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维生素 D 在预防和治疗 1 型糖尿病中的潜在作用

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1 型糖尿病的发病率在全球范围内呈上升趋势，所有年龄组（包括儿童和青少年）中缺乏维生素 D 的人数也在增加。近几十年来，研究表明维生素 D 除了调节钙稳态和骨代谢外，还具有抗炎和免疫调节作用。流行病学数据表明维生素 D 缺乏与 1 型糖尿病的发病机制有关。对维生素 D 代谢很重要的基因多态性也会调节 1 型糖尿病的风险。多项研究评估了维生素 D 作为辅助免疫调节疗法在新诊断的 1 型糖尿病患者中的作用。本综述的目的是提供有关维生素 D 参与 1 型糖尿病发病机制的最新数据，并评估其作为预防该疾病和额外用于胰岛素治疗的药物的作用。

关键词： 1型糖尿病；维生素D；胆钙化醇。

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Potential role of vitamin D in the prevention and treatment of type 1 diabetes mellitus

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The incidence of type 1 diabetes mellitus is increasing worldwide, and the number of people with vitamin D deficiency in all age groups, including children and adolescents, is simultaneously growing in the world. Over the past decades, it has been found that vitamin D, in addition to participating in the regulation of calcium homeostasis and bone metabolism, has an anti-inflammatory and immunomodulatory effect. Epidemiological evidence suggests the involvement of vitamin D deficiency in the pathogenesis of type 1 diabetes mellitus. Polymorphisms in genes important for vitamin D metabolism also modulate the risk of type 1 diabetes mellitus. Several studies have evaluated the role of vitamin D as adjuvant immunomodulating therapy in patients with newly diagnosed type 1 diabetes mellitus. The purpose of this review is to present current data on the involvement of vitamin D in the pathogenesis of type 1 diabetes mellitus and to evaluate its role as a drug for the prevention of the disease and its use in treatment in addition to insulin therapy.

Keywords: type 1 diabetes mellitus; vitamin D; cholecalciferol.

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Потенциальная роль витамина D в профилактике и лечении сахарного диабета первого типа

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Заболеваемость сахарным диабетом 1-го типа в мире увеличивается, также растет количество людей с недостатком витамина D во всех возрастных группах, включая детей и подростков. В последние десятилетия выявлено, что витамин D кроме регуляции гомеостаза кальция и метаболизма костей оказывает противовоспалительное и иммуномодулирующее действие. Эпидемиологические данные свидетельствуют о вовлечении дефицита витамина D в патогенез сахарного диабета 1-го типа. Полиморфизмы в генах, важных для метаболизма витамина D, также модулируют риск возникновения сахарного диабета 1-го типа. В ряде исследований была оценена роль витамина D в качестве адъювантной иммуномодулирующей терапии у пациентов с недавно выявленным сахарным диабетом 1-го типа. Цель данного обзора — представить современные данные об участии витамина D в патогенезе сахарного диабета 1-го типа и оценить его роль в качестве препарата для профилактики заболевания и дополнительного применения при инсулинотерапии.

Ключевые слова: сахарный диабет 1-го типа; витамин D; холекальциферол.

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近几十年来，1型糖尿病(T1DM)的发病率以每年3%的速度增长。此外，注意到在幼儿中显着增加[1-4]。目前，全球有542,000名14岁以下的1型糖尿病儿童和青少年，其中大部分生活在美国、印度、巴西和中国[5]。T1DM发病率最高的是芬兰（每年每10万人口新诊断DT1DM超过60例）和撒丁岛（每年每20万人口超过40例）[3,6]。应该指出的，全世界所有年龄组（包括儿童和青少年）维生素D缺乏症的人数都在同步增长，这表明维生素D缺乏症参与了T1DM的病理生理[7,8]。人群中维生素D缺乏的发生率从20%到90%不等[9-11]。无论地理位置如何，维生素D缺乏症和缺乏症都很常见：81例发现维生素D缺乏症，巴西1%的育龄妇女[10]和俄罗斯西北部84.1%-86.9%的育龄妇女[11]。

关于血清中维生素D的最佳水平没有统一的数据。根据俄罗斯内分泌学家协会的数据，血清中足够的维生素D含量为30－60纳克/毫升（75-150 nmol/l），维生素D水平为20-30纳克/毫升（50-75 nmol/l），维生素D水平低于20纳克/毫升（50 nmol/l）。维生素D水平高于60纳克/毫升（150毫升/升），表明其在血清中的浓度很高[12]。

维生素D的合成与代谢

维生素D包括一组化学结构相似的类固醇：维生素D_1-麦角钙化醇和光甾醇的化合物，维生素D_2-麦角钙化醇，维生素D_3-胆钙化醇，维生素D_4-二氢速甾醇，维生素D_5-谷钙化醇，维生素D_6-西格玛-方解酚[13]。人类中维生素D主要通过紫外线（80%）在皮肤中产生，少量（20%）通过食物进入身体[14]。暴露在阳光下只会促进维生素D的形成，其形式为维生素D_3，由7-脱氢胆固醇在皮肤中产生。然后用维他命D结合蛋白（VDBR）将维他命D_3转运到肝脏，在CYP2R1酶的参与下进行25-羟基化，并在25-羟基环丙二醇-25（He）D-钙二醇中代谢[15]。然后25(OH)D被转运到肾脏，并通过1α-羟基化（CYP27B1酶）转化为1,25-二羟基胆钙化醇[$1,25(OH)_2D_3$]，称为骨化三醇，它是维生素D最具生物活性的代谢物。为了评估临床实践中维生素D的状况，建议测定血清25(OH)D而不是$1.25(OH)_2D$。排除$1.25(OH)_2D$作为诊断指标的主要原因是其半衰期短，为6-8小时，导致血清浓度每日显着波动。25(OH)D的半衰期为3周。此外，在各种疾病中，以及在怀孕期间，$1.25(OH)_2D$的水平可以增加，尽管实际缺乏维生素D[16]。最近的一份临床报告[17]表明，无血清和血清生物可利用25(OH)D，但不是总25(OH)D，是评估维生素D状态的最可靠标志物。

骨化三醇通过与核维生素D受体(VDR)结合启动信号级联反应，后者与视黄酸X受体(RXR)形成异二聚体，然后与特定的DNA序列（VDREs — vitamin D response elements,，维生素D反应元件）结合)，调节转录几个基因[15]。VDR由位于染色体12q12q－q14上的一个大基因编码，包括两个启动子区域、八个蛋白质编码外显子和六个未翻译的外显子(1a-1f)[18]。VDR在几乎所有的人体细胞（包括免疫细胞）中都被发现[19]。维生素D除了止血钙和骨代谢外，还参与细胞生长的调节、抗增殖、抗炎、免疫调节过程[20,21]。

维生素D的免疫调节作用

维生素D通过VDR对先天免疫系统和适应性免疫系统都有影响.功能性VDR已在几乎所有免疫细胞中被鉴定，包括抗原呈递细胞和T淋巴细胞，这是维生素D对免疫系统作用的间接证据[22,23]。免疫细胞，尤其是抗原呈递细胞（活化的巨噬细胞和树突状细胞）表达1α-羟化酶，因此可以在干扰素-γ（IFN-γ）的作用下合成和分泌骨化三醇[24,25]。维生素D的免疫调节作用取决于其生物活性形式骨化三醇调节参与细胞增殖、分化和功能的基因表达的能力[19,26,27]。

钙三醇通过诱导免疫耐受抑制适应性免疫反应，并通过以下机制发挥抗炎作用：

- 抑制树突状细胞（DC）的分化、成熟和功能，阻止其作为成熟抗原表达细胞的作用[28,29]；
- 刺激脱戊嗪的形成，促进巨噬细胞的分化和激活，增强巨噬细胞的抗菌活性，增强趋化性和吞噬作用[30]；
- 通过减少MHCII类分子（组织相容性主要类别的分子）的表面表达来刺激T细胞，并促进巨噬细胞从促炎表型（M1，或“经典激活的”巨噬细胞“）向抗-炎症（M2，或相关的巨噬细胞）；
- 抑制单核细胞和巨噬细胞促炎细胞因子的表达[31-34]；
- 对B细胞的分化和免疫球蛋白的产生有直接抑制作用[35,36]；
- 使调节性T细胞的产生正常化、Th细胞的极化、增加Th_2细胞的数量并抑制Th_1和Th_{17}细胞的产生，从而刺激T细胞从“效应”表型转变为“调节”表型[37,38]；

- 防止$CD8^+$T细胞过度活化，减少IFN-γ和肿瘤坏死因子(TNF-α)的分泌[39]；
- 调节免疫细胞产生细胞因子，增加抗炎细胞因子[白细胞介素(IL)-4,IL-10]的产生并减少促炎细胞因子(IL-1β,IL-2,IL6,IL)的合成-17,IL-22,TNF-α,IFN-γ)[40,41]。

钙三醇的免疫调节作用，即诱导免疫耐受和T细胞贫血，干扰B细胞的活性和抗体的产生，此外，炎症反应的减少意味着维生素D在自身免疫性疾病（包括T1DM）中的治疗潜力。维生素D可能在降低自身免疫性疾病的风险和改善其流动方面发挥重要作用。

