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RESEARCH ARTICLE

THE EFFICACY AND SAFETY OF ORAL IMMUNOTHERAPY FOR FOOD ALLERGIES IN PRESCHOOL-AGED CHILDREN

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Abstract

In the last two decades, food allergy (FA) has emerged as a significant concern, with a continuous rise in prevalence worldwide. Furthermore, increasing awareness about this issue in the general public has prompted rigorous efforts to find long-term solutions to FA. In the pediatric group, most cases of FA are reported during the initial 3 to 5 years. The most common FA in preschoolers include eggs, cow's milk, tree nuts, and peanuts. Conventional approaches for the management of FA include mitigating adverse reactions associated with the consumption of food allergens and avoidance of that particular food allergen. However, constant avoidance remains a challenge, requiring constant due diligence. Therefore, Oral immunotherapy (OIT), an allergen-specific method for managing FA has been introduced. The present review provides an overview of the mechanisms and processes of OIT. The most common OITs studied include peanut, tree nuts, egg, and milk OITs. Furthermore, the literature search yielded significant evidence that showed the safety and efficacy of these OITs. The review also identified the gaps in the literature, which highlight the need for future investigations. Future studies should focus on conducting well-designed clinical trials with larger sample sizes, establishing standardized treatment protocols, investigating immunological mechanisms, and assessing the broader impact of OIT.

Introduction:-

Food allergy (FA) has emerged as a significant concern in the past two decades, with potential economic, social, and individual implications.There is often misperception regarding FA due to different terminologies used interchangeably to describe FA. These terms include hypersensitivity, allergy, intolerance, and pseudo-allergy. Although FA may sound like a simple disease, it is far more multifaceted. It involves adverse immune reactions to food proteins and encompasses a spectrum of clinicopathological conditions rather than being a singular disorder [1].The primary management approach for FA comprisesallergen avoidance and treatment of exposure-related reactions[2]. However,there are certain limitations tothese approaches. For example, practicing avoidance is quite difficult as food allergens comprise common foods. Furthermore, this requires constant monitoring, which could impact the quality of life of affected individuals[3]. Therefore, there is a need for alternate approaches apart from strict avoidance of food allergens. Oral immunotherapy (OIT) is emerging as a promising alternative treatment strategy. It is an allergen-specific methodformanaging FA. OIT is primarily focused onadministering increasing

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doses of the allergentill attaining a maintenance dose,after which a consistent intake of the definite food allergen is required to desensitize the patient to avoidactivating an allergic reaction[4].

Immunoglobulin E (IgE)-mediated FAis risingthroughout the world, with a 50% riseseen in the United States(US) in a very short period[5]. Common allergenic foods are abundant; therefore, their avoidance is challenging. The accidental ingestion of these foods is seen frequently. In the US, almost 40% of kids suffering from FA experience a severe adverse reaction[5].The high prevalence of allergic reactions with significant lifestyle changes poses an economic drain on society and individuals. To counter this increasing burden, FA immunotherapies are gaining popularity, with OIT being the most commonly studied modality. The first OIT drug approved by the US Food and Drug Administration (FDA) for FA was Palforziato help reduce the severity of allergic reactions to peanuts [6].

The primary goal of OIT is the defense against accidentalexposure of a patient to an allergen that can trigger anaphylaxis. OIT must be followed under the course of an allergist as it is not without the risk of some adverse reactions. The adverse effects mostly arise through dose escalation; however, they can also occur at any time during OIT. These negative effects commonly comprise transient abdominal pain and antihistamine-treated oropharyngeal pruritus[5]. However, the most commonly reported beneficial outcomes of OIT trials are sustained unresponsiveness (SU) and desensitization. Desensitization involves raising the reaction threshold to a food allergen during active therapy. In contrast, SU refers to the safe reintroduction of a food after a period of avoidance, specifically following the cessation of OIT.A systemic review and meta-analysis by de Silva et al. reported that OIT improves tolerance in patients. They included 36 studies with 2126 child participants. They further revealed that OIT improved tolerance for peanut (RR 9.9, high certainty), cow's milk (RR 8.9), and egg allergy (RR 8.9). OIT was not associated with increased adverse reactions [7].

There is significant evidence that immunotherapies in preschoolers under the age of 4 lead to improved outcomes. Some latest studies on peanut OIT have displayed SU in more than 70% of preschool participants [8-10]. However,the use of OIT in preschool-age children is controversial. This is because of the natural resolution of many nutritional allergies in such patients. The resolution is more common in egg and milk allergies, which, inmost cases, resolve in early life [6].However, there is a strong argument that the benefits of earlier detection of FA and intervention should outweigh the associated risks. The prospect of achieving remission or desensitization through OIT is compelling.However, the question remains as to whether we have a strong indication ofsustaining the safety and efficiency of OIT. This evidence can relieve the personal, economic, and social burden of FA [6].

