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DIETARY STRATEGIES FOR PRIMARY PREVENTION OF ATOPIC DISEASES – WHAT DO WE KNOW?

STRATEGIE ŻYWIENIOWE W PIERWOTNEJ PREWENCJI CHORÓB ATOPOWYCH – CO WIEMY?

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Abstract

The paper refers to the recently published empirical data and systematic reviews on the impact of diets, foods, nutrients and bioactive substance exposures in pregnancy and in early infancy, on the development of atopic disorders. The results of studies referring to a broad range on dietary factors are mostly conflicting. There are several limitations of these researches. Based on the existing information, it is not possible to establish the role of antioxidants and vitamin D supplementation in atopic disease development. There is no evidence of major effects of prenatal use of folic acid on asthma or allergies. The association of some nutritional interventions with less atopic sensitization seems rather speculative even if such an effect has not been found for some other foods. The findings indicate rather a balanced and diverse diet without restrictions than a special dietary protocol. Farming-related exposures may protect against the development of atopic disorders in children. The hypothesis that the early introduction of complementary food, including the potentially allergenic foods, may reduce the risk of food allergy and atopic dermatitis is currently tested. Long-chain polyunsaturated fatty acids and probiotics seem to be promising candidates for allergy prevention. But specific recommendations regarding pre- and postnatal supplementation strategies, dose, treatment duration etc., are still undetermined. Longitudinal intervention studies in cohorts of pregnant women or newborn infants are needed to match the proper strategies in these issues.

Key words: allergen avoidance, allergen exposure, pregnancy, infant

Streszczenie

Artykuł dotyczy nowo opublikowanych danych doświadczalnych i przeglądów systematycznych na temat diety, pokarmów, składników pokarmowych oraz substancji bioaktywnych stosowanych w ciąży oraz w okresie wczesnego niemowlęctwa i ich wpływu na rozwój chorób atopowych. Wyniki badań nad oddziaływaniem różnych czynników dietetycznych są często sprzeczne. Prace badawcze charakteryzuje szereg ograniczeń. Na podstawie dostępnych informacji nie można ustalić roli antyoksydantów i witaminy D w rozwoju chorób atopowych. Prenatalne stosowanie kwasu foliowego nie ma istotnego wpływu na astmę i alergie. Dane na istnienie związków pomiędzy pewnymi sposobami żywienia a mniejszą atopową sensytyzacją wydają się raczej wynikać ze spekulacji, nawet jeżeli określonego efektu nie wykazano w stosunku do innego składnika diety. Badania przemawiają bardziej za prowadzeniem dobrze zbilansowanej i zróżnicowanej diety bez restrykcji, niż określonym sposobem żywienia. Ekspozycje związane z zamieszkaniem na wsi mogą chronić przed rozwojem chorób atopowych. Obecnie prowadzi się badania nad hipotezą, że wczesne wprowadzanie do żywienia dziecka pokarmów uzupełniających, w tym potencjalnie alergizujących, może przyczyniać się do zmniejszenia ryzyka wystąpienia alergii pokarmowej i atopowego zapalenia skóry. Długołańcuchowe wielonienasycone kwasy tłuszczowe i probiotyki wydają się być obiecującymi kandydatami w prewencji alergii. Jednakże, szczegółowe

rekomendacje dotyczące pre- i postnatalnych strategii suplementacji, dawek, czasu trwania itd., nie są jeszcze określone. W tym celu konieczne są długofalowe badania interwencyjne obejmujące kohorty kobiet ciężarnych i noworodków.