研究表明，年轻时NOD小鼠缺乏维生素D会导致更高的发病率和T1DM的早期发展[42]。钙三醇及其类似物可防止NOD小鼠的T1DM发育，特别是在幼年引入T1DM之前，对β细胞进行免疫介导攻击[43,44]。当钙三醇在更高的年龄和疾病的后期被引入时，疾病的进展可能会停止[45]。C. Mathieu和合著者表明，每天或每隔一天注射的高剂量钙三醇（5微克/千克）的长期治疗降低了NOD小鼠的T1DM发生率，不会引起严重的副作用[44]。S. Gregori和合著者[45]发现对NOD小鼠短期施用骨化三醇类似物可抑制IL-12和IFN-γ的产生，阻止Th_1细胞对胰岛的浸润，增加淋巴中调节性$CD4^+$和$CD25^+$T细胞的数量胰腺的结节，从而抑制糖尿病的发展。用骨化三醇处理的NOD小鼠显示出从Th_1(IFN-γ)到Th_2(IL-4)[37]的细胞因子分泌谱的显着变化。此外，暴露于钙三醇或其类似物TH527的树突状细胞改变了GAD65反应的性质，GAD65反应是T细胞的特异性克隆，抑制增殖，促进凋亡[46]。T. Takiishi和合著者[47]表明在整个生命周期（从3到35周）喂食富含维生素D_3（800 IU/天）的饮食的NOD小鼠中，糖尿病的发病率显着降低，胰腺中的胰岛素含量高于对照动物组。

炎症在1型糖尿病的发病机制中起着重要作用，通过β细胞和免疫细胞产生的细胞因子和趋化因子促进β细胞功能障碍和凋亡[48]。钙三醇提高抗凋亡蛋白A20水平，降低IL-6的产生、氮的合成和MNSI分子在孤立的人类胰岛中的表达受到这种。Z. Wei和合著者[49]发现VDR与染色质重塑复合物(PBAF)的关联增强了VDR依赖的转录程序，并导致细胞因子诱导的β细胞促炎反应减少，并保留了它们在人和NOD小鼠。

维生素D缺乏在1型糖尿病发病机制中的作用

大量工作指出维生素D在β细胞功能和胰岛素分泌中的作用。A.W. Norman和合著者[50]首次表明维生素D的缺乏抑制了大鼠分泌的胰腺胰岛素的分泌。发现人胰腺β细胞既能表达1α-羟化酶，又能表达VDR[51,52]。VDR在人类胰岛素基因启动子中被检测到[53]。根据P.M. Bourlon和合著者[54]骨化三醇促进胰岛素*de novo*的生物合成，并加速大鼠胰岛中胰岛素原向胰岛素的转化。给缺乏维生素D的小鼠和兔服用维生素D可消除胰岛素分泌障碍[50-56]。这表明维生素D及其类似物可以保护β细胞免受免疫介导的攻击，促进Th_1细胞向Th_2细胞的转变，减少Th_1细胞对胰岛的浸润，并减少细胞因子诱导的对β细胞的损伤。

参与维生素D代谢的各种基因多态性，尤其是编码维生素D羟化酶、*VDBR*和*VDR*的基因多态性，可能会影响1型糖尿病的发生风险。2007年E. Ramos-Lopez和合著者[57]确定了*CYP2R1*基因中单核苷酸多态性(SNP)的关联，在T1DM患者中编码维生素D25-羟化酶，和血清25(OH)D水平，在此基础上，他们认为SNPrs10741657的G等位基因易导致到1型糖尿病的发展，然后作为相同SNP的等位基因A提供防止疾病发展的保护。另一项研究发现，*CYP2R1*基因中的单核苷酸多态性rs10741657和rs12794714之间存在显著关联以及患1型糖尿病的风险[58]。英国进行的一项大型病例对照研究中，涉及7854名1型糖尿病患者和8758名健康人，发现编码维生素D1的*CYPB1*基因的两个单核苷酸多态性（rs10877012和rs46536）之间存在关联α-羟化酶与1型糖尿病[59]。作者还报告说，GG基因型*CYP2R1*（SNPrs10741657）或CC基因型*CYP27B1*（SNPrs10877012）会增加患T1DM的风险[60]。具有两种基因型的人患1型糖尿病的风险显着高于仅具有一种基因型的人，表明GG基因型*CYP2R1*和CC基因型*CYP27B1*在确定发生1型糖尿病的风险方面存在潜在协同作用。此外，与分别具有AA*CYP2R1*和AA*CYP27B1*基因型的人群相比，*CYP2R1*GG基因型和*CYP27B1*CC基因型人群的血清25(OH)D水平显着降低。然而，丹麦研究人员并未发现*SNPCYP2R1*和*CYP27B1*（分别为rs10741657和rs4646536）与儿童患T1DM的风险之间存在关联[61]。

已经提出*VDR*基因多态性在1型糖尿病发病机制中的潜在作用。J.M. Norris和合著者[62](2004-2010).进行了主要的TEDDY调查424788名新生儿接受了检查（在美国6个州和欧洲5个国家）。根据初步筛查的结果，该研究包括8676名患有1型糖尿病的一线亲属患1型糖尿病风险增加的儿童（儿童中存在a/tGADA、IAA、IA-2A）1型糖尿病且

无直系亲属。该研究从4个月大的儿童开始和持续了6年。分析了*VDR*、*CYP24A*、*CYP27B1*、*GC*、*RXR*基因的多态性。TEDDY研究中，42%的儿童和22-67%的1型糖尿病儿童存在维生素D25(OH)缺乏症。具有维生素D受体的次要等位基因*VDRrs7975232*的儿童中，维生素D25(OH)的血浆浓度最高，并且患1型糖尿病的风险较低。J.M. Norris和合著者表明较高水平的25(OH)D有助于减少对具有发展为1型糖尿病的遗传易感性的儿童胰腺胰岛器官可能的自身免疫性损伤。最近的一项研究发现，脐带血中较高水平的25(OH)D是*VDR*rs11568820G/G基因型纯合子儿童患T1DM风险降低的有利预测因素[63]。N. Habibian和合著者[64]证明了1型糖尿病风险增加与*VDR*基因（尤其是Bsm-I和Fok-I）中的一些多态性之间存在关联，尽管最易患1型糖尿病的等位基因仍未确定。血清中足够水平的25（OH）D（≥30ng/ml）和*VDR*基因中的一些SNP基因型（TaqI和BsmI）与新诊断的1型糖尿病患者的C肽水平升高有关，这可能有助于保留胰腺的功能残余β细胞[64]。研究表明，对维生素D的合成、运输和作用很重要的基因中的SNP可能会影响患1型糖尿病的风险。

1型糖尿病患者的维生素D水平

近几十年来，维生素D缺乏症和1型糖尿病的患病率和频率有所增加[3,7,65-67]。DIAMOND研究小组发现，在纬度较高（紫外线辐射低）的国家，1型糖尿病的发病率较高（从1990年到1994年收集的数据）。在芬兰，首次发现1型糖尿病的病例为每年每10万人中有36.5例，瑞典为27.5/100000，挪威为21.2/10000[68]。几项研究表明1型糖尿病的发病具有季节性模式：冬季、早春和深秋发病率增加，夏季暂停[69-71]。S.D. Mohr和合著者[71]发现低强度的紫外线辐射导致儿童期1型糖尿病的发病率较高。此外，作者显示芬兰1型糖尿病的发病率逐渐增加（从1965年的每10万人18人增加到2005年的每10万人64人），在他们看来，这与引入官方政府建议有关逐渐减少每日维生素D的摄入量[71]。新诊断的1型糖尿病患者中，25(OH)D水平显着低于健康人[72-75]。根据在瑞典进行的一项研究，该研究涉及459名15-34岁的1型糖尿病患者，他们血液中的25(OH)D含量显着低于对照组[92]。印度、意大利、卡塔尔、科威特的研究人员也得出了类似的结果[73-76]。在瑞士129名患有1型糖尿病的儿童和青少年在60.5%的病例中被发现缺乏维生素D，在26.4%的病例中发现维生素D缺乏[77]。

维生素D对1型糖尿病病程的影响：流行病学证据

1型糖尿病患者缺乏维生素D的问题是众所周知的，但尚不清楚维生素D浓度不足是1型糖尿病的诱因还是疾病的后果。根据文献，维生素D对1型糖尿病风险的影响可能取决于患者的年龄[78]。挪威的一项队列研究纳入了29,072名患者，结果表明，在其子女在生命的前15年中发展为T1DM的妇女在怀孕期间的25(OH)D水平显着降低[79]。此外，在孕早期25（OH）D水平≤21.6 ng/ml的孕妇中，儿童患T1DM的风险高两倍。R. Jacobsen和合著者[80]研究表明与母亲使用维生素D强化人造黄油的儿童相比，14岁以下儿童患1型糖尿病的风险显着（高1.5-2倍），这些儿童的母亲在怀孕期间未食用强化维生素D的人造黄油。然而，M.E. Miettinen和合著者[81]与对照组妇女相比，没有发现其孩子随后（到7岁）发展为T1DM的母亲在怀孕期间的25(OH)D水平存在显着差异。J.Y. Dong和合著者[82]发现女性在怀孕期间摄入维生素D与其后代患T1DM的风险之间没有显着关联。K. Silvis和合著者[83]发现在怀孕期间服用维生素D不会影响遗传易感性增加的儿童患1型糖尿病的风险。

同时，根据各种研究，儿童早期摄入维生素D对降低患1型糖尿病风险的作用比宫内摄入这种维生素更显着。芬兰的一项研究发现，婴儿出生后第一年补充维生素D可降低T1DM的发病率。此外，与每天服用少于2000 IU的药物相比，每天服用2000 IU的维生素D能更显着地降低发生T1DM的风险（4-5倍）[84]。在多中心研究EURODIAB2中，发现从儿童早期摄入维生素D（使用标准化问卷和调查收集的数据）有助于降低晚年患T1DM的风险[85]。L.C. Stene和合著者[86]显示了儿童时期维生素D摄入时机的重要性。在6个月前接受这些食品添加剂的儿童相比，在7至12个月大时接受鱼肝油补充剂的儿童患1型糖尿病的风险较低。这可能是因为适应性免疫系统在生命的最初几个月没有完全成熟，并且缺乏维生素D的有益免疫调节作用。因此幼儿中维生素D可以防止1型糖尿病的发展。目前正在讨论维生素D及其在怀孕期间补充维生素D对发生T1DM风险的影响，需要加以澄清。

