FEATURES OF VITAMIN-D METABOLISM IN PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

Diabetic nephropathy (DN) is a specific kidney damage in diabetes mellitus (DM), caused by the influence of hemodynamic and metabolic factors. It is in the kidneys that an important stage of vitamin D metabolism occurs—1α-hydroxylation, which results in the formation of its main biologically active form. A decrease in the number of functioning nephrons in DN leads to disruption of vitamin D metabolism, contributing to the development of a number of complications. In this review, we dwell in detail on both the normal metabolism of vitamin D and the peculiarities of vitamin D metabolism in chronic kidney disease (CKD). DN is the most common cause of CKD and, as a consequence, kidney transplantation, as well as one of the leading causes of cardiovascular morbidity and mortality in patients with diabetes. Mineral and bone disorders due to CKD, caused by abnormal vitamin D metabolism, are also independent factors of high mortality among patients with DN. The final part of our review briefly highlights modern approaches to vitamin D therapy in CKD, and in particular DN. It is worth noting that, despite the growing number of patients with DN, there is currently no consensus on the use of vitamin D as a therapeutic agent for this pathology.

Keywords: vitamin D; vitamin D metabolism; diabetic nephropathy; chronic kidney disease; colecalciferol; alfacalcidol; paricalcitol.

INTRODUCTION

Vitamin D deficiency and insufficiency are highly prevalent both in the general population and among patients with CKD [1]. CKD develops in approximately 40% of patients with diabetes and is the main reason for switching to renal replacement therapy [2]. The increasing prevalence of CKD in patients with diabetes is directly proportional to the rapid increase in the prevalence of both type 1 and type 2 diabetes worldwide [3]. CKD is an independent factor of increased risk of cardiovascular diseases, and in particular one of the leading causes of death in patients with diabetes [4]. Between 1990 and 2012. the number of deaths associated with diabetic nephropathy (DN) increased by 94% [5]. This increase is one of the highest among all chronic diseases [6]. The steady increase in the number of patients with DN requires a careful and comprehensive approach to the management of this pathology. Mineral and bone disorders due to CKD, due to impaired vitamin D metabolism, are known factors of increased mortality in this pathology. NORMAL

VITAMIN D METABOLISM

Vitamin D exists in two native, biologically inactive forms: vitamin D3 (colecalciferol), the most important source in the human/animal body, synthesized in the skin, and vitamin D2 (ergocalciferol), its plant analogue [7]. In the cells of the outer layers of the skin, vitamin D3 is formed from a precursor substance - 7-dehydrocholesterol (7DHC). Exposure to ultraviolet radiation in the range of 290–315 nm leads to the formation of previtamin D, followed by thermal isomerization of the latter into vitamin D [8]. Vitamin D concentrations depend on the activity of the enzyme 7-dehydrocholesterol reductase (DHCR7), which is involved in the conversion of 7DHC to cholesterol. In this case, the formation of vitamin D is limited by the amount of available substrate, i.e. 7DHC itself. On the other hand, loss of DHCR7 activity enhances the biosynthesis of colecalciferol and reduces cholesterol formation [9]. Inactive forms of vitamin D are converted to biologically active forms through a two-step sequential hydroxylation process, which allows the concentration of active forms of vitamin D to be controlled within a narrow range and therefore prevents the potential adverse effects of excess. The first stage of metabolic activation of vitamin D occurs in the liver, where 25-hydroxyvitamin D (25(OH)D), or calcidiol, is formed under the action of 25-hydroxylase. There are many enzymes that have 25-hydroxylase activity, such as CYP2R1 and CYP27A1 [10]. They are distinguished by their ability to hydroxylate various native forms of vitamin D, namely colecalciferol or ergocalciferol. Most of vitamin D is hydroxylated at position 25 (C25) during its first passage through the liver [11]. 25(OH)D is the main form of vitamin D, forming its reserves and also circulating in the bloodstream; it is the indicator of the level of vitamin D in the body [12]. 25(OH)D undergoes a final activation step to become 1,25-