Słowa kluczowe: eliminacja alergenów, ekspozycja alergenowa, ciąża, niemowlę

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INTRODUCTION

In recent years, there has been a worldwide increase in the prevalence of atopic diseases. Several factors are suggested to be involved, including genetic background, individual immune response as well as outdoor and indoor environment, lifestyle, dietary intake, microbial exposure, economic status and awareness of disease. Environmental pollutants such as tobacco smoke, diesel exhaust particle or volatile organic compounds are supposed to exacerbate allergic immune responses. However, an exposure to environmental factors may not only exert allergy-promoting effects but may also be protective. Some recent reviews explore the immunological mechanisms of atopic disease, rural-urban enigma and role of gut microbiota in the development of allergy [1, 2]. The prenatal period and the early stages of extrauterine life are periods of time when maturation of the immune system and of other body systems is attained. Atopic predisposition in mothers contributes considerably more than such predisposition in fathers to allergic disease in the offspring. This suggests that the mother's immune system may educate the offspring by other means than genomic heritage. Maternal allergen immunisation during gestation substantially reduces the allergen-specific IgE response in adult offspring exposed to the same allergen [1]. Furthermore, the development of allergic disease may be mediated by the variations in innate immunity receptor genes that can influence the mRNA expression of these genes or receptor-mediated cytokine production [3]. The neonatal Toll-like receptor (TLR) system is critical in the programming, maturation, and patterns of T-cell development [3]. Thus, early immune function and future allergy susceptibility appear to result from a combination of maternal phenotype, infant genotype, and environmental exposures in utero that affect early gene expression. Therefore, strategies for primary prevention of allergy might ideally start in prenatal period and early childhood.

The paper refers to the recently published empirical data and systematic reviews on the impact of diets, foods, nutrients and bioactive substance exposures in pregnancy and in early life on the development of atopic diseases. The goal of literature retrieval and choosing articles are to bring the reader up-to-date with the current relevant studies and to identify gaps and inconsistencies in the area.

FARMING ENVIRONMENT

It has been shown that maternal exposure to various animals and to an environment rich in microbial compounds, for example, prevalent in farm settings, may protect against the development of atopic sensitization in children, reviewed in reference [1]. In addition, maternal and infant consumption of unprocessed cow's milk was repeatedly associated with protection from childhood asthma and allergies [1]. Farming-related exposures were associated with a change in gene expression of innate immunity receptors in early life [3]. Farming status of pregnant mothers was associated with increased gene expression of TLR7 and TLR8 receptors at birth [3]. The child's consumption of raw farm milk during the first year of life was associated with increased gene expression of TLR4, TLR5, and TLR6 receptors at year 1 [3]. The TLR-mediated innate response pathways are believed to be important in promoting regulatory pathways that inhibit the allergic immune response [3]. Higher expression of certain TLRs may lead to higher interleukin-10 production in farmers' children [3].

DIETARY ANTIGEN AVOIDANCE DURING PREGNANCY OR LACTATION

According to Kramer and Kakuma, an antigen avoidance diet by a high-risk woman during pregnancy is unlikely to substantially reduce her child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition, or both [4]. Such a procedure during lactation may reduce child's risk of developing atopic dermatitis (AD) and severity of the disease in infants with AD, but larger trials are needed [4]. Maternal cow's milk avoidance during breastfeeding resulted in lower levels of cow's milk-specific IgA, which were associated with the development of cow's milk allergy in infants, suggesting that prophylactic maternal dietary restrictions may in fact be detrimental in the development of neonatal oral tolerance [5]. At this time, the European and American guidelines state that avoidance diets during pregnancy and lactation are not recommended.

ANTIOXIDANT HYPOTHESIS AND DIET RICH IN VITAMINS A, E AND C, COPPER, ZINC SELENIUM, FLAVONOIDS AND OTHER POLYPHENOLS

The existing evidence on the beneficial effects of antioxidants for atopic diseases prevention is weak and data are inconsistent. Allan et al. showed that low maternal vitamin E intake during pregnancy was associated with

increased risk of children developing asthma in the first 10 years of life [6]. A significant correlation between prenatal vitamin E and zinc intake and a reduction of wheezing in the first two years of life was revealed by Litonjua et al. [7]. According to Maslova et al., maternal vitamin A and E intake protected against child allergic rhinitis [8]. Study of West el al. suggested that maternal diet of fresh foods rich in vitamin C was associated with reduced risk of infant wheeze, and that copper intake was associated with reduced risk of several allergic outcomes [9]. But the authors were unable to show a relationship between β-carotene, vitamin E or zinc and any allergic outcomes [9]. There was no relationship between an extra intake of vitamin C and beta-carotenes in pregnant women and the reduced risk of posterior wheezing in their offspring in Allan's et al. study [6]. Elevated selenium levels during pregnancy and in umbilical cord blood were associated to a decreased risk of early wheezing in the first two years of life, but no such effects were seen at five years of age [10]. Systematic review and meta-analysis of Nurmatov et al. found the beneficial effects of fruits and vegetables in maternal diet for the prevention of asthma and allergic disorders in the offspring [11]. Beneficial results regarding apples consumption (but not with total fruit intake) during pregnancy in relation to wheezing and asthma at five years of age was recorded in the study of Willers et al.[12] It is however not clear whether these effects can be ascribed to the elevated polyphenol uptake or to prenatal exposure to antigens that leads to tolerance. In a Finnish prospective study, low maternal consumption of leafy vegetables, malaceous fruits, and chocolate during pregnancy increased the risk of wheezing in the offspring at 5 years of age [13]. On the other hand, high consumption of fruit and berry juices was a risk factor for development of allergic rhinitis [13]. Depner et al revealed associations of atopic sensitization in the first year of life with the consumption of fruits during pregnancy, which appeared to be a risk factor for IgE to seasonal allergens [14]. An explanation might be found in cross-reactivity of pollen allergens with the Bet v 6 – called a "defense-related protein"- or Bet v 2- profilin-related allergen. Cross-reactivity to pathogenesis-related group 10 protein (PR-10) molecules, like Mal d 1 from apple with Bet v 1, is also important. Thus, novel antigen exposure et certain doses during nursing life may lead to sensitization.