年轻时，维生素D对1型糖尿病的发展有明显的影响。按照E.D. Gorham和合著者[87]美国军事人员中进行的一项研究表明，1型糖尿病患者在确诊前一年的25(OH)D水平显着降低。

另一项研究中，与25(OH)D水平<75 nmol/L的个体相比，25(OH)D水平正常(≥100 nmol/L)的个体患T1DM的可能性较小[88]。25(OH)D水平最低的人群中，T1DM风险也有升高的趋势。

维生素D缺乏与糖尿病的各种血管并发症有关。加拿大，对14项研究进行了分析，其中包括10,007名患有糖尿病视网膜病变的1型糖尿病患者。发现维生素D缺乏的严重程度与糖尿病视网膜病变之间存在统计学上显着的关系[89]。EURODIAB前瞻性研究纳入了532名40±10岁的1型糖尿病患者，结果表明25(OH)D水平越高，大量白蛋白尿的发生率越低。维生素D水平与其他血管并发症（微量白蛋白尿、非增殖性和增殖性视网膜病变）之间没有联系[90]。一项针对75名T1DM合并糖尿病视网膜病变患者的日本研究发现，维生素D水平与T1DM并发症之间没有关系[91]。

维生素D作为1型糖尿病的辅助治疗

大量研究表明，T1DM患者的维生素D对维持胰腺β细胞的残余功能和血糖控制具有积极作用[92,93]。观察到的患者在空腹和/或每日胰岛素剂量较低时表现出较高水平的受刺激C肽。A. Mishra和合著者[94]除胰岛素治疗外还接受维生素D的1型糖尿病患者中，观察到胰腺β细胞残余功能减慢的趋势。此外，钙二醇的摄入有助于显着抑制自身攻击性，并对β细胞的功能具有保护作用[95]。M.A. Gabbay和合著者[96]证明每天将胆钙化醇以2000 IU的剂量添加到胰岛素中，持续12个月有助于新诊断的1型糖尿病患者（病程小于6个月）调节性T细胞数量的显着增加。6个月后的HbA1c水平，以及18个月后针对GAD65的抗体滴度。与接受安慰剂的患者相比，服用骨化醇组的患者显着降低。在1型糖尿病患者中进行的两项回顾性研究表明，使用不同剂量（400至6000 IU/天）的胆钙化醇进行为期三个月的辅助治疗可改善血糖参数并降低治疗后的HbA1c水平[93,95]。R.P. Panjiyar和合著者[97]一项前瞻性研究中发现，每天添加3000 IU的胆钙化醇作为辅助治疗12个月。导致1型糖尿病儿童血糖参数的改善和β细胞残余功能的缓慢下降。研究结束时，与单独接受胰岛素治疗的对照患者相比，这些儿童的平均空腹血糖、HbA1c和每日总胰岛素剂量较低，平均刺激C肽水平较高。重要的是T1DM患者的平均血清25(OH)D水平在所有后续访问中保持在足够的范围内（>30 ng/ml）。

然而，其他研究并没有发现在胰岛素治疗中添加维生素D后1型糖尿病的病程发生显着变化。E.M. Shih和合著者[98]据报道胆钙化醇的使用剂量为每周20,000 IU，持续6个月。不影响HbA1c水平、每日胰岛素需求。2007年R. Perchard和合著者[99]表明单次口服100,000或160,000 IU胆钙化醇不会导致维生素D和T1DM缺乏症儿童的HbA1c水平出现任何显着差异。作者假设单次高剂量口服胆钙化醇无法在延长的随访期内维持残留的血清25(OH)D水平。

其他研究中发现在1型糖尿病患者中，当胆钙化醇与omega-3多不饱和脂肪酸联合使用时，观察到对胰腺β细胞功能的保护作用。S. Niinisto和合著者研究中[100],致力于芬兰糖尿病的预后和预防，包括7782名HLA易患1型糖尿病的儿童。作者表明在3个月大时，血清中花生四烯酸和二十二碳六烯酸的比例增加。以及6个月大时更高的omega-6/omega-3比率。与患1型糖尿病的风险增加显着相关。X.Bi和合著者实验工作中[101]证明用omega-3补充NOD小鼠的饮食可降低严重糖尿病的发生率和促炎细胞因子的水平。根据一项回顾性研究，在怀孕期间和出生后第一年服用鱼肝油（大量维生素D和omega-3）可降低以后患T1DM的风险，这表明维生素D和omega-3具有协同作用-3多不饱和脂肪酸[86,102]。

过去十年的研究中，已经确定维生素D的作用不仅与钙磷稳态的调节有关，而且与其抗炎和免疫调节作用有关。

越来越多的证据表明维生素D缺乏可能在T1DM的发病机制中起作用。充足的维生素D摄入量，尤其是在儿童早期，可以降低晚年患糖尿病的风险。因此，在具有发展为T1DM的高遗传风险的儿童中，在生命的最初几年及时发现和消除维生素D缺乏症可能会在未来防止这种疾病的发展。2019年鉴于全球普遍存在维生素D缺乏症，英国科学咨询委员会(SCAN)建议4岁及以上人群的膳食维生素D摄入量为每天400 IU[103]。美国内分泌学家协会建议儿童（一岁以下）每天至少摄入400 IU维生素D，儿童、青少年和成人每天至少摄入600 IU[104]。

因此，维生素D恢复免疫耐受、抵消自身免疫反应、减缓或停止疾病进展、维持残留β细胞的质量和功能以及改善血糖控制的潜在能力值得研究该药物作为T1DM的辅助治疗。个体对维生素D摄入的反应取决于基线维生素D状态、体脂百分比、性别、种族、遗传因素和药物治疗等因素[105,106]。只有当血清25(OH)D水平高于正常骨骼健

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康所需的水平(≥30 ng/ml)时，才能观察到维生素D在自身免疫性疾病中的阳性免疫学作用。

需要进一步研究维生素D羟化酶、VDBP和VDR中的基因多态性，以评估它们对维生素D状态和作用的影响。这将允许识别可能需要更高剂量维生素D的患者群体，以达到预防和治疗T1DM所需的目标血清25(OH)D水平。

此外

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REFERENCES

1. Ajlamazjan JeK, Abashova EI, Arzhanova ON, et al. Saharnyj diabet i reproduktivnaja sistema zhenshhiny: rukovodstvo dlja vrachej. Moscow: GJeOTAR-Media; 2017. (In Russ.)

2. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *Lancet*. 2016;387(10035):2340–2348. DOI: 10.1016/S0140-6736(16)30507-4

3. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet*. 2009;373(9680):2027–2033. DOI: 10.1016/S0140-6736(09)60568-7

4. Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? *Diabetes Metab Res Rev*. 2011;27(1):3–13. DOI: 10.1002/dmrr.1141

5. International Diabetes Federation [Internet]. IDF Diabetes Atlas. 8th edition. 2017. [cited 10 Sept 2018]. Available from: https://diabetesatlas.org/upload/resources/previous/files/8/IDF_DA_8e-EN-final.pdf

6. Infante M, Ricordi C, Sanchez J, et al. Influence of vitamin D on islet autoimmunity and beta-cell function in type 1 diabetes. *Nutrients*. 2019;11(9):2185. DOI: 10.3390/nu11092185

7. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord*. 2017;18(2):153–165. DOI: 10.1007/s11154-017-9424-1

8. Huh SY, Gordon CM. Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment. *Rev Endocr Metab Disord*. 2008;9(2):161–170. DOI: 10.1007/s11154-007-9072-y

9. Hilger J, Friedel A, Herr R, et al. A systematic review of vitamin D status in populations worldwide. *Br J Nutr*. 2014;111(1):23–45. DOI: 10.1017/S0007114513001840

10. Lopes VM, Lopes JR, Brasileiro JP, et al. Highly prevalence of vitamin D deficiency among Brazilian women of reproductive age. *Arch Endocrinol Metab*. 2017;61(1):21–27. DOI: 10.1590/2359-3997000000216

11. Karonova TL, Grinyova EN, NikitiM IL, et al The prevalence of vitamin D deficiency in the Northwestern region of the Russian Federation among the residents of St. Petersburg and Petrozavodsk. *Osteoporosis and Bone Diseases*. 2013;16(3):3–7. (In Russ.). DOI: 10.14341/osteo201333-7

12. Pigarova EA, Rozhinskaja LJa, Belaja ZhE, et al. Deficit vitamina D u vzroslyh: diagnostika, lechenie i profilaktika. Klinicheskie rekomendacii Ministerstva zdravoohranenija Rossijskoj Federacii. Ed by II Dedov, GA Mel'nichenko. Moscow; 2015. [cited 2021 Mar 17]. Available from: https://minzdrav.gov-murman.ru/documents/poryadki-okazaniya-meditsinskoy-pomoshchi/D %20 19042014.pdf. (In Russ.)