By examining the available studies that focus on preschool-aged children, this review seeks to provide insights into the unique considerations, challenges, and outcomes associated with implementing OIT in young children. This literature review aims to explore the current research landscape surrounding the safety and worth of OIT in this vulnerable population.

Background on Food Allergies in Preschoolers

In the pediatric group, FA arises in the first 3 to 5 years of life.The most common allergens that cause FA in 90% of preschoolers include eggs, proteins, wheat, cow’s milk, soy, nuts, peanuts, shellfish, and fish [11]. Preschoolers develop tolerance to milk proteins usually at the age of 3 years (70-80%) and eggs at the age of five (50%) [12].The development of tolerance is less in patients who suffer from shellfish or nut FA. The parents-reported prevalence of FA in preschoolers was reported to be 1.6 to 38.7% in a study. This prevalence was translated into a range of 4.1 to 21.5% positive IgE essay to 3.2 to 4.5% positive skin test range after investigation [12].The global prevalence of FA in preschoolers is assessed to be 4%, with an increased incidence reported in the past two decades [1].

FA poses many negative impacts on children. Most importantly, the health-related quality of life and psychosocial well-being of the children are affected by FA. Recently, Golding et al., in their systemic review, provided evidence of reduced quality of life (QoL) among children with FA, particularly those with more severe clinical manifestations. Their findings showed that FA is linked with significant psychological distress. Qualitative evidence summarized in their review highlighted that psychological consequences stem from fear of exposure external to the home and the social implications of FA [13]. Allergic illnesses are also related to mental health disorders in children. FA raises the risk of somatic disorders in children. School-aged children are affected behaviorally and developmentally due to FA [14]. FA-associated elimination of diets can place a risk of impaired growth, especially with the elimination of milk from the food [15]

Nurturing a child with FA can also lead to low QoL and family functioning. A recent systematic review reported that parents recognized anxiety as the most troublesome form of FA-specific emotional stress [16,17]. Owning to these situations, it is important to look for a possible solution, and early immunotherapy is a potential option to improve long-term outcomes. Extensive reviews of FA immunotherapy trials, primarily focusing on children undergoing OIT, have consistently demonstrated a high success rate of desensitization [6].

General Overview of Oral Immunotherapy

FA-specific immunotherapy, including epicutaneous immunotherapy (EPIT), sublingual immunotherapy (SLIT), and OIT has presented promising treatment of IgE-mediated FA. OIT is the most comprehensively studied modality so far. Peanut OIT is the only treatment for FA that has been approved in the US[18]. Most of the OIT trials applied single-allergen OIT, usually milk, peanut, and egg;however, multi-allergen OIT is also undergoing exploration [19]. Early humoral fluctuations in the course of OIT involve a primary rise in allergen-specific IgE, which ultimately decreases to below-baseline levels as OIT advances. Furthermore, a continuous increase in allergen-specific IGA and IgG4 is noted tolast throughout OIT. Basophil hyperresponsiveness,lowered skin prick test,and wheel size were observed in the first year of OIT. Continuation of OIT after the completion of therapy has been associated with SU [20].

The advancement of natural oral tolerance includes a complicated interplay among cells and tissues resident in the intestinal mucosa. In a retinoic acid-dependent procedure and TGFβ, SD103+ dendritic cells (DCs) move food antigens from the lamina propria to mesenteric lymph nodes. Here, they intermingle with the T-cells and endorse the creation of forkhead box protein 3 (FOXP3) positive regulatory T (Treg) cells. They move to the lamina propria and do an extension, the former of which is reliant on the production of IL-10 by CX3CRI+ macrophages [21]. Other factors like the intestinal microbiome, timing, and dose of antigen revelation also play a role in oral tolerance [20].In food-allergic substances, a break of natural oral tolerance primes to the reduced development of T cells in favor of allergen-specific T_H2 cells. These cells include an allergen-specific T_H2 (T_H2A) subset. These cells produce the T_H2 cytokines IL-9, IL-13,IL-4 and IL-5. During OIT,constant high-dose allergen exposure central to the T_H2 and T_H2A deletion and a rise in governing cells, including IL-10 and Tregs-producing CD4+ cells is also seen [20].

