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Research progress of the relationship and molecular mechanism between vitamin D and type 2 diabetes mellitus in children and adolescents

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Abstract: The incidence of type 2 diabetes mellitus(T2DM) is increasing globally. With the growing prevalence of obesity in childhood, the incidence of T2DM is also on the rise among children. Children with T2DM have worse persistent ability in glycemic control and are more prone to complications than adults. In recent years, some studies have found that vitamin D deficiency is closely related to T2DM in adult patients, and its relationship in children and adolescents has also been reported by more and more studies. In terms of mechanism, vitamin D possess the ability of improving insulin sensitivity and regulating insulin secretion, the former has a relationship with renin angiotensin aldosterone system(RAAS), peroxisome proliferator activated receptor(PPAR), oxidative stress system and other pathways, and later with protein kinase A (PKA), L-type voltage-dependent calcium channel (L-type VDCC), phospholipase C (PLC), ATP sensitive potassium channel (K_{ATP}) and other signaling molecules. Thus, the review aims to explore the relationship between the vitamin D deficiency and the incidence of T2DM in children and adolescents and its possible molecular mechanism, so as to provide a reference for the prevention and treatment of T2DM in children and adolescents.

Keywords: Type 2 diabetes; Vitamin D; Children and adolescents; Renin angiotensin aldosterone system; Peroxisome proliferator activated receptor; Protein kinase A; L-type voltage-dependent calcium channel; Phospholipase C; ATP sensitive potassium channel

In recent years, the prevalence of diabetes has been steadily increasing, making it a significant global public health challenge that urgently needs addressing. According to the World Health Organization, the worldwide prevalence of obesity more than doubled between 1990 and 2022., while prevalence of obesity in children and adolescents aged 5–19 in 2020 is 4 times higher than in 1990. The risk of type 2 diabetes mellitus (T2DM) among children and adolescents has also risen accordingly [1]. Therefore, reducing the incidence of T2DM during childhood and adolescence has become imperative.

T2DM results from the interaction of environmental and genetic factors. Compared to adults with T2DM, children and adolescents often have poorer long-term blood sugar control [2]. Inadequate long-term control can lead to earlier onset of complications such as cardiovascular damage, vision impairment, and diabetic nephropathy [3-4].

Among the essential fat-soluble vitamin families in the human body, vitamin D is crucial. Approximately 80% to 90% of vitamin D is typically synthesized in the skin, although it can also be obtained through dietary intake and supplements. Vitamin D needs to specifically bind to the vitamin D receptor (VDR) to exert its biological effects. VDR belongs to the steroid hormone receptor family involved in DNA transcription. Research has identified vitamin D response elements in the promoter of the insulin receptor gene, suggesting that vitamin D may participate in insulin transcriptional control [5-6]. Once bound to VDR, vitamin D promotes insulin secretion from beta cells and enhances insulin sensitivity [7-8].

Increasingly, studies have found a close association between vitamin D deficiency and the incidence of type 1 diabetes mellitus (T1DM) among children and adolescents [9-10]. Therefore, to further understand the relationship between vitamin D and the onset of T2DM in children and adolescents, this review elaborates on its molecular mechanisms and research progress.

1 Current status of T2DM among children and adolescents

A study in the United States showed a significant increase in the incidence of T2DM among 10- to 19-year-olds from 2002 to 2015, rising from 9.0 per 100,000 in 2002 to 13.8 per 100,000 in 2014, with annual percent change (APC) of 4.8% [11]. Research from Auckland, New Zealand, covering 21 years from 1995 to 2015, revealed an annual increase of approximately 5% in the incidence of T2DM among those under 15 years old [12]. In Thailand, a study of trends in childhood diabetes over 20 years at a tertiary medical center showed a gradual increase in the proportion of new cases of T2DM, rising from 10%-15% in 1995-2003 to 25%-30% in

2004-2008, and further to 35%-40% in 2009-2014 [13].

In China, a study spanning from 1995 to 2010 found that the incidence of T2DM among children and adolescents increased from 4.1 per 100,000 to 10.0 per 100,000 [14]. A retrospective analysis covering the years 2010 to 2016 showed a 51.2% increase in newly diagnosed diabetic children compared to 2010, with T1DM accounting for 71.7% and T2DM for 20.0% [15].

