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Research Progress and Clinical Translation of Vitamin AD in the Prevention and Treatment of Allergic Diseases in Children

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Abstract: The incidence of allergic diseases in children continues to rise, posing a significant public health challenge. Vitamin AD, as a critical nutrient, has increasingly demonstrated its pivotal role in the synergistic regulation of immune homeostasis, in addition to its classical functions. This study, based on clinical data analysis of 696 enrolled children, reveals a high prevalence of vitamin D insufficiency/deficiency at 64% (446/696) and vitamin A deficiency at 48% (331/696), particularly pronounced among children with recurrent respiratory infections and allergic diseases. Notably, even among those regularly supplemented with vitamin AD drops, a substantial proportion of children still exhibit deficiencies, underscoring the necessity for precise monitoring and individualized supplementation, and providing a crucial target for clinical intervention. Substantial evidence indicates a strong correlation between vitamin AD deficiency and the high incidence of allergic diseases in children. Through mechanisms such as synergistically regulating the Th1/Th2 imbalance, promoting Treg cell-mediated immune tolerance, enhancing the intestinal mucosal barrier, and inhibiting abnormal inflammatory responses, vitamin AD plays a key role in the prevention and treatment of allergic diseases. This article systematically reviews the immunomodulatory mechanisms of vitamin AD (especially its synergistic effects), the latest research progress in the prevention and treatment of common pediatric allergic diseases, existing controversies, and clinical translation pathways based on the concept of precision medicine, aiming to provide a scientific basis and actionable strategies for constructing a precise and efficient prevention and treatment system for pediatric allergic diseases.

Keywords: Vitamin AD; Pediatric allergic diseases; Immunomodulation; Prevention and treatment; Clinical translation; Individualized supplementation

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1. Introduction

Allergic diseases, also known as hypersensitivity diseases, are tissue damage or dysfunctional disorders caused by abnormal immune responses to allergens in the body. Their pathogenesis is closely related to genetic susceptibility,

environmental exposure, and immune dysfunction. According to statistics from the World Health Organization, the global incidence of allergic diseases in children has exceeded 20% and is growing at a rate of 2–3 times every 10 years, making it one of the major threats to children's health in the 21st century [1]. In China, a multi-center epidemiological survey conducted nationwide in 2019 revealed that the incidence of allergic rhinitis in children aged 0-14 years was 14.4%, asthma was 3.02%, atopic dermatitis was 12.94%, and food allergies were 6.1% [2]. Moreover, children with recurrent respiratory infections often coexist with allergic diseases, severely affecting their sleep, learning, and social skills. Some severely affected children may experience life-threatening complications such as suffocation and anaphylactic shock.

In recent years, the association between nutrients and immune function has become a research hotspot in the field of pediatrics. As nutrients with dual activities of fat-soluble vitamins, the role of vitamin AD in immune regulation has been continuously explored. The clinical data analysis of 696 children selected for this study revealed that the prevalence of vitamin D insufficiency and deficiency reached 64% (446/696), while the prevalence of vitamin A deficiency was 48% (331/696). Moreover, children with recurrent respiratory tract infections and allergic diseases had significantly lower levels of vitamin AD compared to healthy children. This "supplementation paradox" profoundly reveals that individual heterogeneity factors, such as genetic background and metabolic capacity, have a decisive impact on the homeostasis of vitamin AD in the body. Traditional "one-size-fits-all" supplementation strategies are no longer suitable for the development needs of precision pediatrics, and there is an urgent need to transition to personalized and precise supplementation plans based on individual-level monitoring.

2. Research progress and translational potential of vitamin AD in the prevention of common allergic diseases in children

The preventive value of vitamin AD supplementation for allergic diseases in children has been confirmed by multiple studies. Despite some controversies, based on the empirical data of 696 children in this study, individualized supplementation based on precise monitoring can significantly reduce the risk of disease onset in high-risk children, demonstrating clear prospects for clinical translation.

2.1. Allergic rhinitis

Allergic rhinitis is one of the most prevalent allergic diseases in childhood, characterized by chronic inflammation of the nasal mucosa. Clinical manifestations include symptoms such as nasal itching, sneezing, runny nose, and nasal congestion, which significantly affect the quality of life of affected children. Epidemiological studies have clearly shown that vitamin AD deficiency is closely associated with a high incidence of allergic rhinitis in children [3]. The research conducted by Jin Guoping et al. indicated that the incidence rate of allergic rhinitis among children with serum vitamin A deficiency was 23.5%, significantly higher than that in the adequate group (12.1%) [4]. The incidence rate in the vitamin D deficiency group was 25.3%, higher than that in the adequate group (11.8%). Moreover, the incidence rate in the group with dual deficiency of vitamins A and D reached as high as 31.2%, providing disease-specific evidence for the association between vitamin AD deficiency and low immunity in children found in this study.

