Plant Archives

THE ROLE OF IL-4, IL-10 AND SPECIFIC IGE IN A SAMPLE OF IRAQI FOOD ALLERGY PATIENTS

Entisar Manfi Ahmed[1] , Talib Abdulah Hussein[1] and Suaad Almas Barkhas[2]

[1]Department of Biology, College of science for women, University of Baghdad, Iraq

[2]Clinical immunology laboratory, Specialized Center of allergy in Baghdad, Al- Russafa, Iraq

Email: entisarm.ahmed@gmail.com

ABSTRACT

This study is designed to shed light on the role of IL-4, IL-10, and specific IgE for 10 food allergens. The total food allergic patients have been 60 within the age group (3-72) years, and Apparently Healthy Control (AHC) 28 samples. Their age group (8-66) years. The groups have been collected from the Specialized Center of allergy in Baghdad /Al-Russafa and the AL-Zahra Specialized Center for Allergy and Asthma in Karkh during the period from October 2019 to March 2020. Some immunological changes were studied including (IL-4, IL-10 and specific IgE) which measured by using Enzyme Linked Immunosorbent Assay (ELISA) for all subjects. The results showed that there were significant differences between the number of patients who had immunoglobulin specific to food sensitivities (Specific IgE) and the healthy people with a negative result of food allergy to (bananas, meat, chicken, eggs, cheddar cheese, cow's milk, tomato, potato, green pea, and chocolate). Bananas recorded the highest incidence of food allergy, followed by chicken then meat and egg, while the Potato and Chocolate recorded the lower percentage. Highly significant increase in Interlukin4 (IL-4) level in food allergy patients compared with the control group, and there were no significant differences in the level of Interlukin10 (IL-10) when comparing the patient group and the healthy control group, in addition there was a positive correlation between IL-4 and IL-10 (r = 0.569), (P= 0.01).

Keywords : Food allergy, specific IgE, IL-4, IL-10

Introduction

An allergy was originally defined by Clemens von Pirquet in 1906 as "changed reactivity", to mean the body's increased ability to react to the foreign substance. Today the term allergy means an over-sensitivity to a foreign substance which is normally harmless (Al-jebori, 2014). Hypersensitivity is the global term describing not tolerating an environmental factor tolerated by the majority. Hypersensitivity can be mediated either by an immunological mechanism, i.e., allergy, or by non-immunological mechanisms. It does not include infection, autoimmunity or toxic reactions (Rahman, 2017). Hypersensitivity reaction: refers to a state of change reactivity in the body mounts against an antigen with enhancing immune response. A hypersensitivity reaction is classified into four classes (Type I, II, III, IV) each with different biological behavior (Hong, 2019).

Immunoglobulin E (IgE) has been known for several years as the main molecule in the mediation of what are now called hypersensitivity reactions of type 1. Studies have shown a relationship between allergens with allergic disease and the findings represent a strong link between specific immunoglobulin E or total IgE antibodies and allergic conditions (Al & Abdulla, 2013). Experimental evidence showed that IgE is involved in immediate and delayed hypersensitivity-reactions triggered, Playing a critical role in antigen processing and stimulation of T lymphocytes via Antigen-Presenting Cells (APCs) (Abd al-wahaab, 2007).

A food allergy (FA) is defined as a harmful effect occurring from a specific immune response, which happen reproducibly on exposure to a given food after two hours and can produce the sudden onset of itching, hives, swelling of the face, tongue, or back of the throat that may be accompanied by difficulty breathing and hypotension (Carrard *et al.,* 2015; Sicherer& Sampson, 2018). It may occur in every organ but the most common in the skin (urticaria) (Savic *et al*., 2020; Kliene-Tebbe & Davies, 2014). Allergens are antigens that induce allergies. The majority of allergens that react with IgE and IgG antibodies are proteins, mostly with side chains of carbohydrates. However, pure carbohydrates were believed to be allergens in some circumstances (Puc, 2003).

Interleukin-4 is the inflammatory response of type II signature cytokines. It is a key player in the inflammatory or allergy responses that is caused by an aggressive parasite or allergens (Egholm *et al*., 2019). It has a critical role in regulating Th0 cell differentiation, and IL-4-driven Th_2 cells guide host responses to parasite infections (Hasoon, 2019).

