РОЛЬ ДЕФИЦИТА ВИТАМИНА D В РАЗВИТИИ САХАРНОГО ДИАБЕТА 2 ТИПА И ДИАБЕТИЧЕСКОЙ НЕЙРОПАТИИ

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Сахарный диабет (СД) 2 типа является глобальной эпидемией и ассоциируется с развитием тяжелых сосудистых осложнений. Диабетическая нейропатия (ДН) относится к частым хроническим осложнениям СД, приводящим к ухудшению прогноза и качества жизни больных. Масштабы проблемы определяют актуальность исследований, направленных на уточнение механизмов развития и прогрессирования СД и ДН. В обзоре обсуждаются современные представления о вкладе витамина D в патофизиологические и биохимические основы метаболизма глюкозы, рассматривается участие в регуляции процессов воспаления. Приведены данные о том, что изменение активности рецептора витамина D или концентрации вне- и внутриклеточного кальция в условиях дефицита витамина D могут оказывать неблагоприятное воздействие на функциональное состояние β-клеток поджелудочной железы и приводить к уменьшению синтеза и секреции инсулина. Также приведены современные представления о роли дефицита витамина D в развитии инсулинорезистентности. Обсуждаются ключевые аспекты патогенеза нейропатии у больных СД. Представлены возможные механизмы, посредством которых витамин D принимает участие в формировании ДН. Приведены результаты исследований, посвященных вопросам терапии препаратами витамина D при СД. Учитывая изложенные в обзоре факты, авторами обосновывается идея о том, что дефицит витамина D может рассматриваться как неклассический фактор риска развития не только СД, но и его осложнений.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; диабетическая нейропатия; 25(OH)D; недостаток/дефицит витамина D

ROLE OF VITAMIN D DEFICIENCY IN TYPE 2 DIABETES MELLITUS AND DIABETIC NEUROPATHY DEVELOPMENT

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Type 2 diabetes mellitus (DM) is a global epidemic associated with severe vascular complications development. Diabetic neuropathy is the most common chronic complication of DM that worsens patients' life quality and prognosis. Therefore, studies dealing with DM and diabetic neuropathy underlying mechanisms are extremely relevant. The review discusses current views on vitamin D role in glucose metabolism and inflammatory processes. It is reported that vitamin D deficiency can contribute to insulin resistance development, and change in vitamin D receptor activity or extra- and intracellular calcium concentration due to vitamin D deficiency can affect pancreatic β-cells function and lead to decrease in insulin production. Key pathogenic mechanisms of diabetic neuropathy as well as possible relationship between vitamin D deficiency and neuropathy development are in focus of this review. Results of recent clinical trials regarding vitamin D supplementation in patients with DM are also discussed. The presented data suggest that vitamin D deficiency can be considered as a non-classical risk factor for the development of not only DM but its complications as well.

KEYWORDS: diabetes mellitus; diabetic neuropathy; 25(OH)D; vitamin D deficiency

PREVALENCE OF DIABETES MELLITUS AND VITAMIN D DEFICIENCY

More studies on the pleiotropic effects of vitamin D are being conducted [1–3]. Large-scale population studies revealed that vitamin D deficiency is nearly as prevalent as type 2 diabetes mellitus (DM2) [4–7]. Both DM and vitamin D deficiency occur in populations throughout the world, regardless of race, age or gender characteristics. According to the European Association for the Study of Diabetes Mellitus (EASD), the number of patients with DM aged 20 to 79 years reached 415 million in 2015; that number could reach 642 million by 2040 [8]. As of early 2015, DM2 prevalence in the Russian Federation amounted to 2.8% of the total population [9]. According to the NATION study, it was estimated at 5.4% [10]. Similar statistics are observed when assessing the prevalence of vitamin D deficiency [11]. Vitamin D deficiency is common both in northern latitude regions and in countries of Southeast Asia and the Middle East, while its prevalence in the USA reaches 75% and in Japan and South Korea it is 90% [6]. Possible reasons for such a

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high prevalence of vitamin D deficiency in regions with a high level of insolation may be the wearing of clothing covering the whole body, genetically determined skin pigmentation, urban air pollution in cities and vitamin D-depleted nutrition [5]. Data on the prevalence of vitamin D deficiency in the Russian Federation are mainly represented by isolated studies and do not differ from the global statistics. Thus, among residents of large megacities such as St. Petersburg, the rate of vitamin D deficiency among the adult population was reported to be 83.2% [7] and 61.2% in three-year-old children; also, the vitamin D insufficiency was estimated at 24.8% [12].

Thus, both DM2 and vitamin D deficiency are widespread diseases/conditions throughout the world and studies should be conducted to find possible mechanisms for their interrelation.