dihydroxyvitamin D (1,25(OH)2 D), or calcitriol. 1,25(OH)2 D is formed predominantly in the epithelial cells of the proximal tubules of the kidneys under the action of CYP27B1, a mitochondrial enzyme with 1α-hydroxylase activity [13]. It has now been proven that CYP27B1 is expressed by cells not only of the kidneys, but also of a number of other organs, including the placenta, pancreas, intestines, parathyroid glands (PTG) and macrophages [14]. Another step in the vitamin D metabolic pathway is 24-hydroxylase (CYP24A1)-controlled inactivation in the kidneys. The addition of a hydroxyl group at the 24th position (C24) promotes the catabolism of both 25(OH)D and 1,25(OH)2 D with the formation of an intermediate product - 1,24,25-trihydroxyvitamin D (1,24,25(OH)3 D) and ultimately water-soluble calcitroic acid and the inactive metabolite 24,25-dihydroxyvitamin D (24,25(OH)2 D) [7]. Of interest is the participation of human CYP24A1 in the alternative pathway of degradation of vitamin D molecules through 23-hydroxylation, however, its contribution to the catabolism process is significantly lower [15]. Renal CYP27B1 activity is regulated by Ca2+, PO43-, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Hypocalcemia stimulates the secretion of PTH, which increases the activity of CYP27B1. On the other hand, in response to hyperphosphatemia, bone tissue cells produce FGF23, which inhibits the activity of CYP27B1 [16]. Increasing the concentration of 1,25(OH)2 D also directly reduces the activity of CYP27B1, increasing the activity of CYP24A1, which leads to degradation of the active form of vitamin D (Fig. 1) [17]. Thus, the metabolism of vitamin D is under strict control of various factors, which prevents the accumulation of excessive concentrations of calcitriol with the potential development of hypercalcemia and hyperphosphatemia. VITAMIN D AND CHRONIC KIDNEY DISEASE The kidneys are a key organ in the regulation of vitamin D metabolism, so impaired kidney function can lead to vitamin D insufficiency/deficiency, which is often observed in patients with CKD, regardless of the previous etiological factor. Violation of vitamin D metabolism in CKD is caused by several mechanisms. As CKD progresses, the number of functioning nephrons and, consequently, the expression of CYP27B1 decreases, which slows down the process of 1α-hydroxylation in the kidneys [18, 19]. A gradual decrease in glomerular filtration rate (GFR) limits the delivery of 25(OH)D to the zone of its activation [20]. As a result, insufficient concentrations of 1,25(OH)2 D in patients with CKD may stimulate the development of secondary hyperparathyroidism (SHPT) [21]. Hyperphosphatemia is an equally important factor that reduces the concentration of the active form of vitamin D in CKD. In response to an increase in the level of phosphorus in the blood, the synthesis of FGF23, a protein responsible for its homeostasis in the body, increases [22]. FGF23 inhibits the expression of 1α-hydroxylase while stimulating the expression of 24-hydroxylase, which enhances the catabolism of

vitamin D. Thus, the main effect of FGF23 on phosphorus metabolism is hypophosphatemic, but it also indirectly contributes to a decrease in intestinal calcium absorption and, as a result, hypocalcemia and increased PTH (Fig. 2) [18, 23]. Under normal conditions, vitamin D metabolites circulate bound to transport proteins, the main of which is vitamin D binding protein (VDBP). Its concentration significantly exceeds the concentration of all forms of vitamin D metabolites [10]. Therefore, most VDBP circulates in an unbound form as an alloprotein. It has been suggested that the excess of VDBP may be due to its protective role against toxic excess vitamin D [24]. 25(OH)D and VDBP pass through the glomerular filter and are then reabsorbed in the proximal renal tubules by megalin [25]. Megalin is a multiligand receptor that mediates the endocytosis of 25(OH)D and thus its delivery for 1α-hydroxylation [26]. A decrease in the filtration capacity of the kidneys and the development of proteinuria contribute to the loss of both VDBP, and the associated 25(OH)D itself and its metabolites [18, 27].

PATHOPHYSIOLOGICAL RELATIONSHIP OF VITAMIN D AND DIABETIC NEPHROPATHY

A fairly large number of preclinical studies have been carried out on rats and mice, which assessed the nephroprotective effect of vitamin D on the development of DN, including in the form of a significant decrease in blood creatinine levels and the rate of albumin excretion in urine, as well as an improvement in the histological picture of the kidneys [32]. The study of the molecular mechanisms of this process revealed its direct dependence on the presence of an active vitamin D receptor [32, 33]. Noteworthy are the results of a study conducted by Y. Wang et al., in which the authors showed that restoration of the expression of the vitamin D receptor in podocytes in mice with streptozotocin-induced diabetes almost completely blocks the development of DN [34].

MODERN APPROACHES TO VITAMIN D THERAPY

Currently, there is no consensus on the target level of 25(OH)D, the dose of vitamin D and the management of SHPT in patients with mineral and bone disorders due to CKD due to the lack of a significant evidence base. The 2017 Kidney Disease Initiative to Improve Global Outcomes (KDIGO) guidelines do not suggest specific targets for 25(OH)D levels in patients with CKD. It is proposed to assess 25(OH)D levels in patients with CKD C3a–5D and correct vitamin D deficiency and insufficiency according to the strategy recommended for the general population [40].