Overall, diabetes incidence among children and adolescents is rising rapidly, with T2DM accounting for an increasingly larger proportion of total diabetes cases. Therefore, preventing the onset of T2DM during childhood and adolescence and managing blood sugar levels in affected individuals are urgent priorities.

2 International and domestic studies on the relationship between vitamin D levels and T2DM

Research has revealed that compared to non-diabetic individuals, patients with T2DM had lower serum vitamin D levels [16]. Vitamin D levels during childhood and adolescence are associated with the risk of T2DM in adulthood [17]. Afzal *et al.* [18] conducted a prospective cohort study and meta-analysis on the relationship between T2DM and vitamin D during a 29-year follow-up. They categorized 9,841 subjects based on serum vitamin D levels into sufficient, insufficient, deficient, and severely deficient groups, with serum vitamin D level of ≥50 nmol/L, 25-49.9 nmol/L, 12.5-24.9 nmol/L, and <12.50 nmol/L, respectively. The results showed that lower levels of serum vitamin D were associated with an increased risk of T2DM (*RR*=1.35, 95%*CI:* 1.09-1.66 for the severely deficient group compared to the sufficient group). Additionally, a 50% decrease in vitamin D levels was associated with a multivariate adjusted *RR* of 1.12 (95%*CI*: 1.03-1.21) for T2DM. Their meta-analysis of 16 prospective cohort studies further confirmed the association between low vitamin D levels and T2DM incidence (*RR*=1.50, 95%*CI*: 1.33-1.70).

A cross-sectional survey in China found that T2DM patients with metabolic syndrome had significantly lower serum vitamin D levels compared to those without metabolic syndrome (P<0.001). Patients were divided into four groups based on vitamin D levels. It was found that the lower the serum vitamin D level in T2DM patients, the greater the risk of developing metabolic syndrome [20]. A case-control study found that serum vitamin D levels were lower in children with T2DM nephropathy compared to the non-diseased group, and vitamin D levels were negatively correlated with urinary microalbumin/creatinine ratio and fasting blood glucose in diabetic nephropathy children (r=-0.302, P<0.05; r=-0.469, P<0.01), while positively correlated with insulin and C-peptide levels (r=0.447, P<0.05; r=0.246, P<0.05) [21]. Another study on the correlation between vitamin D levels and diabetic nephropathy showed that populations with lower serum vitamin D levels had a higher risk of diabetic nephropathy (*OR*>1, P<0.05) [22].

These domestic and foreign studies suggest that the onset of T2DM may be associated with vitamin D deficiency, a finding that holds true for children and adolescents with T2DM patients as well.

3 Molecular mechanisms of vitamin D in the onset of T2DM

T2DM involves insulin resistance and/or insulin secretion defects, leading to poor blood glucose control. Factors contributing to insulin resistance include irrational dietary behaviors, lack of exercise, while insulin secretion defects are mainly influenced by genetic factors and pancreatic β-cell function. The potential protective role of vitamin D in T2DM may be related to enhancing insulin sensitivity and improving pancreatic β-cell activity [23].

3.1 Vitamin D and insulin resistance

The renin-angiotensin-aldosterone system (RAAS) is one of the pathways through which vitamin D regulates insulin. Vitamin D regulates skeletal muscle cell Ca^{2+} concentration by inhibiting RAAS, thereby enhancing insulin sensitivity [24]. An important gene influencing the renin-angiotensin system is the angiotensin-converting enzyme gene. Animal experiments and clinical observations confirm that angiotensin-converting enzyme inhibitors can enhance insulin sensitivity [25]. An animal study indicated that intervention with vitamin D effectively improved insulin resistance and impaired glucose tolerance in metabolic syndrome rats [26]. A recent animal experiment found that vitamin D intervention not only improved weight in streptozotocin and high-fat diet-induced diabetic rats but also reduced insulin resistance index (P<0.05) [27].

Vitamin D can also increase the expression levels of insulin receptors in target tissues by binding with VDR, thereby stimulating peroxisome proliferators-activated receptors (PPAR) and reducing skeletal muscle cell insulin resistance caused by free fatty acids, thus enhancing cellular and tissue sensitivity to insulin [24]. Studies have shown that vitamin D treatment in diabetic patients activates PPAR-γ, protein kinase B (Akt), lowers glucose transporter 4, and insulin receptor substrate-1 (IRS-1) expression compared to the control group [24-25, 28-29]. Additionally, animal experiments demonstrate a significant increase in downstream targets of the Akt signaling pathway after vitamin D intervention (P<0.01) [30].

Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and other pro-inflammatory cytokine levels increase in T2DM patients, leading to increased IRS serine phosphorylation levels, inhibition of tyrosine phosphorylation, thereby disrupting glucose metabolism and inhibiting peripheral tissue sensitivity to insulin [24, 28]. After binding with VDR, vitamin D activates antioxidant-related gene expression, thereby alleviating oxidative stress response and inhibiting inflammatory factor damage to pancreatic β-cells, promoting the production of anti-inflammatory cytokines [6, 8, 24].

Cell studies have shown that vitamin D binding with VDR improves cell damage caused by excessive respiration and reactive oxygen species (ROS). ROS signal molecules activate cell stress-sensitive pathways, including nuclear factor-kappa B (NF-κB), p38 mitogen-activated protein kinase (p38MAPK), leading to cell damage and inflammatory responses [31]. Animal experiments indicate that simultaneous vitamin D deficiency and high-fat diet in rats increase inflammation-related RNA and miRNA overexpression, activating the NF-κB signaling pathway [32]. Guo *et al.* [33] found consistent results through animal and cell experiments, showing that calcitriol treatment can improve proteinuria severity in diabetic nephropathy rats, reduce apoptosis of renal tubular epithelial cells, and significantly promote VDR expression, while its effect on p38MAPK is opposite. A recent cross-sectional study found that serum vitamin D levels decrease sequentially from the non-T2DM group (n=113) to the prediabetes group (n=84) and the T2DM group (n=94) ($P<0.05$), and serum NF-κB expression levels increase accordingly ($P<0.05$), which may be one of the factors contributing to insulin resistance in T2DM patients [34].

Therefore, vitamin D may improve insulin resistance by activating PPAR, Akt, inhibiting RAAS, reducing insulin resistance mediated by free fatty acids, and improving insulin resistance by inhibiting IRS-1, glucose transporter 4, IL-6, TNF-α, NF-κB, p38MAPK, etc. Vitamin D deficiency may increase the risk of insulin resistance, thereby increasing the risk of T2DM onset.

3.2 Vitamin D and insulin secretion

Insulin secretion is a calcium-dependent process, and the action of insulin also relies on the mediation of calcium ions. Changes in calcium ion levels within target cells and tissues impair insulin signal transduction, reducing glucose transporter activity and promoting insulin resistance [35]. Studies indicated that vitamin D deficiency leaded to increased calcium ion concentrations [29]. Elevated levels of vitamin D in the body stimulate insulin secretion through several pathways: firstly, by activating protein kinase A (PKA) to stimulate L-type voltage-dependent calcium channels (L-type VDCC) and phosphorylation of proteins involved in exocytosis; secondly, by mediating phospholipase C (PLC) to synthesize 1,4,5-triphosphate inositol, causing depolarization of the cytoplasmic membrane and activating L-type VDCC and ATP-sensitive potassium channels (KATP), thereby inducing influx of extracellular calcium ions into pancreatic β-cells and promoting insulin secretion [25, 36].

Additionally, PLC can mobilize vesicular transport in cells, promoting insulin secretion in conjunction with Ca^{2+} [37]. Calcium/calmodulin-dependent protein kinase II (CaMKII), a serine-threonine protein kinase located in insulin secretion vesicles, plays a key role in phosphorylating proteins involved in mobilization and exocytosis processes [38]. cAMP-response element binding protein (CREB) is associated with insulin gene transcription, pancreatic β-cell activity, glucose susceptibility, and insulin exocytosis; induction of insulin gene expression by CREB can increase intracellular Ca2+ levels [39].

Researchers have found in animal experiments that vitamin D can stimulate insulin synthesis and vesicular transport by activating pathways such as PKA, KATP, L-type VDCC, and K+-Ca2+, upregulating signaling molecules like CaMKII and CREB, stimulating calcium ion influx, and promoting insulin exocytosis and secretion to regulate insulin secretion [37-39].