13. Kumar R, editors. Vitamin D: basic and clinical aspects. New York: Springer; 2012.

14. 14. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. *Am J Clin Nutr*. 1990;51(6):1075–1081. DOI: 10.1093/ajcn/51.6.1075

15. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. *Physiol Rev*. 2016;96(1):365–408. DOI: 10.1152/physrev.00014.2015

16. Napiórkowska L, Franek E. Rola oznaczania witaminy D w praktyce klinicznej. *Choroby Serca i Naczyń*. 2009;6(4):203–210. [cited 2021 Mar 17]. Available from: https://journals.viamedica.pl/choroby_serca_i_naczyn/article/view/12035/9913

17. Yu C, Xue H, Wang L, et al. Serum bioavailable and free 25-hydroxyvitamin D levels, but not its total level, are associated with the risk of mortality in patients with coronary Artery disease. *Circ Res*. 2018;123(8):996–1007. DOI: 10.1161/CIRCRESAHA.118.313558

18. Hossein-Nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D_3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. *PLoS One*. 2013;8(3):e58725. DOI: 10.1371/journal.pone.0058725

19. Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? *Arch Biochem Biophys*. 2012;523(1):123–133. DOI: 10.1016/j.abb.2012.04.001

20. Caprio M, Infante M, Calanchini M, et al. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. *Eat Weight Disord*. 2017;22(1):27–41. DOI: 10.1007/s40519-016-0312-6

21. Gatti D, Idolazzi L, Fassio A. Vitamin D: not just bone, but also immunity. *Minerva Med*. 2016;107(6):452–460.

22. White JH. Vitamin D metabolism and signaling in the immune system. *Rev Endocr Metab Disord*. 2012;13(1):21–29. DOI: 10.1007/s11154-011-9195-z

23. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients*. 2013;5:2502–2521. DOI: 10.3390/nu5072502

24. Overbergh L, Decallonne B, Valckx D, et al. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. *Clin Exp Immunol*. 2000;120(1):139–146. DOI: 10.1046/j.1365-2249.2000.01204.x

25. Stoffels K, Overbergh L, Giulietti A, et al. Immune regulation of 25-hydroxyvitamin-D_3-1alpha-hydroxylase in human monocytes. *J Bone Miner Res*. 2006;21(1):37–47. DOI: 10.1359/JBMR.050908

26. Singh PK, van den Berg PR, Long MD, et al. Integration of VDR genome wide binding and GWAS genetic variation data reveals co-occurrence of VDR and NF-κB binding that is

linked to immune phenotypes. *BMC Genomics*. 2017;18(1):132. DOI: 10.1186/s12864-017-3481-4

27. Jensen SS, Madsen MW, Lukas J, et al. Inhibitory effects of 1alpha,25-dihydroxyvitamin D(3) on the G(1)-S phase-controlling machinery. *Mol Endocrinol*. 2001;15(8):1370–1380. DOI: 10.1210/mend.15.8.0673

28. Piemonti L, Monti P, Sironi M, et al. Vitamin D_3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *J Immunol*. 2000;164(9):4443–4451. DOI: 10.4049/jimmunol.164.9.4443

29. Ferreira GB, Vanherwegen AS, Eelen G, et al. Vitamin D_3 induces tolerance in human dendritic cells by activation of intracellular metabolic pathways. *Cell Rep*. 2015;10(5):711–725. DOI: 10.1016/j.celrep.2015.01.013

30. Amado Diago CA, García-Unzueta MT, Fariñas Mdel C, Amado JA. Calcitriol-modulated human antibiotics: New pathophysiological aspects of vitamin D. *Endocrinol Nutr*. 2016;63(2):87–94. DOI: 10.1016/j.endonu.2015.09.005

31. Korf H, Wenes M, Stijlemans B, et al. 1,25-Dihydroxyvitamin D_3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. *Immunobiology*. 2012;217(12):1292–1300. DOI: 10.1016/j.imbio.2012.07.018

32. Zhang X, Zhou M, Guo Y, et al. 1,25-Dihydroxyvitamin D_3 Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARγ Signaling Pathway. *Biomed Res Int*. 2015;2015:157834. DOI: 10.1155/2015/157834

33. Zhang Y, Leung DY, Richers BN, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol*. 2012;188(5):2127–2135. DOI: 10.4049/jimmunol.1102412

34. Müller K, Heilmann C, Poulsen LK, Barington T, Bendtzen K. The role of monocytes and T cells in 1,25-dihydroxyvitamin D_3 mediated inhibition of B cell function *in vitro*. *Immunopharmacology*. 1991;21(2):121–128. DOI: 10.1016/0162-3109(91)90015-q

35. Heine G, Anton K, Henz BM, Worm M. 1alpha,25-dihydroxyvitamin D_3 inhibits anti-CD40 plus IL-4-mediated IgE production *in vitro*. *Eur J Immunol*. 2002;32(12):3395–3404. DOI: 10.1002/1521-4141(200212)32:12<3395::AID-IMMU3395>3.0.CO;2-#

36. Chen S, Sims GP, Chen XX, et al. Modulatory effects of 1,25-dihydroxyvitamin D_3 on human B cell differentiation. *J Immunol*. 2007;179(3):1634–1647. DOI: 10.4049/jimmunol.179.3.1634

37. Overbergh L, Decallonne B, Waer M, et al. 1alpha,25-dihydroxyvitamin D_3 induces an autoantigen-specific T-helper 1/T-helper 2 immune shift in NOD mice immunized with GAD65 (p524-543). *Diabetes*. 2000;49(8):1301–1307. DOI: 10.2337/diabetes.49.8.1301

38. Boonstra A, Barrat FJ, Crain C, et al. 1alpha,25-Dihydroxyvitamin D_3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol*. 2001;167(9):4974–4980. DOI: 10.4049/jimmunol.167.9.4974

39. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential *Front Immunol*. 2017;7:697. DOI: 10.3389/fimmu.2016.00697

40. Cippitelli M, Santoni A. Vitamin D_3: a transcriptional modulator of the interferon-gamma gene. *Eur J Immunol*. 1998;28(10):3017–3030. DOI: 10.1002/(SICI)1521-4141(199810)28:10<3017::AID-IMMU3017>3.0.CO;2-6

41. Chang SH, Chung Y, Dong C. Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression. *J Biol Chem*. 2010;285(50):38751–38755. DOI: 10.1074/jbc.C110.185777

42. Giulietti A, Gysemans C, Stoffels K, et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. *Diabetologia*. 2004;47(3):451–462. DOI: 10.1007/s00125-004-1329-3

43. Mathieu C, Waer M, Casteels K, et al. Prevention of type I diabetes in NOD mice by nonhypercalcemic doses of a new structural analog of 1,25-dihydroxyvitamin D_3, KH1060. *Endocrinology*. 1995;136(3):866–872. DOI: 10.1210/endo.136.3.7867594

44. Mathieu C, Laureys J, Sobis H, et al. 1,25-Dihydroxyvitamin D_3 prevents insulitis in NOD mice. *Diabetes*. 1992;41(11):1491–1495. DOI: 10.2337/diab.41.11.1491

45. Gregori S, Giarratana N, Smiroldo S, et al. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. *Diabetes*. 2002;51(5):1367–1374. DOI: 10.2337/diabetes.51.5.1367

46. van Halteren AG, Tysma OM, van Etten E, et al. 1alpha,25-dihydroxyvitamin D_3 or analogue treated dendritic cells modulate human autoreactive T cells via the selective induction of apoptosis. *J Autoimmun*. 2004;23(3):233–239. DOI: 10.1016/j.jaut.2004.06.004

47. Takiishi T, Ding L, Baeke F, et al. Dietary supplementation with high doses of regular vitamin D3 safely reduces diabetes incidence in NOD mice when given early and long term. *Diabetes*. 2014;63(6):2026–2036. DOI: 10.2337/db13-1559

48. Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. *Nat Rev Endocrinol*. 2009;5(4):219–226. DOI: 10.1038/nrendo.2009.21

49. Wei Z, Yoshihara E, He N, et al. Vitamin D switches BAF complexes to protect β cells. *Cell*. 2018;173(5):1135–1149.e15. DOI: 10.1016/j.cell.2018.04.013

50. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science*. 1980;209(4458):823–825. DOI: 10.1126/science.6250216

51. Bland R, Markovic D, Hills CE, et al. Expression of 25-hydroxyvitamin D_3-1alpha-hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol*. 2004;89–90(1–5):121–125. DOI: 10.1016/j.jsbmb.2004.03.115

52. Johnson JA, Grande JP, Roche PC, Kumar R. Immunohistochemical localization of the $1,25(OH)_2D_3$ receptor and calbindin D28k in human and rat pancreas. *Am J Physiol*. 1994;267(3 Pt 1):E356–E360. DOI: 10.1152/ajpendo.1994.267.3.E356

53. Maestro B, Dávila N, Carranza MC, Calle C. Identification of a Vitamin D response element in the human insulin receptor gene promoter. *J Steroid Biochem Mol Biol*. 2003;84(2–3):223–230. DOI: 10.1016/s0960-0760(03)00032-3

54. Bourlon PM, Billaudel B, Faure-Dussert A. Influence of vitamin D_3 deficiency and 1,25 dihydroxyvitamin D_3 on *de novo* insulin biosynthesis in the islets of the rat endocrine pancreas. *J Endocrinol*. 1999;160(1):87–95. DOI: 10.1677/joe.0.1600087

55. Alvarez JA, Ashraf A. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *Int J Endocrinol*. 2010;2010:351385. DOI: 10.1155/2010/351385

56. Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat *in vivo*. *Endocrinology*. 1986;119(1):84–90. DOI: 10.1210/endo-119-1-84

57. Ramos-Lopez E, Brück P, Jansen T, et al. CYP2R1 (vitamin D 25-hydroxylase) gene is associated with susceptibility to type 1 diabetes and vitamin D levels in Germans. *Diabetes Metab Res Rev*. 2007;23(8):631–636. DOI: 10.1002/dmrr.719