The use of commercially available tests and biomarker profiles such as bead-based epitope and basophil activation testing are reliable tests to predict clinical tolerance threshold. They show promising results but require additional validation and investigation for application in clinical practice and OIT. Furthermore, the OIT protocol is also dependent on the age, dose, and duration of the treatment [5]. The range of food commonly involved in the OIT depends on the treatment plan and the condition of the patients [19].

Specific Food Allergies and OIT

Milk

Cow's milk is one of the most commonIgE-dependent food allergens in children. Cow's milk contains around 30-35g of proteins in one liter. It is composed of more than forty different proteins. Whey and casein account for 20% and 80% of milk proteins in this milk. Most of the children with FAare polysensitized to caseins and whey. This allergen affects 0.5 to 3% of children. Cow's milk allergy usually develops in the first year of life and outgrows with age. OIT can potentially alleviate this FA but treatment requires a long time [22]. The safety and efficacy of using OIT to treat milk FA is still controversial. Maeda et al. investigated the safety and efficacy of OIT in their study. The results of this study suggested that the effect of OIT was 50%; however, the incidence of negative effects was high [23]. However, a similar study found that OIT is a safe procedure for treating milk allergy as the reaction rate was low, and two-thirds of the OIT subjects tolerated cow's milk after OIT [24]. Todoric and Merill in their review found that the target maintenance dose in reported studies was 100 to 250 mL of milk [5].Milk OIT (MOIT) has been studied extensively in children; however, there is a paucity of literature that primarily focuses on MOIT in preschoolers.

Berti et al., in their study, investigated the efficacy of early OIT in children who had cow's milk protein allergy. They included 73 infants below the age of 12 months in their trial. Their findings showed that 97% of the participants reached the target of the protocol, which was defined as the ability to bear 150 ml of cow's milk without any adverse reaction [25]. Similarly, in another study, Calvo et al. retrospectively reviewed the data of 335 infants below the age of one year who were treated with OIT. Their findings showed that 98% of the infants became tolerant to milk allergy and demonstrated no adverse reaction [26]. Mortell et al. also showed evidence of oral desensitization in children aged 24-36 months withcow's milk protein allergy. The study comprised 60 participants

who were divided into two groups: the treatment group (group A) undergoing oral desensitization, and group B was kept on a milk-free diet. The follow-up duration of the study was one year. The findings of the study revealed that in group A, 90% of the participants were completely tolerant compared to group B, in which only 23% developed tolerance [27]. Currently, there is a dearth of research on MOIT exclusively in preschoolers. Most studies included subjects with a wide range of age groups without any sub-group analysis.

Some other estimates suggest that following MOIT, a total of 36% to 97% of patients attained desensitization [28,29]. Higher rates of desensitization were obtained (98%) when a low dose of milk (0.5-10 mL) was increased to 150 to 200 mL in children below one year[26,30]. Moreover, long-term MOIT can raise the tolerance threshold and induce SU and desensitization [31,32]. The introduction of basked milk OIT significantly increased the tolerance threshold and time of desensitization. Patients with cow's milk allergy (70%) tolerated baked milk, and this tolerance may accelerate the resolution of this FA [33]. OIT can also lower life-threatening reactions in milk allergy patients. Badina et al. reported two times lower severe reactions (3.5% vs.6.3%) among people consuming milk throughout OIT than those who quit the protocol. Furthermore, more severe or fatal reactions that require ICU admission were also seen in patients who stopped milk OIT [34]. However, milk OIT is not void of adverse reactions. A previous study found that the most common negative effects that prevented the accomplishment of milk OIT were asthma and acute respiratory symptoms [35]. Lodge et al., in their systemic review,reported that their analyzed 16 studies found the efficacy of OIT for all types of allergens, including peanut (RR 11.32), cow's milk (RR 13.98), and hen's egg (RR 4.67) [36].