Cohort studies have further confirmed the preventive effect of supplementation. The research by Liang Yanchang et al. found that among children who started regular vitamin AD supplementation within six months after birth, the incidence rate of allergic rhinitis at the age of five was 8.3%, significantly lower than that in the non-supplemented group [5]. For premature infants, a high-risk group, the study by Zhang Yu et al. showed that due to inadequate vitamin AD reserves, immature intestinal barrier function, and incomplete immune system development in premature infants, the risk of developing allergic rhinitis increased significantly [6]. However, starting vitamin AD supplementation within one week after birth and continuing until the age of two could significantly reduce the incidence rate at the age of three. Combining the data from this study, even among children receiving regular supplementation, there is still a relatively high deficiency rate, suggesting potential issues such as insufficient dosage or individual differences in absorption in the current

supplementation regimen. Therefore, the key to clinical translation lies in incorporating vitamin AD level monitoring into routine physical examinations for high-risk children (e.g., those with a family history of allergies or a history of recurrent respiratory infections) and adjusting the supplementation dosage based on the monitoring results, rather than solely relying on fixed recommended dosages. The expert consensus in China recommends a basic dosage of 1500–2000 IU/day of vitamin A and 400-800 IU/day of vitamin D [7]. For children identified as deficient through monitoring, appropriate adjustments can be made under the guidance of a doctor to avoid the risk of adverse reactions caused by excessive supplementation and to achieve precise prevention.

2.2. Asthma

Asthma is a common chronic respiratory disease in childhood, characterized by airway hyperresponsiveness, chronic inflammation, and airway remodeling. It poses a serious threat to children's respiratory health, and some children's conditions persist into adulthood with poor prognosis. In recent years, the association between vitamin AD and childhood asthma has become a research hotspot. Epidemiological studies have shown that vitamin AD deficiency significantly increases the risk of asthma. Research by Guo Li et al. indicates that for every 10 μg/dL decrease in serum vitamin A levels, the risk of childhood asthma increases by 1.23 times; for every 10 nmol/L decrease in vitamin D levels, the risk increases by 1.18 times, which is highly consistent with the conclusion of this study that vitamin AD levels are positively correlated with immunity [8].

Several intervention studies have confirmed the preventive value of supplementation. A three-year follow-up randomized controlled trial by Zhong Xiaomei et al. found that the asthma incidence rate in the supplemented group was 2.8%, significantly lower than that in the control group (6.4%) [9]. Research by Du Mengsi et al. on high-risk children (with a family history of asthma) showed that the earlier the supplementation, the more significant the preventive effect [10]. Children who started supplementation within three months after birth had a more pronounced reduction in asthma risk, and the mechanism is related to vitamin AD regulating the Th1/Th2 balance, promoting Treg cell differentiation, and inhibiting airway inflammatory responses. Based on the data from this study, a "risk stratification-precision intervention" system needs to be established for translational application: Firstly, high-risk infants should be identified using factors such as family history, premature birth, and a history of recurrent wheezing. Secondly, baseline vitamin AD levels should be tested during early life (e.g., within three months after birth). Thirdly, individualized supplementation plans should be formulated based on test results (deficiency, insufficiency, sufficiency), such as intensive supplementation for those with deficiencies, and vitamin AD levels should be dynamically monitored during supplementation to achieve closed-loop management. In the future, precision prevention randomized controlled trials (RCTs) based on biomarkers and genotyping should be conducted to determine the optimal dosage and treatment duration for different subgroups.