58. Cooper JD, Smyth DJ, Walker NM, et al. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. *Diabetes*. 2011;60(5):1624–1631. DOI: 10.2337/db10-1656
59. Bailey R, Cooper JD, Zeitels L, et al. Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes. *Diabetes*. 2007;56(10):2616–2621. DOI: 10.2337/db07-0652
60. Hussein AG, Mohamed RH, Alghobashy AA. Synergism of CYP2R1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Egyptian children. *Cell Immunol*. 2012;279(1):42–45. DOI: 10.1016/j.cellimm.2012.08.006
61. Thorsen SU, Mortensen HB, Carstensen B, et al. No association between type 1 diabetes and genetic variation in vitamin D metabolism genes: a Danish study. *Pediatr Diabetes*. 2014;15(6):416–421. DOI: 10.1111/pedi.12105
62. Norris JM, Lee HS, Frederiksen B, et al. Plasma 25-Hydroxyvitamin D concentration and risk of islet autoimmunity. *Diabetes*. 2018;67(1):146–154. DOI: 10.2337/db17-0802
63. Tapia G, Mårild K, Dahl SR, et al. Maternal and newborn vitamin D-binding protein, vitamin D levels, vitamin D receptor genotype, and childhood type 1 diabetes. *Diabetes Care*. 2019;42(4):553–559. DOI: 10.2337/dc18-2176
64. Habibian N, Amoli MM, Abbasi F, et al. Role of vitamin D and vitamin D receptor gene polymorphisms on residual beta cell function in children with type 1 diabetes mellitus. *Pharmacol Rep*. 2019;71(2):282–288. DOI: 10.1016/j.pharep.2018.12.012
65. You WP, Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth. *BMJ Open Diabetes Res Care*. 2016;4(1):e000161. DOI: 10.1136/bmjdrc-2015-000161
66. Pettitt DJ, Talton J, Dabelea D, et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. *Diabetes Care*. 2014;37(2):402–408. DOI: 10.2337/dc13-1838
67. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med*. 2017;376(15):1419–1429. DOI: 10.1056/NEJMoa1610187
68. Karvonen M, Viik-Kajander M, Moltchanova E, et al. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care*. 2000;23(10):1516–1526. DOI: 10.2337/diacare.23.10.1516
69. Karvonen M, Jäntti V, Muntoni S, et al. Comparison of the seasonal pattern in the clinical onset of IDDM in Finland and Sardinia. *Diabetes Care*. 1998;21(7):1101–1109. Corrected and republished from: *Diabetes Care*. 1998;21(10):1784. DOI: 10.2337/diacare.21.7.1101
70. Ostman J, Lönnberg G, Arnqvist HJ, et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983–2002. *J Intern Med*. 2008;263(4):386–394. DOI: 10.1111/j.1365-2796.2007.01896.x
71. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia*. 2008;51(8):1391–1398. DOI: 10.1007/s00125-008-1061-5
72. Pozzilli P, Manfrini S, Crinò A, et al. Low levels of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 in patients with newly diagnosed type 1 diabetes. *Horm Metab Res*. 2005;37(11):680–683. DOI: 10.1055/s-2005-870578
73. Greer RM, Portelli SL, Hung BS, et al. Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. *Pediatr Diabetes*. 2013;14(1):31–41. DOI: 10.1111/j.1399-5448.2012.00890.x
74. Federico G, Genoni A, Puggioni A, et al. Vitamin D status, enterovirus infection, and type 1 diabetes in Italian children/adolescents. *Pediatr Diabetes*. 2018;19(5):923–929. DOI: 10.1111/pedi.12673
75. Rasoul MA, Al-Mahdi M, Al-Kandari H, et al. Low serum vitamin-D status is associated with high prevalence and early onset of type-1 diabetes mellitus in Kuwaiti children. *BMC Pediatr*. 2016;16:95. DOI: 10.1186/s12887-016-0629-3
76. Littorin B, Blom P, Schölin A, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). *Diabetologia*. 2006;49(12):2847–2852. DOI: 10.1007/s00125-006-0426-x
77. Bener A, Alsaied A, Al-Ali M, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. *Acta Diabetol*. 2009;46(3):183–189. DOI: 10.1007/s00592-008-0071-6
78. Reinert-Hartwall L, Honkanen J, Härkönen T, et al. No association between vitamin D and β-cell autoimmunity in Finnish and Estonian children. *Diabetes Metab Res Rev*. 2014;30(8):749–760. DOI: 10.1002/dmrr.2550
79. Sørensen IM, Joner G, Jenum PA, et al. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes*. 2012;61(1):175–178. DOI: 10.2337/db11-0875
80. Jacobsen R, Moldovan M, Vaag AA, et al. Vitamin D fortification and seasonality of birth in type 1 diabetic cases: D-tect study. *J Dev Orig Health Dis*. 2016;7(1):114–119. Corrected and republished from: *J Dev Orig Health Dis.* 2016;7(4):429. DOI: 10.1017/S2040174415007849
81. Miettinen ME, Reinert L, Kinnunen L, et al. Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. *Diabetologia*. 2012;55(5):1291–1294. DOI: 10.1007/s00125-012-2458-8
82. Dong JY, Zhang WG, Chen JJ, et al. Vitamin D intake and risk of type 1 diabetes: a meta-analysis of observational studies. *Nutrients*. 2013;5(9):3551–3562. DOI: 10.3390/nu5093551
83. Silvis K, Aronsson CA, Liu X, et al. Maternal dietary supplement use and development of islet autoimmunity in the offspring: TEDDY study. *Pediatr Diabetes*. 2019;20(1):86–92. DOI: 10.1111/pedi.12794
84. Hyppönen E, Läärä E, Reunanen A, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet*. 2001;358(9292):1500–1503. DOI: 10.1016/S0140-6736(01)06580-1
85. The EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. *Diabetologia*. 1999;42(1):51–54. DOI: 10.1007/s001250051112
86. Stene LC, Joner G; Norwegian Childhood Diabetes Study Group. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. *Am J Clin Nutr*. 2003;78(6):1128–1134. DOI: 10.1093/ajcn/78.6.1128
87. Gorham ED, Garland CF, Burgi AA, et al. Lower prediagnostic serum 25-hydroxyvitamin D concentration is associated with higher risk of insulin-requiring diabetes: a nested case-control study. *Diabetologia*. 2012;55(12):3224–3227. DOI: 10.1007/s00125-012-2709-8

88. Munger KL, Levin LI, Massa J, et al. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. *Am J Epidemiol*. 2013;177(5):411–419. DOI: 10.1093/aje/kws243
89. Zhang J, Upala S, Sanguankeo A. Relationship between vitamin D deficiency and diabetic retinopathy: a meta-analysis. *Can J Ophthalmol*. 2017;52 Suppl 1:S39–S44. DOI: 10.1016/j.jcjo.2017.09.026
90. Engelen L, Schalkwijk CG, Eussen SJ, et al. Low 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 levels are independently associated with macroalbuminuria, but not with retinopathy and macrovascular disease in type 1 diabetes: the EURODIAB prospective complications study. *Cardiovasc Diabetol*. 2015;14:67. DOI: 10.1186/s12933-015-0231-2
91. Shimo N, Yasuda T, Kaneto H, et al. Vitamin D deficiency is significantly associated with retinopathy in young Japanese type 1 diabetic patients. *Diabetes Res Clin Pract*. 2014;106(2):e41–e43. DOI: 10.1016/j.diabres.2014.08.005
92. Felício KM, de Souza ACCB, Neto JFA, et al. Glycemic variability and insulin needs in patients with type 1 diabetes mellitus supplemented with vitamin D: A pilot study using continuous glucose monitoring system. *Curr Diabetes Rev*. 2018;14(4):395–403. DOI: 10.2174/1573399813666170616075013
93. Bogdanou D, Penna-Martinez M, Filmann N, et al. T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential crossover. *Diabetes Metab Res Rev*. 2017;33(3): e2865. DOI: 10.1002/dmrr.2865
94. Mishra A, Dayal D, Sachdeva N, Attri SV. Effect of 6-months' vitamin D supplementation on residual beta cell function in children with type 1 diabetes: a case control interventional study. *J Pediatr Endocrinol Metab*. 2016;29(4):395–400. DOI: 10.1515/jpem-2015-0088
95. Giri D, Pintus D, Burnside G, et al. Treating vitamin D deficiency in children with type I diabetes could improve their glycaemic control. *BMC Res Notes*. 2017;10(1):465. DOI: 10.1186/s13104-017-2794-3
96. Gabbay MA, Sato MN, Finazzo C, et al. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual β-cell function in new-onset type 1 diabetes mellitus. *Arch Pediatr Adolesc Med*. 2012;166(7):601–607. DOI: 10.1001/archpediatrics.2012.164
97. Panjiyar RP, Dayal D, Attri SV, et al. Sustained serum 25-hydroxyvitamin D concentrations for one year with cholecalciferol supplementation improves glycaemic control and slows the decline of residual β cell function in children with type 1 diabetes. *Pediatr Endocrinol Diabetes Metab*. 2018;2018(3):111–117. DOI: 10.5114/pedm.2018.80992
98. Shih EM, Mittelman S, Pitukcheewanont P, et al. Effects of vitamin D repletion on glycemic control and inflammatory cytokines in adolescents with type 1 diabetes. *Pediatr. Diabetes*. 2016. Vol. 17. No. 1. P. 36–43. DOI: 10.1111/pedi.12238
99. Perchard R, Magee L, Whatmore A, et al. A pilot interventional study to evaluate the impact of cholecalciferol treatment on HbA1c in type 1 diabetes (T1D). *Endocr Connect*. 2017;6(4):225–231. DOI: 10.1530/EC-17-0045
100. Niinistö S, Takkinen HM, Erlund I, et al. Fatty acid status in infancy is associated with the risk of type 1 diabetes-associated autoimmunity. *Diabetologia*. 2017;60(7):1223–1233. DOI: 10.1007/s00125-017-4280-9
101. Bi X, Li F, Liu S, et al. ω-3 Polyunsaturated fatty acids ameliorate type 1 diabetes and autoimmunity. *J Clin Invest*. 2017;127(5):1757–1771. DOI: 10.1172/JCI87388
102. Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring. *Diabetologia*. 2000;43(9):1093–1098. DOI: 10.1007/s001250051499
103. Scientific Advisory Committee on Nutrition [Internet]. SACN Vitamin D and Health Report. London; 2016. [cited 3 September 2019]. Available from: https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report
104. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911–1930. DOI: 10.1210/jc.2011-0385
105. Mazahery H, von Hurst PR. Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation. *Nutrients*. 2015;7(7):5111–5142. DOI: 10.3390/nu7075111
106. Rak K, Bronkowska M. Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of type 1 diabetes mellitus-A narrative review. *Molecules*. 2018;24(1):53. DOI: 10.3390/molecules24010053