IL-10 family cytokines that also contain (IL-19; IL-20; IL-22; IL-24; IL-26; IL-28; and IL-29) exercise important roles to maintain homeostasis of tissue during infection and inflammation by reducing excessive inflammatory responses, upregulating innate immunity, and promoting tissue repair mechanisms (Ouyang & O'Garra, 2019 ; Perucha *et al.,*

2019). IL-10 reduces late reaction and eosinophil and lymphocyte influxes; IL-10 could have beneficial effects on allergic diseases. IL-10 is mainly produced from macrophages (Trifunović *et al.*, 2015), and it inhibits eosinophilia via the suppression of IL-5 and GM-CSF and via its direct effect on eosinophil apoptosis (Wilson *et al.*, 2020).

In general food allergies can be divided into two major division (IgE-mediated and non-IgE-mediated) (Olivier, 2013).

IgE-mediated disease: are normally of speedy stimulate with generally developing clinical symptoms during minutes to little hours of ingestion (Anvari *et al.*, 2019). This food allergy group is correlated with the possibility of severe or lethal reactions (Yu *et al.*, 2016).

Non- IgE-mediated disease: is usually chronic and can be very hard to manage with food avoidance alone than IgE-mediated disease. Many of Allergies to known non-IgE -mediated foods mainly affect the gastrointestinal tract, not the skin and respiratory tract. Such as, allergen-specific T cells in the largely unknown aetiologies are thought to have roles of Food Protein-Induced Enterocolitis Syndrome (FPIES), Food Protein-Induced Proctocolitis (FPIP) and Food Protein Enteropathy (FPE). FPIES, FPIP and FPE primarily include children and infants allergic to cow's milk and resolved usually after (one- five) years (Nowak-Węgrzyn *et al.*, 2015).

As already mentioned, more than 170 food allergens are well known to cause allergic responses in humans (Taylor, 2000). Moreover to the eight food or food categories, the United States considers for (ninety percent) of severe reactions of allergy include: eggs; milk; fish (e.g.; salmon; flounder; and cod), crustacean shellfish (e.g.; crab; lobster; and shrimp); wheat; soy; peanuts; and tree nuts (e.g.; walnuts; almonds; and pecans) (Gupta *et al.*, 2011).

Material and Method

The study has included 60 patients with food allergy aged between (3-74) years with a mean age is 33.1 years. Patient samples obtained from Baghdad/Al-Resafa Specialized Center Of Allergy and Al-Zahraa Center of Allergy in Baghdad/Al-Kargh during the period from October 2019 to March 2020. Specialized physicians in dermatitis diagnosed these cases, which are clinically diagnosed according to international criteria. The study also included 28 relatively stable people in control with mean age 35.11 years.

Five ml of blood have been taken from each subject by using disposable plastic syringes under sterile conditions. they collected in the gel tube and left at room temperature (20-25°C) before coagulated. It had been centrifuged at 3000 rpm for 5 minutes after blood clotting and then divided the serum into equal parts in Eppendorf tubes for immunological testing (S IgE, IL-4 and IL-10) and kept at -20°C (Bain *et al.*, 2016).

Determination of Allergen Specific IgE in the Serum of Patients and Control

The DR.FOOK profile kit is projected for the detection of specific IgE (s-IgE) *in vitro* to diagnoses the different type of food allergen. It is a multi-parameter assay that contains10 of the most common Iraqi food allergens (Euroimmune *et al.*, 2006). As listed in the table (1).

Table 1 : The Antigens Abbreviations.

Series	Allergen Code	Name of Allergen
1	F2	Cow's milk
2	F1	Egg white
3	F75	Egg yolk
4	F81	Cheddar- cheese
5	F27	Beef
6	F83	Chicken
7	F29	Banana
8	F52	Chocolate
9	F25	Tomato
10	F35	Potato

Detection of the Serum level of IL-4 and IL-10 in patients and control serum.

There is detection of cytokines level in the serum of patients (60 with food allergy and 28 healthy control). Two cytokines (IL-4, IL-10) have been detected according to the Mybiosource ELISA kit procedure.