CONCLUSION

The current state of the analyzed issue is characterized by the lack of a significant evidence base regarding the treatment of mineral and bone disorders due to CKD in DN and a consensus on the cut-off values of PTH levels necessary to initiate therapy

with active vitamin D metabolites, especially in the pre-dialysis stages. All this significantly complicates the treatment of such patients. Taking into account that the incidence of DN is steadily increasing, it is necessary to conduct more randomized clinical trials in order to form a unified concept of vitamin D therapy for patients with DN.

REFERENCES:

1. Отамуродов УГ угли, Абдужамбилов АН угли, Сабирова ДШ. Гипертиреоз. Science and Education. 2023;4(5):134-139.
2. Шухратовна СД, Рустамовна РГ, Нодир Р. Изменения уровня хг в системе мать-плацента-плод при резус несовместимой беременности. Достижения науки и образования. 2020;(10 (64)):91-93.
3. Хамраев Х, Содиков С, Хамраева Д, Собирова Д. Клинико-функциональное состояние печени у больных с сахарным диабетом. ЖПБМ. 2018;(1 (99)):189-191.
4. Даминов АТ, Хакбердиева В, Жаникулов С, Муродхонов С. КЛИНИЧЕСКИЙ СЛУЧАЙ ПЕРВИЧНЫЙ ГИПОТИРЕОЗ. Educational Research in Universal Sciences. 2024;3(3 SPECIAL):131-134.
5. Shukhratovna SD, Suratovich OF. МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ КОРЫ НАДПОЧЕЧНИКОВ ПОТОМСТВА КРЫС В ОНТОГЕНЕЗЕ В УСЛОВИЯХ ВНУТРИУТРОБНОГО ВОЗДЕЙСТВИЯ ПЕСТИЦИДОВ ЧЕРЕЗ ОРГАНИЗМ МАТЕРИ (ОБЗОРНАЯ СТАТЬЯ). JOURNAL OF BIOMEDICINE AND PRACTICE. 2023;8(4). Accessed January 12, 2024. https://tadqiqot.uz/index.php/biomedicine/article/view/8217
6. Мизамова МАК, Эшпулатова ГНК, Эшмуродова ЗНК, Салимова ДЭ. Осложнения акромегалии, связанные со здоровьем, текущие и перспективные варианты лечения. Science and Education. 2023;4(4):187-195.
7. Нарбаев А, Джураева З, Курбонова Н, Кувондиков Г, Давранова А, Содиков С. Особенности изучения многофакторного управления сахарным диабетом 2 типа. Журнал проблемы биологии и медицины. 2017;(4 (97)):78-79.
8. Ибрагимов УС, Туракулов ЖТУ, Гуломов ШНУ, Салимова ДЭ. Просвещение пациентов: Гипогликемия (низкий уровень глюкозы в крови) у людей с диабетом. Science and Education. 2023;4(4):226-233.
9. Содиков С, Каримова Н, Каримова З. Реабилитация больных пожилого возраста сахарным диабетом 2-типа. ЖПБМ. 2017;(4 (97)):105-106.
10. Хамидова МН, Исматова ИФ, Бердиеров ЖШ, Негматова ГШ, Даминов АТ. САХАРНЫЙ ДИАБЕТ И COVID-19. Eurasian Journal of Medical and Natural Sciences. 2022;2(13):190-204.
11. Шухратовна СД, Кахрамонович ЮУ, Махмудович КТ. Структурные