СПИСОК ЛИТЕРАТУРЫ

1. Айламазян Э.К, Абашова Е.И., Аржанова О.Н. и др. Сахарный диабет и репродуктивная система женщины: руководство для врачей. Москва: ГЭОТАР-Медиа, 2017.
2. Rewers M., Ludvigsson J. Environmental risk factors for type 1 diabetes // Lancet. 2016. Vol. 387. No. 10035. P. 2340–2348. DOI: 10.1016/S0140-6736(16)30507-4
3. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005-20: a multicentre prospective registration study // Lancet. 2009. Vol. 373. No. 9680. P. 2027–2033. DOI: 10.1016/S0140-6736(09)60568-7
4. Vehik K., Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? // Diabetes. Metab. Res. Rev. 2011. Vol. 27. No. 1. P. 3–13. DOI: 10.1002/dmrr.1141
5. International Diabetes Federation [Internet]. IDF Diabetes Atlas. 8th edition. 2017. [дата обращения 17.09.2018]. Доступ по ссылке: https://diabetesatlas.org/upload/resources/previous/files/8/IDF_DA_8e-EN-final.pdf
6. Infante M., Ricordi C., Sanchez J. et al. Influence of vitamin D on islet autoimmunity and beta-cell function in type 1 diabetes // Nutrients. 2019. Vol. 11. No. 9. P. 2185. DOI: 10.3390/nu11092185
7. Holick M.F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention // Rev. Endocr. Metab. Disord. 2017. Vol. 18. No. 2. P. 153–165. DOI: 10.1007/s11154-017-9424-1
8. Huh S.Y., Gordon C.M. Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment // Rev. Endocr. Metab. Disord. 2008. Vol. 9. No. 2. P. 161–170. DOI: 10.1007/s11154-007-9072-y
9. Hilger J., Friedel A., Herr R. et al. A systematic review of vitamin D status in populations worldwide // Br. J. Nutr. 2014. Vol. 111. No. 1. P. 23–45. DOI: 10.1017/S0007114513001840
10. Lopes V.M., Lopes J.R., Brasileiro J.P. et al. Highly prevalence of vitamin D deficiency among Brazilian women of reproductive

age // Arch. Endocrinol. Metab. 2017. Vol. 61. No. 1. P. 21–27. DOI: 10.1590/2359-3997000000216

11. Каронова Т.Л., Гринева Е.Н., Никитина И.Л. и др. Распространенность дефицита витамина D в Северо-Западном регионе РФ среди жителей г. Санкт-Петербурга и г. Петрозаводска // Остеопороз и остеопатии. 2013. Т. 16. № 3. С. 3–7. DOI: 10.14341/osteo201333-7

12. Пигарова Е.А., Рожинская Л.Я., Белая Ж.Е. и др. Дефицит витамина D у взрослых: диагностика, лечение и профилактика. Клинические рекомендации Министерства здравоохранения Российской Федерации / под ред. И.И. Дедов, Г.А. Мельниченко. Москва, 2015. [дата обращения: 17.03.21]. Доступ по ссылке: https://minzdrav.gov-murman.ru/documents/poryadki-okazaniya-meditsinskoy-pomoshchi/D %2019042014.pdf

13. Kumar R., editors. Vitamin D: basic and clinical aspects. New York: Springer, 2012.

14. Webb A.R., Pilbeam C., Hanafin N., Holick M.F. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston // Am. J. Clin. Nutr. 1990. Vol. 51. No. 6. P. 1075–1081. DOI: 10.1093/ajcn/51.6.1075

15. Christakos S., Dhawan P., Verstuyf A., Verlinden L., Carmeliet G. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects // Physiol. Rev. 2016. Vol. 96. No. 1. P. 365–408. DOI: 10.1152/physrev.00014.2015

16. Napiórkowska L., Franek E. Rola oznaczania witaminy D w praktyce klinicznej // Choroby Serca i Naczyń. 2009. Vol. 6. No. 4. P. 203–210. [дата обращения: 17.03.21]. Доступ по ссылке: https://journals.viamedica.pl/choroby_serca_i_naczyn/article/view/12035/9913

17. Yu C., Xue H., Wang L. et al. Serum bioavailable and free 25-Hydroxyvitamin D levels, but not its total level, are associated with the risk of mortality in patients with coronary Artery disease // Circ. Res. 2018. Vol. 123. No. 8. P. 996–1007. DOI: 10.1161/CIRCRESAHA.118.313558

18. Hossein-Nezhad A., Spira A., Holick M.F. Influence of vitamin D status and vitamin D_3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial // PLoS One. 2013. Vol. 8. No. 3 P. e58725. DOI: 10.1371/journal.pone.0058725

19. Wang Y., Zhu J., DeLuca H.F. Where is the vitamin D receptor? // Arch. Biochem. Biophys. 2012. Vol. 523. No. 1. P. 123–133. DOI: 10.1016/j.abb.2012.04.001

20. Caprio M., Infante M., Calanchini M. et al. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects // Eat. Weight. Disord. 2017. Vol. 22. No. 1. P. 27–41. DOI: 10.1007/s40519-016-0312-6

21. Gatti D., Idolazzi L., Fassio A. Vitamin D: not just bone, but also immunity // Minerva Med. 2016. Vol. 107. No. 6. P. 452–460.

22. White J.H. Vitamin D metabolism and signaling in the immune system // Rev. Endocr. Metab. Disord. 2012. Vol. 13. No. 1. P. 21–29. DOI: 10.1007/s11154-011-9195-z

23. Prietl B., Treiber G., Pieber T.R., Amrein K. Vitamin D and immune function // Nutrients. 2013. Vol. 5. P. 2502–2521. DOI: 10.3390/nu5072502

24. Overbergh L., Decallonne B., Valckx D. et al. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages // Clin. Exp. Immunol. 2000. Vol. 120. No. 1. P. 139–146. DOI: 10.1046/j.1365-2249.2000.01204.x

25. Stoffels K., Overbergh L., Giulietti A. et al. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes // J. Bone. Miner. Res. 2006. Vol. 21. No. 1. P. 37–47. DOI: 10.1359/JBMR.050908

26. Singh P.K., van den Berg P.R., Long M.D. et al. Integration of VDR genome wide binding and GWAS genetic variation data reveals co-occurrence of VDR and NF-κB binding that is linked to immune phenotypes // BMC Genomics. 2017. Vol. 18. No. 1. P. 132. DOI: 10.1186/s12864-017-3481-4

27. Jensen S.S., Madsen M.W., Lukas J. et al. Inhibitory effects of 1alpha,25-dihydroxyvitamin D(3) on the G(1)-S phase-controlling machinery // Mol. Endocrinol. 2001. Vol. 15. No. 8. P. 1370–1380. DOI: 10.1210/mend.15.8.0673

28. Piemonti L., Monti P., Sironi M. et al. Vitamin D_3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells // J. Immunol. 2000. Vol. 164. No. 9. P. 4443–4451. DOI: 10.4049/jimmunol.164.9.4443

29. Ferreira G.B., Vanherwegen A.S., Eelen G. et al. Vitamin D_3 induces tolerance in human dendritic cells by activation of intracellular metabolic pathways // Cell. Rep. 2015. Vol. 10. No. 5. P. 711–725. DOI: 10.1016/j.celrep.2015.01.013

30. Amado Diago C.A., García-Unzueta M.T., Fariñas Mdel C., Amado J.A. Calcitriol-modulated human antibiotics: New pathophysiological aspects of vitamin D // Endocrinol. Nutr. 2016. Vol. 63. No. 2. P. 87–94. DOI: 10.1016/j.endonu.2015.09.005

31. Korf H., Wenes M., Stijlemans B. et al. 1,25-Dihydroxyvitamin D_3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism // Immunobiology. 2012. Vol. 217. No. 12. P. 1292–1300. DOI: 10.1016/j.imbio.2012.07.018

32. Zhang X., Zhou M., Guo Y. et al. 1,25-Dihydroxyvitamin D_3 Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARγ Signaling Pathway // Biomed. Res. Int. 2015. Vol. 2015. P. 157834. DOI: 10.1155/2015/157834

33. Zhang Y., Leung D.Y., Richers B.N. et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1 // J. Immunol. 2012. Vol. 188. No. 5. P. 2127–2135. DOI: 10.4049/jimmunol.1102412

34. Müller K., Heilmann C., Poulsen L.K., Barington T., Bendtzen K. The role of monocytes and T cells in 1,25-dihydroxyvitamin D3 mediated inhibition of B cell function *in vitro* // Immunopharmacology. 1991. Vol. 21. No. 2. P. 121–128. DOI: 10.1016/0162-3109(91)90015-q