Data Analysis

The data of this study were analyzed for normality, homogeneity and normal distribution firstly to determine the suitable statistical tests for calculating the mean, standard error and the probability (two-tailed) by using student T-test, ANOVA test, Pearson's chi- square test and Pearson's correlation via using the IBM SPSS version 26.0 (1). The probability considered significant when it ≤ 0.05.

Results

Serum Level of Specific IgE to Food allergens

In this study, the SIgE tests performed using 10 allergens, has been selected (60 patients with food allergy and 28 healthy control). The results of current study to food allergens showed that the highest percentage of allergens in F29 (Banana) (36/60) was (60.0%), while in F83 (Chicken)(21/60)(35.0%), and in F27 (Beef) (20/60) (33.33%). Followed by F1, F75 (Egg white, Egg yolk) (18/60) each (30.0%), F81 (Cheddar-cheese) (17/60) (28.33%), F2, F25 (cow's milk, Tomato) (14/60)(23.33%), F35 (Potato)(13/60)(21.67%), and the lowest is F52 (Chocolate) was (12/60)(20.0%). Statistically, there were a significant differences between the patient s' group and control group (p<0.05), as shown in table (2).

Table 2 : The Results of Serum Level Specific IgE to Food Allergens

Food allergens		Patients		Control		Probability
		N	%	N	%	
F29	Positive	36	60	0	0.0	
	Negative	24	40	28	100.0	1.0×10^{-8}
	Total	60	100	28	100.0	
F83	Positive	21	35	0	0.0	
	Negative	39	65	28	100.0	8.2×10^{-5}
	Total	60	100	28	100.0	
F27	Positive	20	33.33	0	0.0	
	Negative	40	66.67	28	100.0	2.1×10^{-4}
	Total	60	100	28	100.0	
F1,F75	Positive	18	30	0	0.0	
	Negative	42	70	28	100.0	4.8×10^{-4}
	Total	60	100	28	100.0	
F81	Positive	17	28.33	0	0.0	
	Negative	43	71.67	28	100.0	9.3×10^{-4}
	Total	60	100	28	100.0	
F2, F25	Positive	14	23.33	0	0.0	
	Negative	46	76.67	28	100.0	3.8×10^{-3}
	Total	60	100	28	100.0	
F35	Positive	13	21.67	0	0.0	
	Negative	47	78.33	28	100.0	7.5×10^{-3}
	Total	60	100	28	100.0	
F52	Positive	12	20	0	0.0	
	Negative	48	80	28	100.0	8.1×10^{-3}
	Total	60	100	28	100.0	

The Serum Level IL – 4

The results of the current study in relation to the Interleukin - 4 (IL-4); food allergy patients were (70.76 ± 18.13) pg/ml, and healthy control individuals were (24.90 ± 1.80) pg/ml. There were significant differences between studied groups, but there was no significant difference between male and female groups, as shown in the table (3).

Table 3 : The Distribution of IL-4 levels (pg/ml) in studied groups.

Gender	Mean ± SE of the IL-4 level (pg/ml)		Probability
	Patients group (n=60)	Healthy control group (n=28)	
Male	53.71 ± 18.35	26.38 ± 4.14	P > 0.05
Female	88.40 ± 31.67	23.78 ± 0.73	P > 0.05
Total	70.76 ± 18.13	24.90 ± 1.80	P < 0.05
Probability	P > 0.05	P > 0.05	

The Serum Level IL –10

The results of this study disclosed that the level of IL-10 increased in the serum of food allergic patients. The level of IL-10 (Mean ± SE) in the group of Allergic food was (8.67 ± 2.16) pg/ml and (3.37 ± 2.32) pg/ml in the control group. The statistical analysis showed that there was no significant difference between the food allergy group and control group, as shown in the table (4).

Table 4 : The Distribution of IL-10 in studied group.

Gender	Mean ± SE of the IL-10 level (pg/ml)		Probability
	Patients group (n=60)	Healthy control group (n=28)	
Male	4.45 ± 2.58	0.49 ± 0.06	P > 0.05
Female	12.90 ± 3.33	5.53 ± 4.02	P > 0.05
Total	8.67 ± 2.16	3.37 ± 2.32	P > 0.05
Probability	P > 0.05	P > 0.05	

The correlation between the interleukins in the patients' group

The present study has demonstrated that there is a relationship between the IL-4 and IL-10, where it was found a positive correlation with significant differences(r=0.569) (p<0.01), as shown in the table (5).