4 Clinical intervention studies of vitamin D and T2DM

In a 12-week randomized double-blind placebo-controlled trial, researchers included 48 T2DM patients aged 30-60 years. They found that compared to the placebo group, vitamin D supplementation significantly reduced advanced glycation end products (AGEs), TNF-α serum levels, and gene expression of RAGE in peripheral blood mononuclear cells of T2DM patients with deficient or insufficient vitamin D levels [40]. AGEs play a crucial role in microvascular and macrovascular complications in diabetes. However, a community-based randomized controlled trial (RCT) showed no statistically significant difference in the incidence of T2DM after 2 years of vitamin D supplementation in prediabetic individuals compared to the control group (P=0.701) [41].

A meta-analysis of 23 RCTs involving 1,797 T2DM patients showed that compared to the placebo group, vitamin D intervention had no significant effect on HbA1c levels but significantly improved fasting blood glucose levels in patients [42]. Another meta-analysis[43] of 20 studies (n=2,703) found that vitamin D supplementation increased serum vitamin D levels in T2DM patients and significantly reduced the insulin resistance index, although it did not significantly affect fasting glucose, HbA1c, or fasting insulin levels. Furthermore, Santos *et al.* [44] suggested that for T2DM patients with stable blood glucose control or sufficient vitamin D levels, vitamin D supplementation did not normalize blood glucose levels, and there was insufficient evidence to support that vitamin D supplementation improves glucose metabolism or insulin action.

There is limited research on RCTs of vitamin D supplementation for treating or preventing T2DM in children. A recent meta-analysis included 7 RCTs of vitamin D intervention in obese children and adolescents (aged 2-19 years) with impaired glucose tolerance. Results from 4 RCTs showed improvements in insulin levels, fasting blood glucose, and insulin resistance following vitamin D intervention, while results from the other 3 RCTs did not show statistically significant associations with glucose parameters [45].

Conclusions drawn from RCTs involving healthy individuals, prediabetic individuals, and T2DM patients vary, but supplementation of vitamin D in patients with vitamin D deficiency has a beneficial effect on glycemic

control.

5 Conclusion

In summary, the incidence of T2DM among children and adolescents is increasing. Vitamin D deficiency may increase the risk of T2DM and affect glycemic control and the severity of related complications in affected children. The protective mechanisms of vitamin D on pancreatic islets may involve improving sensitivity to insulin and enhancing pancreatic β-cell activity. Vitamin D regulates insulin sensitivity through systems such as RAAS, PPAR, and oxidative stress, and stimulates insulin secretion through pathways including PKA, L-type VDCC, PLC, and KATP. Supplementation of vitamin D in patients with vitamin D deficiency has favorable effects [46], although whether supplementation of vitamin D can positively impact fasting blood glucose, fasting insulin, and HbA1c in T2DM patients with sufficient vitamin D levels or stable blood glucose control remains unclear. Furthermore, there is a lack of high-quality RCTs or cohort studies on whether preventive vitamin D supplementation can reduce the risk of developing T2DM.

The authors report no conflict of interest

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· 研究进展 ·

维生素 D 与儿童和青少年 2 型糖尿病发病分子机制研究进展

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摘要：2 型糖尿病(T2DM)在全球的发病率不断上升。随着儿童肥胖率的增加,T2DM 的发病率在儿童当中也呈现出上升的趋势。与成年患者相比,儿童 T2DM 患者血糖控制持久性更差,且更容易出现并发症。近年来,研究发现成人患者中维生素 D 缺乏与 T2DM 发病密切相关,在儿童与青少年群体中的研究报道也越来越多。机制方面,维生素 D 具有提高胰岛素敏感性和调节胰岛素分泌的作用,维生素 D 调节胰岛的敏感性可能与肾素—血管紧张素—醛固酮系统(RAAS)、过氧化物酶体增殖物激活受体(PPAR)及氧化应激系统等通路有关,也可通过调节蛋白激酶 A(PKA)、L 型电压依赖性钙通道(L-type VDCC)、磷脂酶 C(PLC)、ATP 敏感性钾通道(K_{ATP})等信号分子刺激胰岛素的分泌。本文旨在阐述维生素 D 缺乏与儿童和青少年 T2DM 发病关系及相关分子机制,为儿童和青少年 T2DM 的预防和治疗提供参考。

关键词：2 型糖尿病；维生素 D；儿童和青少年；肾素—血管紧张素—醛固酮系统；过氧化物酶体增殖物激活受体；蛋白激酶 A；L 型电压依赖性钙通道；磷脂酶 C；ATP 敏感性钾通道

