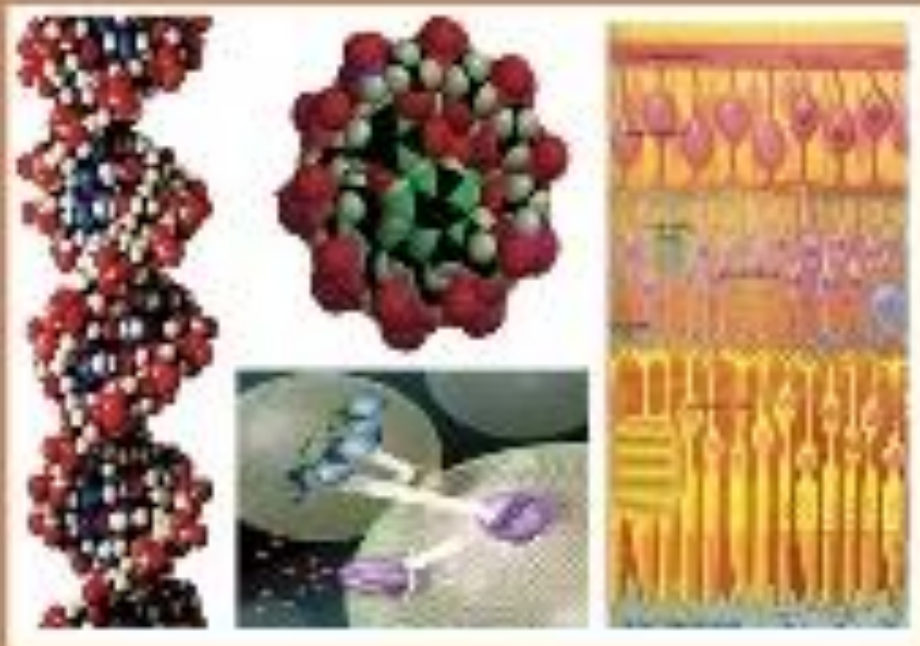




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Study the Hypersensitivity Type 1 in Patients Suffering from Drug and Asthma Allergy

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ABSTRACT

The current study was conducted to measure some immunoglobulin IgE, IgG, IgM, some interleukins interleukin 4 (IL-4), interleukin 5 (IL-5) and a complete blood count (CBC) in patients suffering from hypersensitivity type 1 (drug allergy, and asthma). The study began from 1/9/2022 to 1/3/2023 and included 59 people of all ages. The current results showed that people with drug allergy and asthma had an increase in the concentration of IL-4 (407.8 ± 27.0), (837.6 ± 29.4), IL-5 (323.1 ± 39.7) (568.4 ± 32.1) respectively. The level of IgE, IgG and IgM was elevated in patients suffering from drug allergies (11.2 ± 2.6) (18.1 ± 2.8) and (47.9 ± 5.3) respectively and asthma was (30.3 ± 3.4), (26.1 ± 4.6) and (50.2 ± 8.6) respectively.

The results of the complete blood count showed a significant increase in the white blood cells, Eosinophile. In addition to many differences in blood parameters compared to normal proportions. It was also found that the IgE concentration decreased with age, while the IgG antibody concentration increased compared to the standard sample and with the increase in age groups.

INTRODUCTION

Hypersensitivity or allergic reactions are exaggerated or inappropriate reactions against an antigen or an allergy that usually do not raise the immune system. Hyper-allergic reactions are classified into 4 categories, i.e., 1, 2, 3, and 4. Significantly, the global deployment of the first type of allergy in children has increased in recent years (Turner *et al.*, 2019; Backman *et al.*, 2017). There are some risk factors that increase the risk of allergic diseases. These include geographical distribution, environmental risks such as pollution, social and economic status, genetic preparation, or "hypotheses" (Yang *et al.*, 2012).

The "hygiene hypothesis" indicates that our modern society's practices of good hygiene and lack of early exposure to many microbes or antigens may lead to a failure in the functions of the immune system. The prevalence of anaphylaxis varies widely and is increasing worldwide, not Especially in developed countries, studies have shown that the prevalence of anaphylaxis can range between 1.6 - and 5.1% (Simons *et al.*, 2015).

Allergic diseases that include food and drug allergy, allergic rhinitis, asthma, urticaria, and atopic dermatitis show complex spectrum. It is widespread and affects 20-30% of the world's population and has a negative impact on quality of life and sometimes leads to life-threatening events such as fatal asthma. Because of the different underlying molecular mechanisms, there are no established ways to prevent it. Evidence indicates a role for diet as a factor affecting immune homeostasis and the development of allergic diseases (Kunisawa *et al.*, 2015).