Table 5 : The correlation between IL-4 and IL-10 in patients' group.

		IL10
IL4	r	0.569[**]
	P	0.000

[**]. Correlation is significant at the 0.01 level (2-tailed). **r:** Pearson Correlation **P:** probability [Sig.(2-tailed)]

In these results, there were a significant correlation between Interleukins (IL-4 and IL-10) at the (p< 0.01) level.

Discussion

Numerous factors lead to allergic reactions connected to factors, such as environment, family history, the diet of different types, preparation of the food, hormonal change, occupation and associated disease that involve in the development of food allergy (Locksley, 2010; AL-Araaraji, 2017).

Several studies conducted in Iraq such as (Al & Abdulla, 2013) study showed that the overall rates of seropositive in symptomatic and asymptomatic individuals in chicken were 94.7 % and (Al-Jebori,2014) research referred to a high rate of occurrence of allergy due to exposure to Banana, Peanut, White egg, while exposure to mango, Chicken meat, Mutton lead to a lower rate, in addition to the occurrence of non –response in case exposure to onion and codfish, while the study of (Cingi *et al*., 2010) indicated that the highest response rate to food allergens is milk, eggs, wheat flour and, trees.

The study of (Saleh & Allawi, 2012) showed that the sensitivity to egg, onion and, cacao were (3%),(3%),(1%) respectively, while exposure to other types of no response were recorded.

The differences in results can be attributed to variation in age, the environment, sample size, and, be associated with other diseases. The main allergens were f29, f83, f27, f1and f75 for (Banana, Chicken meat, Meat, Egg) respectively in the allergic patients of foods. This may be because of consuming at a high level as they are available in the markets.

A wide range of antigens can cause allergic reactions resulting in allergic sensitization, but the severity of an allergic reaction depends on how sensitized the person is and the amount of the allergenic component ingested. Moreover, various studies have focused on psycho immunology, emphasizing the involvement of stress, defined as a general response of the body to external or internal challenges to the allergic pathology. Factors like lifestyle and leisure activities may change the behavior of immune cells with a strong impact on the evolution of the disease (Solomon, *et al*., 2019).

Anaphylaxis is a potential reaction that occurs almost instantly (within minutes and up to 2 hours) following the ingestion of cow's milk or dairy (Grief, 2016). Anaphylaxis is the severest type of clinical manifestation of IgE-mediated food allergy. Hence, the typical symptoms of an IgE-mediated food-allergic reaction are typically started quickly and can cause death (Anvari *et al*., 2019).

When people ingested allergens they have a genetic ability to produce IgE antibodies to allergens that are ingestion. Allergic diseases are characterized by the development of IgE antibodies which react with the allergens. Such IgE antibodies bind securely to high-affinity IgE Fc receptors on mast cells in the tissue and on exposure to the allergen that caused the synthesis of IgE, the mast cells release mediators from their granules, like (histamine; bradykinin; eosinophil chemotactic factors; etc.) The resulting clinical signs such as tearing; nasal discharge; scratching and sneezing are induced (Gershwin, 2003).

The result of IL-4 is in agreement with (Al-Yasiri, 2014; Papadopoulos *et al*., 2014). While the results of (García *et al.,* 2011) was noted constant low values of IL-4 with (CU) in children.

Interleukin (IL-4) is an essential cytokine in the development of allergic inflammation. It is linked with the induction of the isotype switch and excretion of IgE by B lymphocytes. So the increased level of IL-4 contributes to allergic disease production, Although CD4, T-cells are differentiated into Th2 cells in the presence of IL-4 and produce IL-4, IL-5, IL-9, and, IL-13, these Th2 cytokines are critical for the development of allergic diseases and the elimination of helminth infections through induction synthesis of IgE, To activate basophils and mast cells, and to recruit eosinophils. The theory of a Th1/Th2 balance offered the base for understanding the mechanisms of immune responses (Yoshimoto, 2018).