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Research progress of the molecular mechanism between vitamin D and type 2 diabetes mellitus in children and adolescents

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Abstract: The incidence of type 2 diabetes mellitus (T2DM) is increasing globally. With the growing prevalence of obesity in childhood, the incidence of T2DM is also on the rise among children. Children with T2DM have worse persistent ability in glycemic control and are more prone to complications than adults. In recent years, some studies have found that vitamin D deficiency is closely related to T2DM in adult patients, and its relationship in children and adolescents has also been reported by more and more studies. In terms of mechanism, vitamin D posses the ability of improving insulin sensitivity and regulating insulin secretion, the former has a relationship with renin angiotensin aldosterone system(RAAS), peroxisome proliferator activated receptor(PPAR), oxidative stress system and other pathways, and later with protein kinase A (PKA), L-type voltage-dependent calcium channel (L-type VDCC), phospholipase C (PLC), ATP sensitive potassium channel (K_{ATP}) and other signaling molecules. Thus, the review aims to explore the relationship between the deficiency of vitamin D and the incidence of T2DM in children and adolescents and its possible molecular mechanism, so as to provide a reference for the prevention and treatment of T2DM in children and adolescents.

Keywords: Type 2 diabetes; Vitamin D; Children and adolescents; Renin angiotensin aldosterone system; Peroxisome proliferator activated receptor; Protein kinase A; L-type voltage-dependent calcium channel; Phospholipase C; ATP sensitive potassium channel

近年来糖尿病的患病率不断上升,已成为全球亟待解决的重大公共卫生难题。据世界卫生组织报道,与 1990 年相比,2022 年全球成人肥胖症增加了一倍多,青少年肥胖症增加了四倍,儿童和青少年 2 型糖尿病(type 2 diabetes mellitus, T2DM)的发病风险也随之攀升[1]。因此,降低儿童及青少年期 T2DM 发病率已迫在眉睫。

T2DM 是环境和基因相互作用的结果,与成年患者相比,儿童和青少年 T2DM 患者的血糖持久性控制较差[2],若长期

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血糖无法得到良好的控制,将会导致患儿较早出现并发症,如心血管系统损伤、视力受损及糖尿病肾病等[3-4]。

在人体所必需的脂溶性维生素家族中,维生素 D 是其中之一。人体中大约 80%~90%的维生素 D 由皮肤合成,此外,还可以通过摄入食物和维生素 D 补充剂获得。维生素 D 想要实现其在机体内的生物学价值,需要与维生素 D 受体(vitamin D receptor,VDR)特异性结合。VDR 属于类固醇激素受体,是参与 DNA 转录的核受体家族中的一员,有研究发现,在胰岛素受体基因的启动子中发现了维生素 D 反应元件区,提示维生素 D 可能参与胰岛素的转录控制[5-6]。维生素 D 与 VDR 结合后,具有促进 β 细胞分泌胰岛素以及提高胰岛素敏感性的作用[7-8]。

越来越多的研究发现,儿童和青少年 1 型糖尿病(type 1 diabetes mellitus, T1DM)发病情况与维生素 D 缺乏密切相关[9-10]。因此,为了进一步了解维生素 D 与儿童和青少年 T2DM 的发病关系,本文对其分子机制及研究进展进行阐述。

1　儿童和青少年 T2DM 的国内外现状

美国的一项调查研究显示,在 2002 年至 2015 年期间,10~19 岁 T2DM 的发病率显著增加,从 2002 年的 9.0/10 万上升到 2014 年的 13.8/10 万,青少年 T2DM 发病率每年上升 4.8%[11]。一份来自新西兰奥克兰的研究发现,1995 年至 2015 年共 21 年期间,15 岁以下 T2DM 发病率以每年约 5%的速度递增[12]。泰国学者调查了一个三级医疗中心 20 年间 0~15 岁儿童糖尿病的发病趋势,发现 T2DM 新发病人数占 DM 发病总人数的比例逐渐上升,从 1995—2003 年的 10%~15%到 2004—2008 年的 25%~30%,2009—2014 年则上升到 35%~40%[13]。

