterlik M. and Cross H.S. Vitamin D and calcium insufficiency-related chronic diseases: molecular and cellular pathophysiology. European Journal of Clinical Nutrition. 2009;63:1377–1386.
26. Kang T.J., Jin S.H., Yeum C.E., Lee S.B., Kim C.H., Lee S.H., Kim K.H., Shin E.S., Chae G.T. Vitamin D Receptor Gene TaqI, BsmI and FokI Polymorphisms in Korean Patients with Tuberculosis. Immune Netw. 2011;11(5):253–257. DOI: 10.4110/in.2011.11.5.253.
27. Taymans S.E., Pack S., Pak E., Orban Z., Barsony J., Zhuang Z., Stratakis C.A. The human vitamin D receptor gene (VDR) is localized to region 12cen-q12 by fluorescent in situ hybridization and radiation hybrid mapping: genetic and physical VDR map. J Bone Miner Res. 1999;14(7):1163–1166. DOI: 10.1359/jbmr.1999.14.7.1163.
28. Valdivielso J.M., Fernandez E. Vitamin D receptor polymorphisms and diseases. Clin Chim Acta. 2006; 371(1–2):1–12. DOI: 10.1016/j.cca.2006.02.016.
29. Baker A.R., McDonnell D.P., Hughes M. Cloning and expression of full-length cDNA encoding human vitamin D receptor. Proceedings of the National Academy of Sciences. 1998;85(10):3294–3298. DOI: 10.1073/pnas.85.10.3294.
30. Фомина Л.А. Роль кальцийрегулирующей системы в патогенезе и саногенезе язвенной болезни и коррекция ее сдвигов при лечении рецидива заболевания. Экспериментальная и клиническая гастроэнтерология 2016;134(10).
31. Храмцова С.Н. Оценка уровня кальция и фосфора в прогнозировании остеопении у детей и подростков. Общественное здоровье и профилактика заболеваний. 2007;2:47–50.
32. Щеплягина Л.А., Моисеева Т.Ю. Дефицит кальция — возможности пищевой коррекции у дошкольников. Consilium medicum. Педиатрия. 2007;1:80–83.
33. Хаустова Г.Г., Банина Т.В., Мухина Ю.Г., Щеплягина Л.С. Дефицит кальция и витамина Д при хронических заболеваниях желудка и тонкой кишки. Доктор.ру. 2008;1:14–18.
34. Лебеда В.Ф., Ясинский О.Р. Остеопатии у детей с хроническим гастродуоденитом. Педиатрия, акушерство и гинекология. 2000;2:29–31.
35. Шевченко С.Д., Ермак Т.А. Остеопенический синдром у детей и подростков, больных сколиозом. Российский педиатрический журн. 2005;1:21–24.
36. Elkin S.L., Fairney A., Burnett S. et al. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: A cross-sectional study. Osteoporoses Int. 2001;12:366–72.
37. Leonard M.B. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. Pediatrics. 2007;119:166–S174.
38. Payne D., Ray D. Glucocorticoid receptor gene polymorphisms and susceptibility to rheumatoid arthritis. Clinical Endocrinology. 2007;67:342–345.
39. Schlienger R.G., Jick S.S., Meier C.R. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics. 2004;114(2):469–473.
40. Targownik L.E., Lix L.M., Prior H.J. et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures .Can. Med. Assoc. J. 2008;179:319–326.
41. Van Rossum E.F., Roks P.H., de Jong F.H. et al. Characterization of a promoter polymorphism in the glucocorticoid receptor gene and its relationship to three other polymorphisms. Clinical Endocrinology (Oxf). 2004;61:573–581.
42. Ishino Y., Sugano K. Acid-suppressive strategy against gastroesophageal reflux diseases and non-erosive reflux diseases: the alternative of proton- pump inhibitors or H2 receptor antagonists. Nippon Rinsho. 2007;65(5):891–894.
43. Suzuki M., Suzuki H., Hibi T. Proton pump inhibitors and gastritis. J. Clin. Biochem. Nutr. 2008;42(2):71–75.
44. Tsirambidis J.V.E., Conwell D.L., Zuccaro G. Osteopenia in a patient with chronic pancreatitis. The American Journal of Gastroenterology. 2003;98(9):S164.
45. Yang Y., Lewis J., Epstein S. et al. Long-term proton pump inhibitor therapy and risk of hip fraction. J. Am. Med. Assoc. 2006;296:2947–2953.
46. Cijevschi C. at al. Osteoporosis in liver cirrhosis. Romanian J Gastroenterology 2005;4:337–41.