35. Heine G., Anton K., Henz B.M., Worm M. 1alpha,25-dihydroxyvitamin D_3 inhibits anti-CD40 plus IL-4-mediated IgE production *in vitro* // Eur. J. Immunol. 2002. Vol. 32. No. 12. P. 3395–3404. DOI: 10.1002/1521-4141(200212)32:12<3395::AID-IMMU3395>3.0.CO;2-#

36. Chen S., Sims G.P., Chen X.X., et al. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation // J. Immunol. 2007. Vol. 179. No. 3. P. 1634–1647. DOI: 10.4049/jimmunol.179.3.1634

37. Overbergh L., Decallonne B., Waer M. et al. 1alpha,25-dihydroxyvitamin D_3 induces an autoantigen-specific T-helper 1/T-helper 2 immune shift in NOD mice immunized with GAD65 (p524-543) // Diabetes. 2000. Vol. 49. No. 8. P. 1301–1307. DOI: 10.2337/diabetes.49.8.1301

38. Boonstra A., Barrat F.J., Crain C. et al. 1alpha,25-Dihydroxyvitamin D_3 has a direct effect on naive CD4(+) T cells to en-

hance the development of Th2 cells // J. Immunol. 2001. Vol. 167. No. 9. P. 4974–4980. DOI: 10.4049/jimmunol.167.9.4974

39. Dankers W., Colin E.M., van Hamburg J.P., Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential // Front. Immunol. 2017. Vol. 7. P. 697. DOI: 10.3389/fimmu.2016.00697

40. Cippitelli M., Santoni A. Vitamin D_3: a transcriptional modulator of the interferon-gamma gene // Eur. J. Immunol. 1998. Vol. 28. No. 10. P. 3017–3030. DOI: 10.1002/(SICI)1521-4141(199810)28:10<3017::AID-IMMU3017>3.0.CO;2-6

41. Chang S.H., Chung Y., Dong C. Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression // J. Biol. Chem. 2010. Vol. 285. No. 50. P. 38751–38755. DOI: 10.1074/jbc.C110.185777

42. Giulietti A., Gysemans C., Stoffels K. et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice // Diabetologia. 2004. Vol. 47. No. 3. P. 451–462. DOI: 10.1007/s00125-004-1329-3

43. Mathieu C., Waer M., Casteels K. et al. Prevention of type I diabetes in NOD mice by nonhypercalcemic doses of a new structural analog of 1,25-dihydroxyvitamin D_3, KH1060 // Endocrinology. 1995. Vol. 136. No. 3. P. 866–872. DOI: 10.1210/endo.136.3.7867594

44. Mathieu C., Laureys J., Sobis H. et al. 1,25-Dihydroxyvitamin D_3 prevents insulitis in NOD mice // Diabetes. 1992. Vol. 41. No. 11. P. 1491–1495. DOI: 10.2337/diab.41.11.1491

45. Gregori S., Giarratana N., Smiroldo S. et al. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice // Diabetes. 2002. Vol. 51. No. 5. P. 1367–1374. DOI: 10.2337/diabetes.51.5.1367

46. van Halteren A.G., Tysma O.M., van Etten E. et al. 1alpha,25-dihydroxyvitamin D_3 or analogue treated dendritic cells modulate human autoreactive T cells via the selective induction of apoptosis // J. Autoimmun. 2004. Vol. 23. No. 3. P. 233–239. DOI: 10.1016/j.jaut.2004.06.004

47. Takiishi T., Ding L., Baeke F. et al. Dietary supplementation with high doses of regular vitamin D_3 safely reduces diabetes incidence in NOD mice when given early and long term // Diabetes. 2014. Vol. 63. No. 6. P. 2026–2036. DOI: 10.2337/db13-1559

48. Eizirik D.L., Colli M.L., Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes // Nat. Rev. Endocrinol. 2009. Vol. 5. No. 4. P. 219–226. DOI: 10.1038/nrendo.2009.21

49. Wei Z., Yoshihara E., He N. et al. Vitamin D switches BAF complexes to protect β cells // Cell. 2018. Vol. 173. No. 5. P. 1135–1149.e15. DOI: 10.1016/j.cell.2018.04.013

50. Norman A.W., Frankel J.B., Heldt A.M., Grodsky G.M. Vitamin D deficiency inhibits pancreatic secretion of insulin // Science. 1980. Vol. 209. No. 4458. P. 823–825. DOI: 10.1126/science.6250216

51. Bland R., Markovic D., Hills C.E. et al. Expression of 25-hydroxyvitamin D_3-1alpha-hydroxylase in pancreatic islets // J. Steroid. Biochem. Mol. Biol. 2004. Vol. 89–90. No. 1–5. P. 121–125. DOI: 10.1016/j.jsbmb.2004.03.115

52. Johnson J.A., Grande J.P., Roche P.C., Kumar R. Immunohistochemical localization of the $1,25(OH)_2D_3$ receptor and calbindin D28k in human and rat pancreas // Am. J. Physiol. 1994. Vol. 267. No. 3. Pt 1. P. E356–E360. DOI: 10.1152/ajpendo.1994.267.3.E356

53. Maestro B., Dávila N., Carranza M.C., Calle C. Identification of a Vitamin D response element in the human insulin receptor gene promoter // J. Steroid. Biochem. Mol. Biol. 2003. Vol. 84. No. 2–3. P. 223–230. DOI: 10.1016/s0960-0760(03)00032-3

54. Bourlon P.M., Billaudel B., Faure-Dussert A. Influence of vitamin D_3 deficiency and 1,25 dihydroxyvitamin D_3 on *de novo* insulin biosynthesis in the islets of the rat endocrine pancreas // J. Endocrinol. 1999. Vol. 160. No. 1. P. 87–95. DOI: 10.1677/joe.0.1600087

55. Alvarez J.A., Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis // Int. J. Endocrinol. 2010. Vol. 2010. P. 351385. DOI: 10.1155/2010/351385

56. Cade C., Norman A.W. Vitamin D_3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat *in vivo* // Endocrinology. 1986. Vol. 119. No. 1. P. 84–90. DOI: 10.1210/endo-119-1-84

57. Ramos-Lopez E., Brück P., Jansen T. et al. CYP2R1 (vitamin D 25-hydroxylase) gene is associated with susceptibility to type 1 diabetes and vitamin D levels in Germans // Diabetes Metab. Res. Rev. 2007. Vol. 23. No. 8. P. 631–636. DOI: 10.1002/dmrr.719

58. Cooper J.D., Smyth D.J., Walker N.M. et al. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes // Diabetes. 2011. Vol. 60. No. 5. P. 1624–1631. DOI: 10.2337/db10-1656

59. Bailey R., Cooper J.D., Zeitels L. et al. Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes // Diabetes. 2007. Vol. 56. No. 10. P. 2616–2621. DOI: 10.2337/db07-0652

60. Hussein A.G., Mohamed R.H., Alghobashy A.A. Synergism of CYP2R1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Egyptian children // Cell. Immunol. 2012. Vol. 279. No. 1. P. 42–45. DOI: 10.1016/j.cellimm.2012.08.006

61. Thorsen S.U., Mortensen H.B., Carstensen B. et al. No association between type 1 diabetes and genetic variation in vitamin D metabolism genes: a Danish study // Pediatr. Diabetes. 2014. Vol. 15. No. 6. P. 416–421. DOI: 10.1111/pedi.12105

62. Norris J.M., Lee H.S., Frederiksen B. et al. Plasma 25-hydroxyvitamin D concentration and risk of islet autoimmunity // Diabetes. 2018. Vol. 67. No. 1. P. 146–154. DOI: 10.2337/db17-0802

63. Tapia G., Mårild K., Dahl S.R. et al. Maternal and newborn vitamin D-binding protein, vitamin D levels, vitamin D receptor genotype, and childhood type 1 diabetes // Diabetes Care. 2019. Vol. 42. No. 4. P. 553–559. DOI: 10.2337/dc18-2176

64. Habibian N., Amoli M.M., Abbasi F. et al. Role of vitamin D and vitamin D receptor gene polymorphisms on residual beta cell function in children with type 1 diabetes mellitus // Pharmacol. Rep. 2019. Vol. 71. No. 2. P. 282–288. DOI: 10.1016/j.pharep.2018.12.012

65. You W.P., Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth // BMJ Open Diabetes Res. Care. 2016. Vol. 4. No. 1. P. e000161. DOI: 10.1136/bmjdrc-2015-000161

66. Pettitt D.J., Talton J., Dabelea D. et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study // Diabetes Care. 2014. Vol. 37. No. 2. P. 402–408. DOI: 10.2337/dc13-1838

67. Mayer-Davis E.J., Lawrence J.M., Dabelea D. et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012 // N. Engl. J. Med. 2017. Vol. 376. No. 15. P. 1419–1429. DOI: 10.1056/NEJMoa1610187

68. Karvonen M., Viik-Kajander M., Moltchanova E. et al. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale

(DiaMond) Project Group // Diabetes Care. 2000. Vol. 23. No. 10. P. 1516–1526. DOI: 10.2337/diacare.23.10.1516

69. Karvonen M., Jäntti V., Muntoni S. et al. Comparison of the seasonal pattern in the clinical onset of IDDM in Finland and Sardinia // Diabetes Care. 1998. Vol. 21. No. 7. P. 1101–1109. Corrected and republished from: Diabetes Care. 1998. Vol. 21. No. 10. P. 1784. DOI: 10.2337/diacare.21.7.1101