The results of IL-10 were agreement with the result of (Papadopoulos *et al.,* 2014; Aleksza et al.,2002) researches showed that the serum levels of IL-10 of the patients are higher in the acute phase compared to the serum levels of the volunteers.

These results were dis agree with the results of (Suga & Sato, 2019) study who showed that the level of IL-10 is less production in patients with (AA) compared to those in the healthy controls. Similarly, (Wahhab, 2013) indicated that the level of serum IL-10 was lower in the asthmatics compared to the control. In addition the current study was disagreement with (Wong *et al*., 2001) who showed that plasma IL-18, IL-12, IL-10, IL-13 concentrations were significantly higher in allergic asthmatic patients than normal control subjects.

IL-10 is the cytokine involved in immune response regulation at the interface between the innate and adaptive immune responses. This regulation is especially important in epithelial compartments such as the gut, lung, uterus and, skin which are interfaces with a loaded with germs external environment, Although IL-10 is in general considered as an immune-suppressive cytokine, In addition, it promotes the proliferation and function of B cells, and was thought to play an immune regulatory role in controlling inflammation (Strom *et al*., 2015; Lino *et al*., 2018; Ouyang & O'Garra, 2019).

Immune response to pathogens includes the rapid activation of pro-inflammatory cytokines that serve to initiate host defense against microbial invasion. However, surplus inflammation can give rising to systemic metabolic and hemodynamic disorder hurtful to the host. That lead to the immune system has developed analogous anti-inflammatory mechanisms that serve to control the production of pro-inflammatory molecules to limit tissue damage and to maintain or restore tissue homeostasis (Iyer & Cheng, 2012).

The current results of correlation between IL-4 and IL-10 are in agreement with the results of (Papadopoulos *et al*., 2014) who showed that the serum levels of the IL-10 of the patients are higher in the acute phase of urticaria compared to the serum levels of the volunteers. Especially for IL-4, this increase was statistically highly significant. While these results were disagreement with (Platt& Wulu, 2017) who showed there was no correlation between the production of IL-10 and the TH2 cytokines IL-4. There was a balance between pro-inflammatory and anti-inflammatory cytokines, such as interleukins (IL- 4, IL-6, IL-10, IL-13, interferon-

gamma (IFN-γ), and Tumor Necrosis Factor-alpha (TNF-α) (Modena *et al*., 2016; Lin *et al*., 2018).

Conclusions

There are highly significant differences in specific IgE and IL-4 between the allergic group and control. In food allergy patients the f29 allergen has the highest percentage , followed by chicken allergens, meat, and egg, and there is a significant positive correlation between IL- 4 and IL-10 in food allergic patients.

References

Abd al-wahaab, Y.B. (2007). Study of the relationship between certain disease in Immunological indicators and severity of people with asthma. Master Thesis. College of Science. University of Baghdad.

AL-Araaraji, S.M. (2017). Study of Some Immunological and Hematological Changes in Iraqi Patients Suffering from Haypersensitivity Type-1. 2017; M.Sc. (Thesis). College of Science for women. University of Baghdad.

Aleksza, M.; Irinyi, B.; Lukacs, A.; Antal-Szalmás, P.; Hunyadi, J.; Szegedi, A. (2002). Increased frequency of intracellular interleukin (IL)-13 and IL-10, but not IL-4, expressing CD4+ and CD8+ peripheral T cells of patients with atopic dermatitis. British Journal of Dermatology. 147(6): 1135-1141.

Al-jebori, A.A. (2014). The occurrence of food allergy in Children and Adults in Kerbala City. karbala journal of pharmaceutical sciences, (8): 85-90.

Al, R.M.; Abdulla, R.F. (2013). Serological study for some chicken allergens in allergic patients. Basrah Journal of Veterinary Research, 12(2): 122-138.

Al-Yasiri, M.Y.K. (2014). Study some Immunological and Haematological changes upon workers of Vegetable Oil factory in Baghdad suffering from hypersensitivity Type -1. 2014. M.Sc. thesis, Collage of Sciences for women. University of Baghdad. Iraq, 1-101.

Anvari, S.; Miller, J.; Yeh, C.Y.; Davis, C.M. (2019). IgE-mediated food allergy. Clinical reviews in allergy & immunology., 57(2): 244-260.