изменения сосудисто-стромального комплекса щитовидной железы при эутиреоидной и токсических формах зоба. Научный журнал. 2019;(10 (44)):67-69.
12. Собиржоновна КН, Саллохидинович СС, Акбаровна ОМ. Эпидемиологический Статус И Факторы Риска Сахарного Диабета На Сегодняшний День. Miasto Przyszłości. 2023;32:212-219.
13. Salimova DE, Daminnov AT. A CLINICAL CASE BASED ON THE EXPERIENCE OF TREATING HYPERTENSION IN A PATIENT WITH TYPE 2 DIABETES MELLITUS, OBESITY AND VITAMIN D DEFICIENCY. Educational Research in Universal Sciences. 2023;2(12):150-154.
14. Takhirovich DA. ASSESSMENT OF HEARING FUNCTION IN INDIVIDUALS WITH TYPE 2 DIABETES. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1(9):124-126.
15. Qahramonov FA, Amirov BY, Tursunboyeva LI, Daminov AT. Autoimmun tireoidit bilan kasallangan bemorlardagi funksional buzilishlarning differensional diagnostikasida qalqonsimon bez zichligini aniqlash. Science and Education. 2023;4(3):82-86.
16. Nazira K, Siddikovna TG, Davranovna DA, Takhirovich DA, Tulkinovich OS. Cardiovascular complications in patients who have had covid on the background of diabetes mellitus 2. 1. 2021;2(3):37-41.
17. Choriyev S, Gadoeva Z, Mardonova F, Jurakulov F, Hafizov S, Daminov AT. Changes in the thyroid gland in the long period after a new coronavirus infection. Science and Education. 2023;4(12):102-106.
18. Kamalov T, Bahriev N, Yuldashev U, Sabirova D. CLINICAL AND HORMONAL CHARACTERISTICS OF PRIMARY HYPOGONADISM IN PRESCHOOL BOYS. MedFarm. 2019;10(9). doi:10.32743/2658-4093.2019.9.10.188
19. Daminov AT, Yuldoshev B, Murodullo I, Naimova N. CLINICAL CASE OF PRIMARY HYPOTHYROIDSIS. Educational Research in Universal Sciences. 2024;3(3 SPECIAL):135-138.
20. Daminov A, Khaydarov O, Hasanova M, Abdukakhorova R. COMPLICATIONS OF GLUCOCORTICOID THERAPY IN PATIENTS DIABETES SURVIVED COVID-19. Евразийский журнал медицинских и естественных наук. 2023;3(4):197-200.
21. Takhirovich DA, Corners SJA, Shukhratovna NG, Shukhratovna SG, Zaynuddinovna MG. COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS. Web of Scientist: International Scientific Research Journal. 2022;3(02):73-76. doi:10.17605/OSF.IO/B6FU2
22. Shukhratovna NG, Erkinovna SD, Suxrobovna XM, Ikromovna AZ. DIABETES

MELLITUS, ISCHEMIC HEART DISEASE AND ARTERIAL HYPERTENSION. PEDAGOG. 2022;5(5):381-386.
23. O‘g‘li SOS, O‘g‘li RSO, Taxirovich DA. DIFFUZ TOKSIK BUQOQ. Лучшие интеллектуальные исследования. 2023;4(1):131-133.
24. Negmatova GS, Toshimova GT qizi, Abdiyev LS o‘g‘li, Daminov AT. EFFECTIVENESS OF CORRECTION OF DYSLIPIDEMIA IN ELDERLY PATIENTS WITH TYPE 2 DIABETES MELLITUS. Educational Research in Universal Sciences. 2024;3(1 SPECIAL):269-274.
25. G.Sh N, D.e S, Oybekovma XS, Qamariddinovna XA, O‘g‘li BJA. ENDOCRINE GLANDS, STRUCTURE, AGE FEATURES, FUNCTIONS. PEDAGOG. 2022;5(5):341-345.
26. Sobirjonovna KN. FACTORS DETERMINING THE CLINICAL SIGNIFICANCE OF DEPIPTIDYL PEPTIDASE 4 INHIBITORS IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS. World Bulletin of Public Health. 2022;8:67-72.
27. Daminov AT, Djabbarova D, Abduvohidova N, Furkatova D, Farxodova S, Ibragimova P. Features of bone tissue remodeling in patients with type 2 diabetes mellitus. Science and Education. 2023;4(11).
28. Daminov Abdurasul Takhirovich RSU. FEATURES OF THE CLINIC, REHABILITATION, TREATMENT OF AUTOIMMUNE THYROIDITIS IN THE CONDITIONS OF THE IODINE-DEFICIENCY REGION. Published online April 12, 2023. doi:10.5281/ZENODO.7820412
29. Shuhratovna NG, Shukhratovna SD. Features of the course of autoimmune hepatitis in children as a variant of autoimmune polyglandular syndrome. Asia Journ of Multidimensi Resear (AJMR). 2020;9(7):89. doi:10.5958/2278-4853.2020.00228.1
30. Erkinovna SD. Features of the Course of Diabetes Mellitus Type 2 with Arterial Hypertension. JournalNX. Published online 2020:460-461.
31. Negmatova GS, Xakimova GD qizi, Abdiyev LS o‘g‘li, Daminov AT. FEATURES OF THE RULES FOR INSULIN INJECTION TECHNIQUES IN ELDERLY AND SENILE PATIENTS WITH DIABETES MELLITUS. Educational Research in Universal Sciences. 2024;3(1 SPECIAL):259-264.
32. Takhirovich DA, Zafarovna KM, Isroilovna IS. FEATURES OF TYPE 1 DIABETES IN CHILDREN WHO HAVE COVID-19. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1(9):121-123.
33. Xudoyorov S, Mirkomilova M, Burxonov U, Sayfieva G, Sheralieva N, Daminov AT. Fourniers gangrene in modern conditions. Science and Education. 2023;4(12):107-117.
34. Alimovna KN, Sobirjanovna KN, Abdurasul D, Tulkinovich OS. GROWTH