2.3. Atopic dermatitis

Atopic dermatitis is a skin disease characterized by impaired skin barrier function and chronic inflammation, with clinical manifestations including dry skin, pruritus, erythema, papules, etc. It tends to recur frequently and seriously affects the quality of life in children. Studies have shown that vitamin AD deficiency is closely related to the occurrence and severity of atopic dermatitis in children. The research by Zhao Hui et al. found that serum vitamin A and D levels in children with atopic dermatitis were significantly lower than those in healthy children, and the more severe the condition, the lower the serum levels [11]. The study by Zhang Xing et al. [12] further confirmed that serum 25-hydroxyvitamin D levels were negatively correlated with the severity of atopic dermatitis. Intervention studies have shown that vitamin AD supplementation can reduce the risk of developing atopic dermatitis. Zhang Xing et al. found that children who began regular vitamin AD supplementation within six months after birth had an atopic dermatitis incidence rate of 9.2% at age two, significantly lower than that of the non-supplemented group (17.5%) [12]. In an RCT study by Fu Jinling et al., high-risk children with a parental history of allergic diseases were randomly divided into a supplementation group (receiving 1500 IU/day of vitamin A and 400 IU/day of vitamin D) and a control group [13]. After one year of follow-up, the

incidence rate in the supplementation group was 10.0%, lower than that in the control group (22.0%). Additionally, topical application of vitamin A derivatives (tazarotene) and vitamin D derivatives (calcipotriol) can improve skin symptoms, with mechanisms related to regulating skin barrier function and inhibiting local inflammatory responses. Based on the data from this study, clinical translation pathways include incorporating vitamin AD level monitoring into early screening for high-risk children with atopic dermatitis and providing systemic supplementation to those deficient. Furthermore, for children already diagnosed with the condition, combining topical vitamin AD derivatives with conventional treatments can enhance therapeutic efficacy. This combined intervention approach has been preliminarily applied in some clinical settings, demonstrating good safety and efficacy, and showing potential for widespread adoption.

2.4. Food allergy

Food allergy is a common allergic disease in childhood, with clinical manifestations including vomiting, diarrhea, rash, dyspnea, and, in severe cases, anaphylactic shock. Impaired intestinal barrier function is a key pathogenic mechanism. Vitamin AD can play a preventive role in food allergies by enhancing intestinal barrier function and regulating immune tolerance. Epidemiological studies have shown a significantly higher incidence of food allergies in children with vitamin AD deficiency. The study by Zhao Hui et al. found that the incidence of food allergies in children with serum vitamin A deficiency was 10.5%, higher than that in the adequate group (4.2%); the incidence in the vitamin D-deficient group was 11.3%, higher than that in the adequate group (3.8%), consistent with the conclusions of this study [14]. Intervention studies have confirmed the preventive effect of supplementation. The study by Yang Zhuling et al. found that children who started vitamin AD supplementation at 1 week after birth and continued until 1 year of age had a food allergy incidence rate of 3.3%, significantly lower than that in the non-supplemented group (8.7%) [15]. The study by Zhang Xudong et al. also found that maternal vitamin AD supplementation during pregnancy could reduce the risk of food allergies in offspring, presumably related to maternal vitamin AD promoting the development of the fetal immune system and intestinal barrier function through the placenta [16]. Based on the data from this study, the key to clinical translation lies in establishing a comprehensive vitamin AD monitoring and supplementation system spanning from pregnancy to infancy. During pregnancy, mothers should routinely monitor their vitamin AD levels to ensure adequate supply. During infancy, especially in high-risk groups for food allergies (with a family history, premature birth, or a history of intestinal dysfunction), vitamin AD levels should be regularly monitored, and individualized supplementation should be provided to enhance intestinal barrier function and immune tolerance, thereby preventing food allergies from occurring at the source. This full-process intervention model has been piloted in some maternal and child health care institutions, with preliminary data indicating a significant reduction in the incidence of food allergies in offspring and demonstrating the conditions for large-scale promotion.

3. Research progress and translational application of vitamin AD in the treatment of common allergic diseases in children

As an adjunct to conventional treatment, vitamin AD supplementation can improve clinical symptoms and enhance therapeutic efficacy in children by regulating immune function and inhibiting inflammatory responses. Given the correlation between vitamin AD levels and immunity confirmed in this study, its translational application in clinical treatment can significantly improve treatment outcomes and enhance the prognosis for children.

3.1. Allergic rhinitis

Conventional treatment for allergic rhinitis in children primarily involves allergen avoidance, intranasal corticosteroids, and oral antihistamines. However, some children may experience suboptimal efficacy and recurrent symptoms. Studies have found that supplementing with vitamin AD in addition to conventional treatment can significantly enhance treatment outcomes. In the study by Zhang Ning et al., the control group received intranasal mometasone furoate combined with oral loratadine, while the treatment group received vitamin AD supplementation (vitamin A 2000 IU/day, vitamin D 800 IU/

day) in addition to the conventional treatment [17]. After 12 weeks of treatment, the clinical symptom scores (nasal itching, sneezing, runny nose, nasal congestion) in the treatment group were significantly lower than those in the control group, with reduced serum IgE levels, increased IFN-γ levels, and improved Th1/Th2 balance. The study by Gao Nan et al. on children with seasonal allergic rhinitis showed that initiating vitamin AD supplementation one month before the onset of the pollen season significantly shortened the duration and reduced the severity of symptoms, as well as decreased the frequency of rescue medication use [18].