There are several limitations of the studies relating dietary intakes of antioxidants. As with all observational studies assessing effects of specific antioxidants there is potential confounding related to the issue of concomitant intakes of other protective nutrients. The potential molecular mechanisms of polyphenol supplementation on allergic responses as well as structure-function relationship are still elusive. Polyphenolics, specifically flavonoids, are attributed both antiallergic and proallergic properties depending on the specific flavonoid studied. Furthermore, the level of phytochemicals in fruits and vegetables depends on various factors, namely, species, variety, growing conditions, seasonal variations, maturity index, processing methods, and storage conditions.

FOLIC ACID SUPPLEMENTATION

There are conflicting results whether folic acid intake before and/or during pregnancy is linked with an increased risk of allergic disease in the offspring. In some studies, exposure to folic acid supplementation was associated with a moderate increase in the risk of lower respiratory tract infections, asthma, wheezing or eczema [15]. Data were equivocal. Infants who developed eczema did not show any differences in cord blood or maternal folate levels compared with children without disease [15]. Maternal folate exposure in pregnancy and childhood asthma and allergy was recently reviewed by some authors [16]. The findings from meta-analysis did not reveal any association between folic acid supplementation in pregnancy and asthma risk in children [16].

VITAMIN D SUPPLEMENTATION

The role of vitamin D as a risk factor for atopic diseases is still unclear. An association between low maternal vitamin D and increased infant atopic diseases derives from studies based on estimates of vitamin D by dietary questionnaires report, whereas those studies that have measured maternal serum vitamin D levels in late pregnancy or in cord blood are more conflicting. Allen et al. showed that vitamin D insufficiency was significantly associated with an increased risk of food sensitization and food allergy at age 12 months [17]. Low maternal vitamin D intake during pregnancy was also associated with increased risk of developing asthma in the first 10 years of life [6]. However, the recent analyses revealed a positive association between maternal or cord blood vitamin D level and risk for food allergy in infants up to 2 years of age [18]. According to Miyake et al., higher maternal intake of vitamin D during pregnancy increased the risk of infantile eczema [19]. Similar results were obtained by Hansen et al.: a high maternal vitamin D concentration was associated with an increased risk of allergic diseases in offspring [20]. It is suggested that it might be due to an inhibition of regulatory T cell numbers at birth [18]. But some evidence exists that vitamin D can also induce regulatory T cells [18]. A randomized controlled trial was performed by Goldring et al. but it was not adequately powered for clinical allergy outcomes [21]. In this study prenatal vitamin D supplementation in late pregnancy that had a modest effect on cord blood vitamin D level, was not associated with decreased wheezing in offspring at age three years [21]. The effect of maternal vitamin D supplementation during pregnancy on allergic disease outcomes is currently evaluated in RCTs (NCT00920621 and NCT00856947). These RCTs are larger (600 -870 women) and are using higher doses (2400 or 4000 IU/day) of maternal vitamin D supplementation during pregnancy.