HORMONE FOR THE TREATMENT OF HEREDITARY DISEASES IN CHILDREN. 10.
35. Negmatova .G.Sh, D.e S, Qizi MZO, Mannobovich MS, Orifjonovich MM. HERPETIC MENINGITIS. PEDAGOG. 2022;5(5):346-348.
36. Ahrorbek N, Myungjae L, Jungjae L, et al. Hormonal Regulation. Texa Jour of Mutl Stud. 2023;25:39-43.
37. Ismoilova SI. Impact of vitamin D deficiency on the risk of developing type 1 diabetes. Science and Education. 2023;4(3).
38. T DA, Umidbekovna UM, Muhitdinovna KN. Methodology of Using Modern Graphics Programs in Teaching Engineering Graphics. 1. Published online December 8, 2023:158-162.
39. Sabirjanovna KN, Takhirovich DA, Jahongir D, Najmiddin X, Samandar G, Mehrangiz X. Negative Impact of Covid-19 on the Endocrine System. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1(8):148-153.
40. Takhirovich DA, Zafarovna KM, Isroilovna IS. NEVROLOGIYADA ENDOKRIN O‘ZGARISHLAR. SO‘NGI ILMIY TADQIQOTLAR NAZARIYASI. 2023;6(12):417-422.
41. Negmatova GS, Salimova DE. Qandli diabet 2-tipning arterial gipertenziya bilan birgalikda kechish xususiyatlari va ularni davolash usullari. Science and Education. 2023;4(2):516-519.
42. Taxirovich DA, J T, O E, I A. QANDLI DIABET-2 TIPI BOR BEMORLARDA COVID-19 KASALLIGINI GLUKOKORTIKOIDLAR BILAN DAVOLASH DINAMIKASINI BAHOLASH. Gospodarka i Innowacje. 2023;34:78-81.
43. G.Sh N, D.e S, Alisherovich BA, Erkin R is the son of S, Bektash U is the son of S. RELATIONSHIP BETWEEN DIABETIC NEPHROPATHY AND CARDIAC DISORDERS IN PATIENTS WITH TYPE 2 DIABETES. PEDAGOG. 2022;5(5):337-340.
44. Daminov AT, Sa’dullayeva SM qizi, Ismoilova SI qizi. SAMARQAND VILOYATIDA QANDLI DIABET ASORATLARI UCHRASH CHASTOTASI. Educational Research in Universal Sciences. 2024;3(3 SPECIAL):139-142.
45. Shukhratovna NG, Erkinovna SD, O‘g‘li IBI, Qizi ADD. THE ROLE OF GASTROINTESTINAL HORMONES IN THE PATHOLOGY OF THE DIGESTIVE SYSTEM. PEDAGOG. 2022;5(6):408-412.
46. Ulugbekovna NP, Bakhtiyorovna RI, Almosovich RA, Takhirovich DA. Thyroid Diseases during Pregnancy and their Impact on Maternal and Fetal Outcomes. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1(8):188-190.
47. Nilufar R, Adkhamjon K. TO THE DEVELOPMENT OF CARDIOVASCULAR

DISEASES EFFECTS OF ENVIRONMENTAL FACTORS. FAN, TA'LIM, MADANIYAT VA INNOVATSIYA JURNALI | JOURNAL OF SCIENCE, EDUCATION, CULTURE AND INNOVATION. 2022;1(4):100-101.
48. Xoldorov X, Omonov F, Jumayev I, Daminov AT. TYPE 1 DIABETES AS A RISK FACTOR FOR BONE HEALTH IN CHILDHOOD. Results of National Scientific Research International Journal. 2023;2(8):131-135.
49. Daminov AT, Xurramova S, Islomov A, Ulashev M, Ikramov R, Mirzakhakimov P. Type 2 diabetes and bone mineral density in postmenopausal women. Science and Education. 2023;4(11).
50. Berkinov A, Safarov F, Tursunova S, Daminov AT. VITAMIN D STATUS IN SENIOR RESIDENTS OF SAMARKAND REGION. Results of National Scientific Research International Journal. 2023;2(8):136-140.
51. Taxirovich DA, N SY, I IM, Z SM. VITAMIN-D YETISHMOVCHILIGINING QANDLI DIABET 1-TIP RIVOJLANISHIGA TA'SIRI. Gospodarka i Innowacje. 2023;34:74-77.