我国学者通过研究 1995—2010 年 15 年期间,14 个临床中心的 433.8 万名儿童和青少年糖尿病患者,发现 T2DM 患病率从 4.1/10 万增至 10.0/10 万,且 T2DM 患病率增长速度快于 T1DM[14]。一项回顾性分析显示,在 2010—2016 年期间收治的 431 例新诊断的糖尿病儿童当中,T1DM 占71.7%,T2DM 占 20.0%,且糖尿病患儿人数逐年增长,2016 年较 2010 年增长了 51.2%[15]。

总体而言,在儿童和青少年群体中,糖尿病的发病率逐年上升,且速度较快,其中 T2DM 发病率占总糖尿病发病率的比重越来越大。因此,预防儿童及青少年期 T2DM 发病及控制 T2DM 患者血糖水平刻不容缓。

2　维生素 D 水平与 T2DM 发病关系的国内外研究

研究揭示,与非糖尿病组相比,T2DM 患者血清维生素 D 水平较低[16-17],且儿童和青少年时期的维生素 D 水平与成年期 T2DM 发病风险相关[18]。Afzal 等[19]对 T2DM 与维生素 D 的关系做了前瞻性队列研究和荟萃分析,在长达 29 年的随访中,将纳入的 9 841 名研究对象按血清维生素 D 水平分为充足组、不足组、缺乏组及严重缺乏组,血清维生素 D 由高到低分别为≥50 nmol/L、25~49.9 nmol/L、12.5~24.9 nmol/L 及<12.50 nmol/L,按临床分组和季节性调整分组后发现低水平的维生素 D 与 T2DM 发病率有关;且 T2DM 的发病率随血清维生素 D 水平浓度的降低而增加(严重缺乏组与充足组 RR=1.35, 95%CI:1.09~1.66);当维生素 D 水平降低 50%时,T2DM 的多变量校正 RR 为 1.12(95%CI:1.03~1.21)。同时,该研究者通过对 16 个前瞻性队列研究进行荟萃分析,也进一步验证了低水平的维生素 D 与 T2DM 发病率有关(RR=1.50, 95%CI:1.33~1.70)。

国内的一项横断面调查研究结果表明,合并代谢综合征 T2DM 患者的血清维生素 D 水平明显比不合并代谢综合征的患者低(P<0.001),将纳入的所有患者按照维生素 D 水平由低到高分成 4 组,以水平低的患者为对照,发现 T2DM 患者血清维生素 D 水平越低,则代谢综合征的患病人数越多,其风险也就越大[20]。一项病例对照研究发现,T2DM 肾病患儿的血清维生素 D 水平较未患病组低,且维生素 D 水平与糖尿病肾病患儿尿微量白蛋白/肌酐比、空腹血糖存在负相关(r=-0.302, P<0.05; r=-0.469, P<0.01),而与胰岛素、C-肽水平呈正相关(r=0.447, P<0.05; r=0.246, P<0.05)[21]。另有一项研究显示,血清维生素 D 水平低的人群发生糖尿病肾病的风险高(OR>1, P<0.05)[22]。

这些国内外的研究表明,T2DM 的发病可能与维生素 D 缺乏有关,在儿童和青少年 T2DM 患者当中亦是如此。

3　维生素 D 与 T2DM 发病的分子机制研究

T2DM 会出现胰岛素抵抗和(或)胰岛素分泌缺陷,使得患者对血糖控制变差。导致胰岛素抵抗的因素包括不合理的饮食行为、缺乏锻炼等,而胰岛素分泌缺陷则主要受遗传因素、胰岛 β 细胞功能影响。维生素 D 对 T2DM 保护作用的潜在机制可能与提高机体对胰岛素的敏感性和改善胰岛 β 细胞活性有关[23]。

3.1　维生素 D 与胰岛素抵抗　肾素—血管紧张素—醛固酮系统(renin-angiotensin-aldosterone system, RAAS)是维生素 D 调控胰岛素的通路之一,维生素 D 通过抑制 RAAS 来调节骨骼肌细胞 Ca^{2+}浓度,进而提高胰岛素敏感性[24]。影响肾素—血管紧张素系统的一个重要基因是血管紧张素转化酶基因。动物实验和临床观察证实,血管紧张素转化酶抑制剂干预可提高机体的胰岛素敏感性[25]。一项动物研究表明,维生素 D 干预后可有效改善代谢综合征大鼠的胰岛素抵抗和糖耐量受损情况[26]。最新一项动物实验发现,维生素 D 干预后不仅可以减轻链脲佐菌素和高脂饮食诱导的糖尿病大鼠的体重,还可以降低胰岛素抵抗指数(P<0.05)[27]。