70. Ostman J., Lönnberg G., Arnqvist H.J. et al. Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983–2002 // J. Intern. Med. 2008. Vol. 263. No. 4. P. 386–394. DOI: 10.1111/j.1365-2796.2007.01896.x

71. Mohr S.B., Garland C.F., Gorham E.D., Garland F.C. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide // Diabetologia. 2008. Vol. 51. No. 8. P. 1391–1398. DOI: 10.1007/s00125-008-1061-5

72. Pozzilli P., Manfrini S., Crinò A. et al. Low levels of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 in patients with newly diagnosed type 1 diabetes // Horm. Metab. Res. 2005. Vol. 37. No. 11. P. 680–683. DOI: 10.1055/s-2005-870578

73. Greer R.M., Portelli S.L., Hung B.S. et al. Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes // Pediatr. Diabetes. 2013. Vol. 14. No. 1. P. 31–41. DOI: 10.1111/j.1399-5448.2012.00890.x

74. Federico G., Genoni A., Puggioni A. et al. Vitamin D status, enterovirus infection, and type 1 diabetes in Italian children/adolescents // Pediatr. Diabetes. 2018. Vol. 19. No. 5. P. 923–929. DOI: 10.1111/pedi.12673

75. Rasoul M.A., Al-Mahdi M., Al-Kandari H. et al. Low serum vitamin-D status is associated with high prevalence and early onset of type-1 diabetes mellitus in Kuwaiti children // BMC Pediatr. 2016. Vol. 16. P. 95. DOI: 10.1186/s12887-016-0629-3

76. Littorin B., Blom P., Schölin A. et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS) // Diabetologia. 2006. Vol. 49. No. 12. P. 2847–2852. DOI: 10.1007/s00125-006-0426-x

77. Bener A., Alsaied A., Al-Ali M. et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children // Acta Diabetol. 2009. Vol. 46. No. 3. P. 183–189. DOI: 10.1007/s00592-008-0071-6

78. Reinert-Hartwall L., Honkanen J., Härkönen T. et al. No association between vitamin D and β-cell autoimmunity in Finnish and Estonian children // Diabetes Metab. Res. Rev. 2014. Vol. 30. No. 8. P. 749–760. DOI: 10.1002/dmrr.2550

79. Sørensen I.M., Joner G., Jenum P.A. et al. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring // Diabetes. 2012. Vol. 61. No. 1. P. 175–178. DOI: 10.2337/db11-0875

80. Jacobsen R., Moldovan M., Vaag A.A. et al. Vitamin D fortification and seasonality of birth in type 1 diabetic cases: D-tect study // J. Dev. Orig. Health. Dis. 2016. Vol. 7. No. 1. P. 114–119. Corrected and republished from: J. Dev. Orig. Health. Dis. 2016. Vol. 7. No. 4. P. 429. DOI: 10.1017/S2040174415007849

81. Miettinen M.E., Reinert L., Kinnunen L. et al. Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring // Diabetologia. 2012. Vol. 55. No. 5. P. 1291–1294. DOI: 10.1007/s00125-012-2458-8

82. Dong J.Y., Zhang W.G., Chen J.J. et al. Vitamin D intake and risk of type 1 diabetes: a meta-analysis of observational studies // Nutrients. 2013. Vol. 5. No. 9. P. 3551–3562. DOI: 10.3390/nu5093551

83. Silvis K., Aronsson C.A., Liu X. et al. Maternal dietary supplement use and development of islet autoimmunity in the offspring: TEDDY study // Pediatr. Diabetes. 2019. Vol. 20. No. 1. P. 86–92. DOI: 10.1111/pedi.12794

84. Hyppönen E., Läärä E., Reunanen A. et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study // Lancet. 2001. Vol. 358. No. 9292. P. 1500–1503. DOI: 10.1016/S0140-6736(01)06580-1

85. The EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus // Diabetologia. 1999. Vol. 42. No. 1. P. 51–54. DOI: 10.1007/s001250051112

86. Stene L.C., Joner G.; Norwegian Childhood Diabetes Study Group. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study // Am. J. Clin. Nutr. 2003. Vol. 78. No. 6. P. 1128–1134. DOI: 10.1093/ajcn/78.6.1128

87. Gorham E.D., Garland C.F., Burgi A.A. et al. Lower prediagnostic serum 25-hydroxyvitamin D concentration is associated with higher risk of insulin-requiring diabetes: a nested case-control study // Diabetologia. 2012. Vol. 55. No. 12. P. 3224–3227. DOI: 10.1007/s00125-012-2709-8

88. Munger K.L., Levin L.I., Massa J. et al. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel // Am. J. Epidemiol. 2013. Vol. 177. No. 5. P. 411–419. DOI: 10.1093/aje/kws243

89. Zhang J., Upala S., Sanguankeo A. Relationship between vitamin D deficiency and diabetic retinopathy: a meta-analysis // Can. J. Ophthalmol. 2017. Vol. 52. Suppl. 1. P. S39–S44. DOI: 10.1016/j.jcjo.2017.09.026

90. Engelen L., Schalkwijk C.G., Eussen S.J. et al. Low 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 levels are independently associated with macroalbuminuria, but not with retinopathy and macrovascular disease in type 1 diabetes: the EURODIAB prospective complications study // Cardiovasc. Diabetol. 2015. Vol. 14. P. 67. DOI: 10.1186/s12933-015-0231-2

91. Shimo N., Yasuda T., Kaneto H. et al. Vitamin D deficiency is significantly associated with retinopathy in young Japanese type 1 diabetic patients // Diabetes Res. Clin. Pract. 2014. Vol. 106. No. 2. P. e41–e43. DOI: 10.1016/j.diabres.2014.08.005

92. Felício K.M., de Souza A.C.C.B., Neto J.F.A. et al. Glycemic variability and insulin needs in patients with type 1 diabetes mellitus supplemented with vitamin D: A pilot study using continuous glucose monitoring system // Curr. Diabetes. Rev. 2018. Vol. 14. No. 4. P. 395–403. DOI: 10.2174/1573399813666170616075013

93. Bogdanou D., Penna-Martinez M., Filmann N. et al. T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential cross-over // Diabetes Metab. Res. Rev. 2017. Vol. 33. No. 3. P. e2865. DOI: 10.1002/dmrr.2865

94. Mishra A., Dayal D., Sachdeva N., Attri S.V. Effect of 6-months' vitamin D supplementation on residual beta cell function in

children with type 1 diabetes: a case control interventional study // J. Pediatr. Endocrinol. Metab. 2016. Vol. 29. No. 4. P. 395–400. DOI: 10.1515/jpem-2015-0088

95. Giri D., Pintus D., Burnside G. et al. Treating vitamin D deficiency in children with type I diabetes could improve their glycaemic control // BMC Res. Notes. 2017. Vol. 10. No. 1. P. 465. DOI: 10.1186/s13104-017-2794-3

96. Gabbay M.A., Sato M.N., Finazzo C. et al. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual β-cell function in new-onset type 1 diabetes mellitus // Arch. Pediatr. Adolesc. Med. 2012. Vol. 166. No. 7. P. 601–607. DOI: 10.1001/archpediatrics.2012.164

97. Panjiyar R.P., Dayal D., Attri S.V. et al. Sustained serum 25-hydroxyvitamin D concentrations for one year with cholecalciferol supplementation improves glycaemic control and slows the decline of residual β cell function in children with type 1 diabetes // Pediatr. Endocrinol. Diabetes. Metab. 2018. Vol. 2018. No. 3. P. 111–117. DOI: 10.5114/pedm.2018.80992

98. Shih E.M., Mittelman S., Pitukcheewanont P. et al. Effects of vitamin D repletion on glycemic control and inflammatory cytokines in adolescents with type 1 diabetes // Pediatr. Diabetes. 2016. Vol. 17. No. 1. P. 36–43. DOI: 10.1111/pedi.12238

99. Perchard R., Magee L., Whatmore A. et al. A pilot interventional study to evaluate the impact of cholecalciferol treatment on HbA1c in type 1 diabetes (T1D) // Endocr. Connect. 2017. Vol. 6. No. 4. P. 225–231. DOI: 10.1530/EC-17-0045

100. Niinistö S., Takkinen H.M., Erlund I. et al. Fatty acid status in infancy is associated with the risk of type 1 diabetes-associated autoimmunity // Diabetologia. 2017. Vol. 60. No. 7. P. 1223–1233. DOI: 10.1007/s00125-017-4280-9

101. Bi X., Li F., Liu S. et al. ω-3 Polyunsaturated fatty acids ameliorate type 1 diabetes and autoimmunity // J. Clin. Invest. 2017. Vol. 127. No. 5. P. 1757–1771. DOI: 10.1172/JCI87388

102. Stene L.C., Ulriksen J., Magnus P., Joner G. Use of cod liver oil during pregnancy associated with lower risk of type I diabetes in the offspring // Diabetologia. 2000. Vol. 43. No. 9. P. 1093–1098. DOI: 10.1007/s001250051499

103. Scientific Advisory Committee on Nutrition [Internet]. SACN vitamin D and health report. London, 2016. [дата обращения 3.09.2019]. Доступ по ссылке: https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report

104. Holick M.F., Binkley N.C., Bischoff-Ferrari H.A. et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline // J. Clin. Endocrinol. Metab. 2011. Vol. 96. No. 7. P. 1911–1930. DOI: 10.1210/jc.2011-0385

105. Mazahery H., von Hurst P.R. Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation // Nutrients. 2015. Vol. 7. No. 7. P. 5111–5142. DOI: 10.3390/nu7075111

106. Rak K., Bronkowska M. Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of type 1 diabetes mellitus-A narrative review // Molecules. 2018. Vol. 24. No. 1. P. 53. DOI: 10.3390/molecules24010053

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