Peanut OIT

Peanut allergy is the most common in children who have an instantaneous peanut-allergic family member. There are genetic and environmental factors that lead to the development of peanut allergy. Moreover,genetic polymorphism is linked with this FA, and heritable peanut allergy is estimated to be 81.6%. Racial differences are also connected with the prevalence of peanut allergy. Gender differences also exist, and boys appear more likely to develop peanut allergies than girls. Vitamin D also plays a part in the development of peanut allergy [37]. There are several uncontrolled [38,39] and randomized trials [40-43]that have proved that peanut OIT (POIT) is very efficient at increasing the tolerance threshold and inducing desensitization till 2 to 18 times the maintenance doses. However, this may depend greatly on the frequency and duration of the dosing [39]. Several studies have been conductedon peanut OIT in preschoolers. Jones et al., in their study, studied peanut OIT in children aged between 12-48 months. The participants in the treatment group were given 2000 mg of peanut protein per day. In week 134, 71% of participants in the treatment group developed desensitization, compared to only 2% in the placebo group. Furthermore, participants who received peanut OIT had decreased peanut-specific and Ara h2-specific IgE at 134 and 160-week assessments [41]. SU is less common and dependent on duration and dose as well as on the age of the person when POIT is begun and specific biomarker parameters (specific IgE) [44]. Lower baseline peanut-specific IgE and young age at screening have been reported to predictremission [41]. A recent study that investigated the POIT in a real-world multicenter background reported that POIT was safe for the majority ofpreschoolers. The adverse symptoms were mild and very few, but life-threatening reactions also occurred in a minority of children (0.4%) [45]. Vickeryet al., in their randomized controlled trial,included 40 children aged 9 to 36 months who were either suspected or had peanut allergies. Their findings showed that in the treatment group, 78% achieved SU. They also noted allergic side effects in most cases; however, they were mild to moderate in nature [46]. Similar findings have been shared by Toit et al. in preschoolers who had peanut allergy. They reported that preschoolers who received peanut OIT were more likely to tolerate ≥600 mg of peanut protein compared to placebo (73.5% vs. 6.3%). They further noted that most participants experienced adverse reactions; however, they were comparable between the treatment and placebo groups [47].

Egg OIT

After cow's milk, eggs are the most common food allergy among young children and infants. The estimated prevalence of this FA is 0.5% to 2.5%. Some children remain allergic through their adulthood. About 70% of young children with egg allergy are capable of tolerating baked eggs with low to no symptoms, and most of them will outgrow the allergy throughout their entire lives. These reactions include edema, urticaria, nasal congestion, bronchospasm, and angioedema of the perioral region [48]. The desensitization rates of egg OIT have been evaluated to range from 36% to 94%. The increase in threshold tolerance is seen by 2 to 10-fold. This increase is dependent on age, maintenance dosing regimen, duration of therapy, and protocol design [5]. The introduction of the baked egg at a low level can reduce the rate of unbaked egg allergy. However, these effects are dependent on the duration and dose; however, they have not been evaluated rigorously in a controlled population [49]. A recent study

aimed at investigating long-term OIT in children with anaphylactic egg allergy found that OIT triggered immunological variations and qualified the ingestion of 3100mg of proteins (egg) in half of patients with anaphylactic egg allergy [50]. However, the study included only participants aged above five years. Some other studies included preschoolers in their study; however, they did not perform sub-group analysis for preschoolers specifically. For example, Kim et al., in their study, included children between the ages of 3 to 16 years who were allergic to eggs [51]. They reported that 43.5% of egg OIT participants achieved SU [51]. However, much higher desensitization rates (93%) were reported by Escudero et al. in their study which included subjects between the ages of 5 and17 years [52]. Caminiti et al., in their study which included much younger participants (4-11 years), found that all the participants achieved desensitization after four months of egg OIT treatment [53].

Tree Nuts OIT

Tree nuts include any nuts that are grown on trees, including walnuts, pistachios, almonds, cashews, etc. The prevalence of tree nut allergy is reported to be 4.9% globally and 1 to 2% in North America. The prevalence of this FA varies on a geographical basis and is more prevalent in the United States and Europe. Cashew is the most common trigger of FA anaphylaxis (32.8%), followed by hazelnut and walnut (20% and 11.5%) respectively [54]. Several studies have shown that hazelnut, cashew, and walnut OIT can induce desensitization and raise the tolerance threshold. However, they require a longer duration of the therapy.Cashew and walnut OIT can also desensitize coallergic tree nuts [5]. Tree nuts OIT has also been conducted in preschool children. A study conducted by Erdle et al. investigated the safety and efficacy of tree nut OIT in preschool children.Their findings showed that 96.7% of the participants achieved tolerance after tree nut OIT. They further showed that 70.7%of children had reactions [54]. Baaske et al., in their study, investigated the safety of tree nut OIT. They enrolled 48 preschool children in the tree nut OIT arm of the study. The findings of the study showed that 76.4% of patients on tree nut OIT developed adverse reactions; however, the majority of the reactions were mild/moderate [55].

Overall Discussion:-

A review of the most robustly designed RCTs found that OIT for milk, peanut, and egg has a good efficacy for remission and desensitization. Numerous methodological issues about RCTs of oral immunotherapy may interfere with the quality of evidence. RCTs are a gold standard for determining how interventions work. This is because of their capability to deal with unknown and known confounders, leaving a few common associations [36]. Currently, there is a paucity of literature regarding the use of OIT in preschool children. The majority of the studies identified in the literature perform combined studies on children without any sub-group analysis for preschoolers. Table 1 summarises the findings of various studies on OIT in preschool children.