维生素 D 还可以通过与 VDR 结合来提高靶组织胰岛素受体的表达水平,通过刺激过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptors, PPAR),降低游离脂肪酸导致的骨骼肌细胞胰岛素抵抗效应,提高机体细胞和组织对胰岛素的敏感性[24]。研究揭示,对糖尿病患者进行维生素 D 治疗后,发现干预组 PPAR-γ、蛋白激酶 B(protein kinase B, Akt)被激活,葡萄糖转运蛋白 4 和胰岛素受体底物-1

(insulin receptor substrate-1, IRS-1)的表达低于对照组[24-25,28-29]。此外,动物实验表明,经过维生素 D 干预后,Akt 信号通路的下游靶点显著增加(P<0.01)[30]。

T2DM 患者体内的肿瘤坏死因子 α(tumour necrosis factor-α, TNF-α)、白介素 6(interleukin-6, IL-6)等促炎细胞因子表达水平增高,提高了 IRS 丝氨酸磷酸化水平,抑制酪氨酸磷酸化,从而干扰血糖等的代谢,抑制周围组织对胰岛素的敏感性[24,28]。维生素 D 与 VDR 结合后,激活抗氧化剂相关的部分基因表达,从而减轻机体氧化应激反应;并且能够抑制炎症因子对胰岛 β 细胞的破坏,促进抗炎细胞因子的产生[6,8,24]。

细胞研究证实,维生素 D 和 VDR 结合,可改善细胞因过度呼吸和活性氧带来的细胞损伤,而活性氧信号分子使细胞应激敏感通路激活,包括核转录因子-κB(NF-κB)、p38 丝裂原活化蛋白激酶(p38MAPK)等,进而引起细胞损伤和炎症反应[31]。动物实验表明,在大鼠高脂饮食的同时若存在维生素 D 缺乏,会导致炎症有关的 RNA 和 miRNA 过度表达,使 NF-κB 信号通路激活[32]。Guo 等[33]通过动物实验和细胞实验得出一致结论,即通过骨化三醇治疗可改善糖尿病肾病大鼠蛋白尿的严重程度,减少肾小管上皮细胞凋亡,且显著促进 VDR 的表达,对 p38MAPK 的作用则与之相反。最近一项横断面研究发现,非 T2DM 组(n = 113)、糖尿病前期组(n = 84)与 T2DM 组患者(n = 94)的维生素 D 水平依次降低(P< 0.05),3 组血清 NF-κB 的水平依次升高(P<0.05),这可能是造成 T2DM 患者胰岛素抵抗的因素之一[34]。

因此,维生素 D 可通过激活 PPAR、Akt,抑制 RAAS 系统、降低游离脂肪酸介导的胰岛素抵抗,通过抑制 IRS-1、葡萄糖转运蛋白 4、IL-6、TNF-α、NF-κB、p38MAPK 等的表达进而改善胰岛素抵抗,维生素 D 缺乏可能会增加胰岛素抵抗风险,进而增加 T2DM 的发病风险。

3.2　*维生素 D 与胰岛素分泌*　胰岛素分泌是依赖钙的过程,胰岛素发挥作用也离不开钙离子的介导。靶细胞和组织内钙离子水平变化导致胰岛素信号转导受损,使葡萄糖转运体活性降低,容易产生胰岛素抵抗[35]。研究表明,维生素 D 缺乏导致钙离子浓度增加[29],体内维生素 D 水平升高,一方面通过介导蛋白激酶 A(protein kinase A, PKA)刺激 L 型电压依赖性钙通道(L-type voltage-dependent calcium channels, L-type VDCC)和胞吐作用的相关蛋白质磷酸化;另一方面通过介导磷脂酶 C(phospholipase C, PLC)合成 1,4,5-三磷酸肌醇,导致细胞质膜去极化,从而使 L-type VDCC 和 ATP 敏感性钾通道(K_{ATP})途径激活,诱导胰岛 β 细胞外钙离子内流,促进胰岛素的分泌[25,36]。