VITAMIN D DEFICIENCY AND RISK OF DEVELOPMENT OF DIABETES MELLITUS TYPE 2

Studies indicate an association between the level of vitamin D and the risk of developing both DM and its chronic complications [13–16]. The Framingham Study showed 40% of patients with a minimum level of 25(OH) D in serum developed DM2 7 years after the start of follow-ups [17]. Similar data in a crossover study among South Koreans over 20 showed DM2 was more common in patients with vitamin D insufficiency and deficiency compared to those with serum levels of 25(OH)D higher than 75 nmol/l [18]. Moreover, a study involving more than five thousand people in Australia suggested a higher risk of DM2 development in individuals with a low level of 25(OH)D and showed that an increased concentration of 25(OH)D per every 25 nmol/l was associated with decrease in DM risk by 24% [19]. In addition, the results of the widely discussed Nurses' Health Study showed that the risk of DM2 development is reduced by 48% in women with serum 25(OH)D level exceeding 33 ng/ml [20]. However, there is contradictory data indicating a lack of association between the risk of DM development and the level of vitamin D sufficiency [21].

Despite data inconsistencies, most experts believe that normal levels of vitamin D help prevent metabolic disorders [22]. Studies indicate that, among participants with serum 25(OH)D level corresponding to the highest quartile, the risk of metabolic disorders is 43% lower than that in those with the lowest levels of 25(OH)D. Each 25-nmol/l increase in 25(OH)D concentration is accompanied by a 13% decrease in the risk of metabolic syndrome development [19]. Thus, vitamin D deficiency can be considered an independent risk factor for developing metabolic disorders, including DM2 [15, 19, 20].

The mechanisms by which vitamin D is involved in glucose metabolism are not fully understood. However, vitamin D and calcium are involved in the control of glucose homeostasis and changes in their concentrations may play a role in developing DM [23]. The effects of vitamin D on pancreatic cells may be mediated by interactions with specific receptors controlling the expression of a number of factors, or it may be caused by direct regulation of the intracellular calcium concentration, thereby regulating insulin synthesis and secretion [24]. In addition, normal intracellular ionised calcium (Ca^2+) levels inhibit free radical generation and protect β-cells from cytokine-mediated apoptosis and necrosis [25]. Thus, a change in activity of the vitamin D receptor or a change in the concentration of extracellular and intracellular calcium under conditions of vitamin D deficiency can adversely affect the functional state of pancreatic β-cells, leading to decreased insulin synthesis and secretion [23]. In addition, evidence of the possible role of vitamin D deficiency in developing insulin resistance has been found [13, 14, 26]. Vitamin D stimulates the expression of the insulin receptor gene and is, thus, involved in the transmembrane transport of glucose [27]. In addition, the normal vitamin D level maintains the intracellular Ca^2+ concentration in a narrow range. Changes in its level under conditions of vitamin D deficiency affect the activity of the intracellular glucose transporters-4 (GLUT-4), leading to development of insulin resistance in peripheral tissues [23, 28].

PATHOGENETIC MECHANISMS OF DIABETIC NEUROPATHY

DM is characterised by microvascular complications triggered by hyperglycaemia, which adversely affects patients' prognoses and quality of life. Diabetic neuropathy (DN) is one of the most frequent microvascular complications [29, 30]. Depending on the diagnostic methods used, DN can be detected in DM patients with a frequency of 10 to 100%. According to the Russian Registry, in St. Petersburg at the beginning of 2015, DN was diagnosed in 32.64% of DM1 patients and in 17.2% of DM2 patients [9]. Moreover, DN is associated with a high risk of non-traumatic amputations [30].

The most common form of DN is diabetic peripheral neuropathy (DPN) [29, 30], which includes symptoms and/or signs of impaired peripheral nerve function in diabetic patients after ruling out other causes [30, 31]. According to Russian authors, DPN can be revealed in 25% of DM patients when conducting simple diagnostic tests and in 70%–90% of patients when conducting a targeted search for a subclinical form of neuropathy using electroneuromyography [29]. This wide range of DPN prevalence indices can be explained by the lack of a universal diagnostic method. Peripheral neuropathy is assessed by neurological symptoms, neurological signs and data from neurotensiometry and electromyograms [29, 30]. Most peripheral nerves are mixed and contain motor, sensory and autonomous fibres. Therefore, DM nerve lesion symptoms include motor, sensory and autonomous disorders [32, 33]. The most common form of DPN is sensory motor neuropathy, manifested by pain, paraesthesia and loss of sensitivity due to the progressive damage to myelinated fibres (segmental demyelination and axonal degeneration) hindering impulse conduction along the nerve fibre [29, 30].

DPN pathogenesis includes both metabolic and vascular changes. Hyperglycaemia triggers DPN [34]. The high glucose level affects the tissues both directly through glucose toxicity, and indirectly, through oxidative stress activation, increased non-enzymatic protein glycation, exacerbation of insulin resistance in DM2, hypoxia and pro-inflammatory reaction activation. As a result of glucose toxicity, endothelial

cell regeneration is inhibited, endothelin production (one of the markers of atherosclerotic lesions) increases, protein glycation occurs, homeostasis changes (increased platelet aggregation, impaired fibrinolysis) and the polyol pathway for glucose disposal is activated [35]. An excess of sorbitol damages the myelin sheath of nerve fibres and impairs neurotransmission [36]. In addition, autoimmune complexes are formed during protein glycation, inhibiting production of nerve growth factor [37, 38]. Microvascular lesions, especially in cases with genetic predispositions, also exacerbate the resulting disorders [39].