Based on the data from this study, the clinical translation plan is as follows: Integrate vitamin AD level monitoring into the routine diagnosis and treatment procedures for children with allergic rhinitis. For those with vitamin AD deficiency or insufficiency, combine individualized vitamin AD supplementation with conventional treatment, adjusting the dosage based on monitoring results (a recommended initial dosage of 2000 IU/day for vitamin A and 800 IU/day for vitamin D). Continuously monitor serum vitamin AD levels during treatment to avoid over-supplementation. This combined treatment approach has been preliminarily validated in clinical practice, significantly improving symptom control rates and enhancing the quality of life for children, demonstrating its broad potential for application.

3.2. Asthma

The treatment goals for childhood asthma are to control symptoms, reduce acute exacerbations, and protect lung function. Conventional treatment medications include inhaled corticosteroids, long-acting β2 agonists, leukotriene modifiers, etc. However, some children still face issues such as poor symptom control and steroid dependence. Studies have shown that vitamin AD supplementation can aid in the treatment of childhood asthma, improving clinical symptoms and lung function. Liu Rui et al. found that asthma children supplemented with vitamin AD on top of conventional treatment had significantly higher ACT scores after 6 months compared to the control group, with fewer acute exacerbations and significant improvements in lung function indicators such as FEV1 and FVC, as well as reduced serum IL-4 and IL-5 levels and increased IFN-γ levels [19]. Guo Li et al. further confirmed that asthma children who received long-term vitamin AD supplementation had significantly lower doses of inhaled corticosteroids compared to the non-supplemented group, with better symptom control outcomes [20].

Based on the findings of this study, the core of clinical translation lies in the following: monitoring vitamin AD levels should serve as a crucial basis for evaluating the condition and adjusting treatment in children with asthma. For children with vitamin AD deficiency, vitamin AD should be supplemented in conjunction with conventional treatment, with individualized dosage adjustments based on monitoring results. Simultaneously, lung function, inflammatory markers, and vitamin AD levels should be dynamically monitored to optimize the treatment plan. It is important to emphasize that vitamin AD supplementation does not replace conventional therapeutic drugs but serves as an adjunctive measure to enhance treatment efficacy and reduce steroid dependence. This treatment model has been gradually adopted in pediatric respiratory specialties, significantly improving the prognosis of children with refractory asthma.

3.3. Atopic dermatitis

Conventional treatments for pediatric atopic dermatitis include skin care, topical corticosteroids, and calcineurin inhibitors, among others. However, some children experience recurrent episodes, and long-term use of corticosteroids may lead to adverse effects. Research has found that vitamin AD supplementation can aid in the treatment of atopic dermatitis and improve skin symptoms. A study by Cheng Jiawei et al. demonstrated that supplementing vitamin AD in addition to conventional treatment significantly alleviated skin dryness and pruritus symptoms and reduced the recurrence rate in children with atopic dermatitis [21]. Another study by Jiang Meilan et al. found that topical application of tazarotene gel (a vitamin A derivative) combined with calcipotriol ointment (a vitamin D derivative) for treating pediatric atopic dermatitis resulted in a significantly higher efficacy rate and a lower incidence of adverse effects compared to the group using corticosteroids alone [22].

Based on the data from this study, the clinical translation plan is as follows: Routine monitoring of vitamin AD

levels should be conducted during the diagnosis and treatment of children with atopic dermatitis. For children with systemic deficiency, oral vitamin AD supplementation should be administered. Simultaneously, based on the condition of skin lesions, topical vitamin AD derivatives should be applied in combination to form a combined treatment model of "systemic supplementation + local intervention". The supplementation dosage should be individualized (recommended at 1500–2000 IU/day for vitamin A and 400–800 IU/day for vitamin D). During the treatment process, vitamin AD levels and skin symptoms should be regularly monitored to adjust the treatment plan accordingly. This combined approach takes into account both systemic immune regulation and local skin barrier repair, and has demonstrated favorable therapeutic effects in dermatological clinical practice, particularly for children who are steroid-dependent or intolerant, thus holding significant clinical application value.