同时,PKC 能够动员细胞囊泡运输,这些囊泡与 Ca^{2+} 一起促进胰岛素的分泌[37]。钙调蛋白激酶Ⅱ(CaM kinase Ⅱ, CaMK Ⅱ)是一种位于胰岛素分泌囊泡中的丝氨酸—苏氨酸蛋白激酶,其主要功能是促进参与胰岛素囊泡动员和胞吐相关过程蛋白质的磷酸化[38]。环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)与胰岛素基因转录、胰腺 β 细胞活性、葡萄糖易感性和胰岛素胞吐作用等有关,通过 CREB 诱导胰岛素基因的表达,可以提高细胞内 Ca^{2+} 水平[39]。

研究者通过动物实验,发现维生素 D 可以通过激活 PKA、K_{ATP}、L-type VDCC 和 K^+-Ca^{2+} 等通路,上调 CaMK Ⅱ、CREB 等信号分子,刺激钙离子内流,促进胰岛素的合成和囊泡运输,从而刺激胰岛素的胞吐和分泌作用,以此来调节胰岛素分泌[37-39]。

4　维生素 D 与 T2DM 的临床干预研究

在一项为期 12 周的随机对照双盲试验中,研究者纳入 48 名 30~60 岁 T2DM 患者,发现与安慰剂组相比,补充维生素 D 可显著降低患有维生素 D 缺乏或不足的 T2DM 患者的晚期糖基化终末产物(advanced glycation end products AGEs)、TNF-α 血清水平以及外周血单个核细胞中 RAGE 的基因表达[40]。AGEs 在糖尿病微血管和大血管并发症中起着至关重要的作用。然而,另有一项基于社区的随机对照试验(RCT)表明,在糖尿病前期人群中,对干预组给予维生素 D 补充 2 年后,与对照组相比 T2DM 的发病率无统计学差异(P=0.701)[41]。

荟萃分析显示,共纳入 1 797 名 T2DM 患者的 23 项的 RCT 中,与安慰剂组相比,维生素 D 干预组对 T2DM 患者的 HbA1c 没有显著影响,但患者的空腹血糖水平可以通过补充维生素 D 得到明显改善[42]。在纳入 20 项研究(n=2 703)的荟萃分析中[43],研究者发现与安慰剂组相比,维生素 D 补充组可提高 T2DM 患者的血清维生素 D 水平,并且在降低胰岛素抵抗指数方面有显著效果;可在改善空腹血糖、HbA1c 和空腹胰岛素方面却没有明显影响。此外,Santos 等[44]认为,对于血糖控制稳定的或体内维生素 D 充足的 T2DM 患者来说,补充维生素 D 不能使其血糖水平正常化,没有充分的证据支持补充维生素 D 可以改善 T2DM 患者的糖代谢或胰岛素作用。

在儿童群体中,有关维生素 D 补充治疗或预防 T2DM 的 RCT 研究较少。最新一篇荟萃分析纳入 7 项维生素 D 干预肥胖儿童和青少年(2~19 岁)糖耐量异常的 RCT 研究,分析发现,其中 4 项 RCT 结果显示经维生素 D 干预后,受试者的胰岛素水平、空腹血糖和胰岛素抵抗得到改善,但另外 3 项 RCT 研究结果则未显示出与血糖参数有关的统计学意义[45]。

通过对健康人群、糖尿病前期及 T2DM 患者进行 RCT 研究,得出的结论不尽相同,但维生素 D 缺乏患者补充维生素 D 对控制血糖具有一定的效果。

5　结　语

综上所述,儿童和青少年的 T2DM 发病率日益上升,维生素 D 缺乏可能会增加 T2DM 发病风险,并影响患儿血糖控制和相关并发症的严重程度,其对胰岛的保护机制可能与提高机体对胰岛素的敏感性和改善胰岛 β 细胞活性有关。维生素 D 可通过 RAAS、PPAR 及氧化应激系统等参与胰岛素敏感性的调节,通过调节 PKA、L-type VDCC、PLC、K_{ATP} 等刺激胰岛素的分泌。维生素 D 缺乏患者补充维生素 D 可对机体产生有利作用[46],但对于维生素 D 充足或血糖控制稳定的 T2DM 患

者,补充维生素 D 能否对空腹血糖、空腹胰岛素和 HbA1c 产生正面影响仍不明确。而 T2DM 的发病风险能否通过预防性补充维生素 D 来降低,仍然缺乏高质量的 RCT 研究或队列研究。

利益冲突　无

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