Table 1:- Characteristics of studies that focused on different OITs in preschool children.

Author and year	Country	Type of allergy	Number of participants	Age	Intervention	Outcome	Adverse Effects	Findings
Berti et al. (2019) [25]	Italy	Milk	73	3 to 11 months	Maximum dose:150 mL	Complete desensitization was achieved in 97% of patients.	_	The majority of the preschoolers developed milk tolerance.
Calvo et al. (2021) [26]	Spain	Milk	335	Less than 1 year	Starting dose 0.5 ml; final dose 150–200 ml of infant formula	98% achieved tolerance to milk	No serious adverse reaction	Milk OIT is safe and effective

Martorell et al. (2011) [27]	Spain	Cow's milk protein allergy	60	24-36 months	200 mL of cow's milk	90% of the participants in the milk OIT group and 23% in the placebo achieved tolerance	80% developed some type of reaction; 47% had moderate reaction; 33% had a mild reaction	Milk OIT is effective in 2-year children
Jones et al. (2022) [41]	United States	Peanut allergy	Treatment group: 146 Placebo: 50	1-4 years	5000 mg	Desensitizationwas achieved in all the patients receiving POIT	Negative effects were seen in 98% of POIT and 80% of placebo group patients.	Initiation of peanut OIT before the age of 4 was linked with increased remission and desensitization.
Soller et al. (2019) [45]	Canada	Peanut allergy	270	9 to 71 months	300 to 320 mg	243/270 reached maintenance	67.8% of the children developed reactions	Life-threatening reactions were seen in only 0.4% of the cases
Vickery et al. (2017) [46]	United States	Peanut allergy	40	9 to 36 months	3000 mg/day peanut protein	78% in the treatment group achieved SU	No treatment-related adverse events	Even at high doses, peanut OIT has an acceptable safety profile
Toit et al. (2023) [47]		Peanut allergy	Treatment group(n=98); placebo group (n=48)	1 to <4 years	≥600 mg peanut protein	Treatment vs placebo (73.5% vs. 6.3%) achieved SU	93.2% had mild to moderate reactions	Treatment for 12 months was effective and safe
Uhl et al. (2024) [56]	Sweden	Peanut allergy	N= 75 Peanut OIT: 50 Control: 25	1-3 years	2750 mg peanut protein	A high degree of desensitization was achieved in the POIT group.	79% mild adverse effects and 1.4% severe effects were seen in the POIT group.	In preschool children, POIT seems safe and effective.

Erdle et al. (2023)[54]	Canada	Tree nut OIT	92	-	300 mg of tree nut protein	96.7% of the participants achieved tolerance after tree nut OIT	70.7% of children had reactions	Preschool tree nut OIT is safe in a multicenter setting
Baaske et al. (2022)[55]	Canada	Tree nut OIT	148	(0-71 months)	-	-	76.4% of patients had adverse reactions	Most reactions to tree nut OIT are mild or moderate

Research Gaps and Future Directions

There are only a few studies that specifically investigated the preschool age group and have shown promising results in desensitizing preschoolers to allergenic foods through OIT, with some representing significant improvements in tolerance levels. There is a need for more robust, well-controlled clinical trials with larger cohorts of preschool-aged children to provide more conclusive evidence on the benefits and risks of OIT in this population. The impact of OIT on the psychosocial well-being, quality of life, and dietary habits of preschool-aged children undergoing treatment is an important area that has been underexplored in the literature.However, this area needs further exploration. The mechanisms underlying the immunological changes induced by OIT in preschoolers are not well understood. The optimal dosing regimens, treatment protocols, and monitoring strategies for OIT in preschoolers remain unclear. Future research should focus on identifying the most effective and safe dosing protocols tailored specifically to preschool-aged children, taking into account their unique physiological and immunological characteristics.

Conclusion:-

The existing research has provided valuable insights into the safety and efficacy of OIT. However, in the case of preschoolers, we found a limited amount of data.Several research gaps need to be addressed to advance our understanding of this treatment modality in this vulnerable population. Future studies should focus on conducting well-designed clinical trials with larger sample sizes, establishing standardized treatment protocols, investigating immunological mechanisms, and assessing the broader impact of OIT on the well-being of preschoolers to fill these gaps and improve the clinical management of food allergies in young children.

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