3.4. Food allergy

The treatment of food allergies in children primarily involves strict avoidance of allergens and symptomatic management. However, some children cannot completely avoid exposure to allergens and require adjuvant therapy to alleviate symptoms and enhance tolerance. Studies have found that vitamin AD supplementation can improve symptoms in children with food allergies and enhance the efficacy of desensitization therapy. Research by Sun Jinlong et al. showed that after vitamin AD supplementation in children with food allergies, the frequency and severity of allergic symptoms significantly decreased [23]. Wang Xia et al.'s study on children with peanut allergies found that desensitization therapy combined with vitamin AD supplementation resulted in a significantly higher success rate of desensitization and a lower incidence of adverse reactions compared to the control group [24]. The mechanism is related to vitamin AD enhancing intestinal barrier function and promoting the formation of immune tolerance.

Based on the findings of this study, the clinical translation pathway is as follows: Routine monitoring of vitamin AD levels should be conducted in children with food allergies, with individualized supplementation provided to those with deficiencies, especially during desensitization therapy, as combined vitamin AD supplementation can enhance therapeutic efficacy. Meanwhile, for children who cannot completely avoid allergens, maintaining appropriate vitamin AD levels over the long term can reduce the frequency of allergic symptom episodes. The supplementation dosage should be adjusted based on age, weight, and monitoring results, with recommended doses of 1500–2000 IU/day for vitamin A and 400–800 IU/day for vitamin D. During treatment, serum vitamin AD levels and allergen-specific IgE levels should be dynamically monitored to optimize the intervention plan. This adjuvant treatment strategy has been gradually applied in pediatric allergy specialties, offering a more comprehensive treatment option for children with food allergies.

4. Summary and clinical translation prospects

Vitamin AD, as a critical limiting nutrient for children's growth and development, establishes its core molecular mechanism and evidence-based foundation in the prevention and treatment of pediatric allergic diseases through multi-target synergistic regulation of immune homeostasis (including Th1/Th2 balance regulation, optimization of Treg cell function, maintenance of mucosal barrier integrity, and precise inhibition of inflammatory responses). Based on a systematic analysis of clinical data from 696 children, this study systematically reveals and quantitatively confirms the key clinical pain point of "high deficiency/insufficiency rates of vitamins A/D under routine fixed-dose supplementation" (with deficiency and insufficiency rates of 64% for vitamin D and 48% for vitamin A). Furthermore, serum vitamin AD levels in children with recurrent respiratory infections and allergic diseases are significantly lower than those in healthy children, providing evidence-based support for the transition from a "one-size-fits-all" approach to a "precision detection-based individualized supplementation" paradigm in the field of pediatric nutritional supplementation.

Combining the data from this study with existing high-level evidence-based research, implementing individualized doses of vitamin AD supplementation during critical windows such as early life and pregnancy, based on risk stratification that considers clinical phenotypes and risk factors (including family history of allergies, premature birth, and a history

of recurrent respiratory infections), can significantly reduce the risk of developing allergic diseases in children, such as allergic rhinitis and atopic dermatitis. As an adjunctive treatment, it can effectively alleviate clinical symptoms, enhance the response rate to first-line treatments, and reduce the risk of drug dependency.

Clinical translation is the core value orientation of this study. Based on existing research findings and the data from this study, the following clinical translation pathways are proposed:

(1) Establish a standardized testing system for serum vitamin A and 25(OH)D (including D2/D3 subtypes) in children, integrating health check-ups for children at high risk of allergic diseases and standardized diagnosis and treatment pathways for children with allergic diseases;

(2) Develop individualized supplementation clinical pathways based on test results (deficiency/insufficiency/sufficiency), dynamically adjusting supplementation doses and durations to avoid the risks of nutritional deficiency or excessive accumulation caused by fixed-dose supplementation;

(3) Construct a closed-loop intervention model of "pregnancy-infancy" full-term monitoring and "prevention-treatment-follow-up" to achieve precise full-term supplementation for high-risk populations, combined supplementation during the treatment period for children with diseases, and dynamic titration of the supplementation plan to improve long-term outcomes;

(4) Establish a collaborative treatment plan combining "systemic nutritional supplementation with local targeted intervention," which, for diseases such as atopic dermatitis, involves combining oral vitamin AD with topical derivatives to optimize clinical treatment outcomes.

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Disclosure statement

The authors declare no conflict of interest.

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