Bain, B.J.; Bates, I.; Laffan, M.A. Dacie and Lewis Practical Haematology E-Book. Elsevier Health Sciences; 2016 Aug 11.

Carrard, A.; Rizzuti, D. and Sokollik, C. (2015). Update on food allergy. Allergy. 70(12): 1511-1520.

Cingi, C.; Demirbas, D. and Songu, M. (2010). Allergic rhinitis caused by food allergies. European archives of oto-rhino-laryngology. 267(9): 1327-35.

Egholm, C.; Heeb, L.E.; Impellizzieri, D. and Boyman, O. (2019). The regulatory effects of interleukin-4 receptor signaling on neutrophils in type 2 immune responses. Frontiers in Immunology. 10: 2507.

Euroimmune, A.G.; Meyer. W.; Siegemund, M.; Stöcker, W. and Vorrichtung, Z. (2006). Immunenzymatischen Nachweis Von Antikorpern in einer flussigen Probe . Eingertragenes deutsches Gebrauchsmister. (006): 622-5.

García, E.; Duarte, S.; Calderón, C.; González, J.M.; Cuéllar, A.; Gómez, A.; Halpert, E. and Rodríguez, A. (2011). Expression of IL-10, IL-4 and IFN-in active skin lesions in children with papular urticaria due to flea bites . Biomedical. 31(4): 525-31.

Gershwin, L.J. (2003). Effects of air pollutants on development of allergic immune responses in the respiratory tract. Clinical and Developmental Immunology. 10(2-4): 119-26.

Grief, S.N. (2016). Food allergies. Primary Care: Clinics in Office Practice. 43(3): 375-91.

Hasoon, B.N. (2019). Immunological and Molecular Changes In a Sample of Asthma and Rhinitis Patients Suffering From House Dust and Storage Mites Allergy. 2019; M.Sc.(Thesis). College of Science for women. University of Baghdad.

Hong, D. and Sloane, D.E. (2019). Hypersensitivity to monoclonal antibodies used for cancer and inflammatory or connective tissue diseases. Annals of Allergy, Asthma & Immunology. 123(1): 35-41.

Gupta, R.S.; Springston, E.E.; Warrier, M.R.; Smith, B.; Kumar, R.; Pongracic, J. and Holl, J.L. (2011). The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 128(1): e9-17.

Kliene-Tebbe, J. and Davies, J.M. (2014). Grass pollen allergens. InGlobal atlas of allergy 2014 (pp. 22-26). European Academy of Allergy and Clinical Immunology (EAACI).

Lino, A.C.; Lampropoulou, V.; Welle, A.; Joedicke, J.; Pohar, J.; Simon, Q.; Thalmensi, J.; Baures, A.; Flühler, V.; Sakwa, I.; Stervbo, U. (2018). LAG-3 inhibitory receptor expression identifies immunosuppressive natural regulatory plasma cells. Immunity. 49(1): 120-33.

Lin, Y.H.; Chen, H.Y.; Chiu, J.C.; Chen, K.J.; Ho, H.Y. and Yang, S.H. (2018). Immunomodulation effects of schizonepeta tenuifolia briq. on the IgE-induced allergic model of RBL-2H3 cells. Evidence-Based Complementary and Alternative Medicine. 2018 Jan 1;2018.

Locksley, R.M. (2010). Asthma and allergic inflammation. Cell. 140(6): 777-783.

Iyer, S.S. and Cheng, G. (2012). Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical Reviews™ in Immunology. 32(1).

Modena, B.D.; Dazy, K. and White, A.A. (2016). Emerging concepts: mast cell involvement in allergic diseases. Translational Research. 174: 98-121.

Nowak-Węgrzyn, A.; Katz, Y.; Mehr, S.S.; Koletzko, S. (2015). Non–IgE-mediated gastrointestinal food allergy. Journal of Allergy and Clinical Immunology. 135(5): 1114-24.

Olivier, C.E. (2013). Food allergy. J Aller Ther S. 2013;3:2.

Ouyang, W.; O'Garra, A. (2019). IL-10 family cytokines IL-10 and IL-22: from basic science to clinical translation. Immunity. 50(4): 871-891.