Nitric oxide production disorders may damage nerve fibres, in cases of hyperglycaemia and decrease nitric oxide concentrations, which under normal circumstances cause vasodilation, damage and dysfunction of small arteries, leading to changes of varying severity, including ischaemia and DPN progression [40].

Pro-inflammatory cytokines play roles in DPN pathogenesis. Possible mechanisms of immune-mediated nerve tissue lesion are being investigated, including deposition of immune complexes in the vascular walls, leading to activation of monocytes and release of pro-inflammatory cytokines that stimulate neutrophil migration to the damage zone and release of free radicals, as well as activation of cell-mediated immunity, which leads to vasa nervorum lesions with the subsequent development of chronic endoneural ischaemia [41, 42].

VITAMIN D DEFICIENCY AND DIABETIC NEUROPATHY

Studies have shown that vitamin D deficiency and other well-studied factors contribute to formation and progression of DPN [43, 44, 45]. For example, studies conducted at Shanghai University revealed an association between 25(OH)D levels in blood serum and the severity of neuropathy in DM2 patients. The greatest changes were found in patients with 25(OH)D levels lower than 16 ng/ml [44]. A possible association between vitamin D deficiency and pro-inflammatory cytokines in patients with DM2 and DPN was also demonstrated by the results of a study conducted in Turkey––not only increased concentrations of interleukins (IL-13 and IL-17), but also a correlation between the level of 25(OH)D in serum and the IL values [45].

The exact mechanisms by which vitamin D deficiency can influence the processes in nerve fibres in patients with DM are not fully understood. On the one hand, because of vitamin D insufficiency and deficiency, glycaemic control probably deteriorates, leading to a higher risk of microvascular complications. On the other hand, the immune-modulating properties of vitamin D and its regulation of oxidative stress suggest effects on systemic inflammation in DM patients [46]. In addition, vitamin D deficiency leads to increased parathyroid hormone levels, the excess of which, in turn, can adversely affect tissue sensitivity to insulin and vascular remodelling parameters [47].

It remains undetermined whether and what doses of vitamin D supplements should be used to compensate for its insufficiency or deficiency in DM2 patients. In one study on the effect of vitamin D therapy, it appeared to improve glycaemic control (at a dose of 200,000 IU per month for 3 months) but the decrease in HbA1c was statistically insignificant between patients with newly diagnosed DM2 and asymptomatic vitamin D deficiency [48]. In another study, a significant reduction in the painful DPN symptoms was noted in patients with DM2 20 weeks after a single intramuscular injection of 600,000 IU of vitamin D [49]. In our own study, supplementing vitamin D at a dose of 50,000 IU per week for three months reduced HbA1c significantly in patients with DM2 and DN [50].

A meta-analysis of 24 controlled studies provided an assessed vitamin D therapy effects on HbA1c levels, fasting plasma glucose and a homeostatic model for insulin resistance assessment (HOMA-IR) in DM patients and established that intake of vitamin D (daily dose of at least 4000 IU) significantly reduces fasting plasma glucose levels, HbA1c and HOMA-IR. [51]. In the above studies, the daily dose of vitamin D was significantly higher than the daily demands and started from 40,000 IU per day, which enabled a more effective control of the glycaemic response and probably improved the tissue sensitivity to insulin in DM2 patients. Moreover, therapy with vitamin D preparations in patients with DM and DPN was accompanied by reduced pain sensations, up to the complete withdrawal of the anaesthetic drug from the group of semi-synthetic opioids, and a 1-ng/ml increase in 25(OH)D was associated with decreased neuropathy and increased conduction along nerve fibre by 2.2% and 3.4%, respectively [43].

According to international recommendations, people with obesity, which is common in DM patients, are at risk for developing vitamin D deficiency [6, 11]. Therefore, therapy with cholecalciferol is recommended for these patients, taking into account the pleiotropic effects of vitamin D, not only to replete the deficiency, but also to improve the glycaemic profile, reduce insulin resistance and, possibly, prevent the development of microvascular complications.

CONCLUSION

Considering the high prevalence of DM2 and DN, as well as their social implications, studies on factors affecting development and progression of the diseases are needed. The results outlined in this review suggest vitamin D deficiency is an independent risk factor for developing not only DM but also its complications. The data on the association between DM and vitamin D deficiency not only expand the current understanding of the mechanisms of DM2 and DN pathogenesis, but also create prerequisites for new studies aimed at preventing the development and progression of chronic diabetes complications using vitamin D preparations.

ADDITIONAL INFORMATION

Conflict of interest. The authors of this article confirmed no conflict of interest.

Authors participation. A.P. Stepanova–analysis of the literature, writing the text; T.L. Karonova–analysis of the literature, writing the text; A.A. Bystrova–analysis of the literature, writing the text; V.B. Bregovsky–analysis of literature, writing the text.

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