LONG-CHAIN POLYUNSATURATED FATTY ACIDS (LC-PUFA) AND FISH CONSUMPTION

There are numerous studies indicating the benefits of fish oil in prevention of allergic disorders and providing valuable

insight into the immunological changes that underlie the effects seen. But some of studies and systematic reviews did not identify any effect or identified only weak effects. D'Vaz et al. assessed the effect of fish oil supplementation from birth to 6 months on infant allergic disease for whom clinical follow-up was completed at 12 months of age [22]. While a relatively high LC-PUFA status at 6 months was somewhat associated with reduced allergic outcomes, direct postnatal fish oil supplementation was not effective in preventing sensitization, eczema, asthma, or food allergy [22]. Moreover, the Munich LISA plus birth cohort study with data on repeated measurements of fatty acids during a period of 10 years failed to show strong and consistent associations [23]. Probably because as this study it was not an interventional study. As it is unlikely that pregnant and lactating women would be able to achieve the intakes of LC-PUFA used in the most effective studies through the diet, omega-3 supplementation may still be an option and the proportionally large intake of omega 6 LC PUF it may have a significant bearing on the possible influence of prenatal omega 3 LC PUFAs on the development of atopy in the offspring. Dose, timing and duration of LC-PUFA supplementation are important considerations and worthy of further investigation. Combined pre- and postnatal supplementation strategies could be potentially most effective.

HYGIENE HYPOTHESIS AND USE OF PROBIOTICS

Increasingly, the hygiene hypothesis is being modified by the "gut microbial deprivation hypothesis", with its emphasis on alterations of indigenous gut microbiota during infancy. The gut microbiota and its role in the development of allergic disease was recently reviewed by West et al. [2]. Some associations between low rates of Bifidobacteria or Lactobacilli colonization and later allergy development as well evidence for early Clostridium difficile colonization during infancy as its risk were found [2]. But it seems that early establishment of a diverse gut microbiota, with repeated exposure to new bacterial antigens, may be more important in shaping a normal immune mucosal and systemic maturation [2]. Thavagnanam et al. found a 20% increase in the subsequent risk of asthma in children who were delivered by Caesarean section (CS), which were shown to delay and alter the development of intestinal bacterial flora [24]. Infants born by elective cesarean delivery had particularly low bacterial richness and diversity [25]. The more long term effects of CS on gut microbiota development were studied by Bäckhed et al. [26]. In contrast to vaginally delivered infants, the gut microbiota of infants delivered by CS showed significantly less resemblance to their mothers [26]. CS was associated with a lower total microbial diversity, delayed colonisation of the Bacteroidetes phylum and reduced Th1 responses during the first 2 years of life [26].

The aim of use of probiotics is to develop tolerance mechanisms through modification of the immune response of the foetus or nursing infant. The results of studies regarding the effects of probiotics provided in the last weeks of pregnancy and in the first few months of life are very different. Some authors reported no protective role of probiotics against allergic processes, particularly AD [27]. On the other hand, in the Norwegian Mother and Child Cohort study consumption of probiotic milk in pregnancy was related to a reduced incidence of AD and rhinoconjunctivitis, but no association was seen for incidence of asthma by 36 months of age [28]. The preventive effect on sensitisation was only observed in studies with combined pre- and postnatal supplementation and not in studies with postnatal supplementation alone [29]. Such supplementation strategies were suggested as potentially most efficacious [29]. However, randomised controlled trials to date have not yielded sufficient evidence to recommend probiotics for the primary prevention of allergic disorders [29]. Actually, the Nutrition Committee of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) does not support routine supplementing with probiotics in infant formulas. The new World Allergy Organization (WAO) guidelines suggest that probiotics should be recommended in mothers of high-risk infants and in infants at high risk of allergic disease. The recommendations are conditional and based on very low quality evidence, with no specific recommendation regarding strains, dose, treatment duration etc. Further scientific confirmations are required to include probiotics and prebiotics in the therapeutic plans.