Papadopoulos, J.; Karpouzis, A.; Tentes, J.; Kouskoukis, C. (2014). Assessment of interleukins IL-4, IL-6, IL-8, IL-10 in acute urticaria. Journal of clinical medicine research. 6(2):133.

Perucha, E.; Melchiotti, R.; Bibby, J.A.; Wu, W.; Frederiksen, K.S.; Roberts, C.A.; Hall, Z.; LeFriec, G.; Robertson, K.A.; Lavender, P. and Gerwien, J.G. (2019). The cholesterol biosynthesis pathway regulates IL-10 expression in human Th1 cells. Nature communications. 10(1): 1-3.

Platt, M.P. and Wulu, J.A. (2017). Rational approach to allergy testing. Otolaryngologic Clinics of North America. 50(6): 1103-1110.

Puc, M. (2003). Characterisation of pollen allergens. Annals of Agricultural and Environmental Medicine. 10(2): 143-150.

Rahman, A.M. (2017). Food Allergy: Methods of Detection and Clinical Studies. CRC Press; 2017 Sep 1.

Saleh, B.T. and Allawi, M.S. (2012). Retrospective Evaluation of Skin prick Tests to Various Allergens in Patients with Atopic Dermatitis. The Medical Journal of Tikrit. 1(181): 26-32.

Savic, L.; Savic, S.; Hopkins, P.M. (2020). Anaphylaxis to sugammadex: should we be concerned by the Japanese experience?. British Journal of Anaesthesia. 124(4): 370-372.

Sicherer, S.H.; Sampson, H.A. (2018). Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. Journal of Allergy and Clinical Immunology. 141(1): 41-58.

Solomon, I.; Ilie, M.A.; Draghici, C.; Voiculescu, V.M.; Căruntu, C.; Boda, D.; Zurac, S. (2019). The impact of lifestyle factors on evolution of atopic dermatitis: An alternative approach. Experimental and therapeutic medicine. 17(2): 1078-1084.

Strom, A.C.; Cross, A.J.; Cole, J.E.; Blair, P.A.; Leib, C.; Goddard, M.E.; Rosser, E.C.; Park, I.; Nilsson, A.H.; Nilsson, J. and Mauri, C.B. (2015). Regulatory cells are increased in hypercholesterolaemic mice and protect from lesion development via IL-10. Thrombosis and haemostasis. 114(10):835-47.

Suga, H. and Sato, S. (2019). IL-10–producing regulatory B cells in skin diseases. Journal of Cutaneous Immunology and Allergy. 2(3):68-74.

Taylor, D. (2000). More than personal change: effective elements of symptom management. InNurse practitioner forum 2000 Jun 1, 11(2): 79-86.

Trifunović, J.; Miller, L.; Debeljak, Ž.; Horvat, V. (2015). Pathologic patterns of interleukin 10 expression–a review. Biochemia medica: Biochemia medica. 25(1): 36-48.

Wahhab, R.S. (2013). Investigate Role of IL-17 and Its Relationship to Some Immunological Indicator and Severity in Patients of Allergic Asthma. M.Sc. (Thesis). College of Basic Education. Al-Mustansiriyah University.

Wilson, M.E.; McCandless, E.E.; Olszewski, M.A. and Robinson, N.E. (2020). Alveolar macrophage phenotypes in severe equine asthma. The Veterinary Journal. 256: 105436.

Wong, C.K.; Ho, C.Y.; Ko, F.W.; Chan, C.H.; Ho, A.S.; Hui, D.S.; Lam, C.W. (2001). Proinflammatory cytokines (IL-17, IL-6, IL-18 and IL-12) and Th cytokines (IFN-γ, IL-4, IL-10 and IL-13) in patients with allergic asthma. Clinical & Experimental Immunology. 125(2): 177-183.

Yoshimoto, T. (2018). The hunt for the source of primary interleukin-4: How we discovered that natural killer t cells and basophils determine T helper type 2 cell differentiation in vivo. Frontiers in immunology. 9: 716.

Yu, W.; Freeland, D.M. and Nadeau, K.C. (2016). Food allergy: immune mechanisms, diagnosis and immunotherapy. Nature Reviews Immunology. 16(12): 751.