PROLONGED BREAST-FEEDING

The effect of breast-feeding on the risk of developing atopic disease remains controversial. Some studies suggested that breast-feeding for 4-6 months could reduce the burden of allergic manifestations and infections in infancy [30]. But according to Nwaru et al., the nature of infant feeding during the first 6 months seemed not to substantially influence the long-term risk of asthma and atopic diseases in children, nor in children at high risk of atopic disease because of family history of atopic disease [31]. Morales et al. assessed the impact of predominant breast-feeding duration and colostrum LC-PUFAs profile on the risk of allergic manifestations (wheezing and AD) and infections [low respiratory tract infections (LRTIs) and gastroenteritis] in infancy [32]. Beneficial effects of breast-feeding on gastroenteritis were found but no significant effects were found on risk of allergic manifestations or LRTIs [32]. According to Zhang et al. breast-feeding influenced the expression of inflammatory symptoms associated with respiratory infections and atopy in early life, but these effects appeared to be inconsistent and transient [33]. In the study of Jelding-Dannemand et al., exclusive breast-feeding did not affect sensitization in early childhood or associated diseases at 7 years of age in at-risk children [34]. Recently, an interesting paradox has been presented: breast-feeding promotes lower intestinal microbiota diversity, and low diversity is associated with an increased risk of atopic disease [25]. New data indicate that prolonged breast-feeding may increase the risk of AD in children <5 years of age, regardless of parental history of atopic diseases [35]. If early introduction of allergenic foods at 3 months of age

alongside breast-feeding vs exclusive breast-feeding for 6 months may reduce the risk of food allergy and AD, this hypothesis deserves further investigation. Despite controversial data, the overall benefits of breast-feeding on the general health of the child are likely to outweigh the potential drawbacks and exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age for primary prevention of atopic disease.

EARLY INTRODUCTION OF COMPLEMENTARY FOOD

Increasing evidence suggests that early introduction of complementary food, like the introduction of fish before 1 year of age or early exposure to cow's milk, may have a protective effect against allergic diseases. Protective effect of the introduction of any complementary food within the first 4 months on AD but only among children with allergic parents was found by Sariachvili et al. [36]. Similar results were obtained by Nwaru et. al.: less food diversity as already at 3 months of age increased the risk of atopic sensitization [37]. These results were particularly evident among high-risk children when the results were stratified by atopic history, indicating the potential for reverse causality [37]. Roduit et al. study showed that children exposed to complementary foods, especially yogurt, and an increased diversity of foods within the first year of life had a reduced risk of AD independently of parental history of allergies [38]. An increased diversity of food during the first year of life had a protective effect on asthma, food allergy, and food sensitization and was associated with increased expression of a marker for regulatory T cells [38]. The early introduction of cereals emerged as a protective factor for sensitization to inhalant allergens [14]. One could speculate that the antioxidant properties and prebiotic potential of cereals could modify the immune response to allergens and protect against manifestation of atopic disease. The findings from studies regarding IgE-mediated food allergy in children showed that early contact with food induced tolerance and desensitisation to foods [39]. According to the European Academy of Allergy and Clinical Immunology (EAACI) Guidelines for Food Allergy and Anaphylaxis, there is no need to avoid introducing complementary foods beyond 4 months, and currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity. In light of the significance of the results of the LEAP study, interim guidance on early peanut introduction and the prevention of peanut allergy in high-risk infants were recently published [40].

SUMMARY AND CONCLUSIONS

The link between prenatal and early postnatal dietary factors and allergy morbidity is not well established. The findings on the impact of diets, foods, nutrients and bioactive substances exposures in pregnancy and in early infancy on the development of atopic diseases in future are mostly conflicting. They indicate rather a balanced and diverse diet than a special dietary protocol. The evidence of the association of some nutritional interventions with less atopic sensitization seems rather speculative even if such an effect has not been found for some other foods. There are several limitations of these researches. The directions of the associations are not always clear. The alternative mechanisms could be at play here. There are needs to be specific interpretation of the data in relation to the many different "allergic" outcomes. Researchers should also be careful with the ages of outcome assessment since age matter very much for these outcomes. The data needs to be interpreted and mechanism suggested that are pertinent to the backdrop of a human pregnancy. Mechanisms in growing or fully-grown adults may not be relevant.

Based on the existing information, it is not possible to establish the role of antioxidants and vitamin D supplementation in atopic disease development. There is no evidence of major effects of prenatal use of folate on asthma or allergies. Farming-related exposures may protect against the development of atopic disorders in children. The hypothesis that the early introduction of complementary food, including the potentially allergenic foods, may reduce the risk of food allergy and AD deserves further investigation. LC-PUFAs and probiotics seem to be promising candidates for allergy prevention. But specific recommendations regarding pre- and postnatal supplementation strategies, dose, treatment duration etc., are still undetermined. Longitudinal intervention studies in cohorts of pregnant women or newborn infants are needed to match the proper strategies of dietary intervention for primary prevention of atopic diseases.

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