This response is categorized into three phases: the early phase reaction, which occurs within seconds to minutes; the late phase reaction, which occurs within several hours; and the chronic phase, which is characterized by continued exposure to inflammatory mediators and stimuli (Barnes, 2011). Tissue mast cells, blood basophils, and eosinophils are important immune cells that play an important role in the inflammatory response to allergens (Galli and Tsai, 2012). The hallmarks of allergy and allergic inflammation include elevated serum IgE eosinophilia, cytokine and chemokine secretion, and airway mucus production, depending on the site of inflammation (Junttila, 2018).

Immediate hypersensitivity is characterized by the production of allergen-specific IgE antibodies. The first step in type 1 hypersensitivity is the priming of allergen-specific type 2 (Th2) helper T cells (Leomicronn, 2017). Production of Th2 cytokines, such as the interleukins IL-4, IL-5, and IL-13, is essential in this process because activation of T cells in the presence of IL-4 increases the differentiation of naive Th0 T cells into Th2 cells (Boonpiyathad *et al.*, 2019). In addition, the secretion of IL-4 and IL-13 by Th2 cells in the presence of allergens recognized by B cells leads to the synthesis and secretion of allergen-specific IgE by plasma cells. The central role of IgE antibodies in type 1 hypersensitivity such as conjunctivitis, allergic rhinitis, or asthma is well known (Prout *et al.*, 2018). Cross-linking of IgE receptors on the surface of effector cells such as basophils and mast cells is performed by complexes of IgE antibodies and allergens. Captured allergy results in an immediate immune reaction characterized by the release of histamine and the synthesis of prostaglandins, leukotrienes, inflammatory cytokines, and other mediators of the allergic response (Rivas and Chatila, 2016).

The course and location of exposure to the allergen determine subsequent symptoms. Inhaled allergens may worsen

allergic rhinitis or asthma by causing nasal congestion, a runny nose, sneezing, and bronchospasm. Oral or intravenous exposure to allergens usually leads to systemic symptoms (Guo and Saltoun, 2019).

MATERIALS AND METHODS

The current study was conducted in Tikrit Teaching Hospital in Salah Al-Din Governorate to study the response and effect of type 1 hypersensitivity on patients with some diseases and infections (drug allergy and asthma) by measuring some immunoglobulin IgE, IgG, IgM, some interleukins interleukin 4, interleukin 5 and a complete blood count (CBC). The study began from 1/9/2022 to 1/3/2023 and included 59 people of all ages. The concentration of these proteins and interleukins was measured in scientific research and development laboratories in Baghdad governorate. Immunological tests were carried out. 5 mL of blood was collected into coagulant-free plastic tubes to obtain serum using a centrifuge at 3,000 rpm for 5 minutes. Serum samples were kept at -20 °C until the time of testing using an Elabscience ELISA device. 1 ml of blood was collected in plastic tubes containing anticoagulant EDTA for CBC test using automation automatic analysis

RESULTS AND DISCUSSION

Effect of Hypersensitivity on CBC According to The Type of Allergy:

Hematological parameters are measurable blood indicators that can be used as markers in the diagnosis and monitoring of certain physiological and pathological abnormalities. Hematological parameters can be affected by disease states that affect hematopoietic physiology and by the immune response (Kelly and Fussell, 2011) for example, Allergies may affect blood parameters, including eosinophils and neutrophils. Allergies are a disorder of the immune system in the form of hypersensitivity in response to an allergen (Price *et al.*, 2016).

Table 1: CBC level in patients with hypersensitivity.

Parameters Levels	Asthma	Drug allergy	Control
WBC 10 ⁹ /L	9.6±2.1a	8.7±1.6ab	5.8±0.9c
NEUT %	57.3±4.0a	56.7±7.7a	59.3±4.8a
LYMPHO%	29.9±5.4b	37.3±7.5a	30.3±5.4b
MONO%	8.1±1.9a	6.9±1.9a	7.1±0.3a
EOS%	4.2±1.9a	4.7±1.3a	0.8±0.4b
BASO%	0.5 ±0.3a	0.3±0.2a	0.5±0.2a
RBC 10 ¹² /L	4.7±0.6a	4.6±0.2a	4.6±0.2a
HGB g/dL	12.6±2.9a	12.1±0.3a	12.6±0.9a
HCT%	38.0±5.6a	31.3±3.9b	37.5±1.9a
MCVfL	82.3±4.1a	82.0±2.9a	82.4±2.0a
MCH pg	27.8±1.8a	26.3±1.3a	28.7±1.4a
MCHC g/dL	33.8±1.4a	32.5±0.7a	33.6±1.1a

The results shown in Table 1, indicated that there was a difference in WBC concentrations; it was found that patients with asthma had the highest number of WBC, and this result is consistent with the researcher's (Chakraborty and Burns, 2019). Leukocytosis is part of the systemic inflammatory response syndrome (SIRS), which is defined as an excessive immune response against a pathogen mediated by an increased level of cytokines, causing organ damage. The inflammatory response that is driven by the innate and adaptive immune systems during an acute asthma attack increases Leukocyte count, mediated by released chemokines and cytokines. Therefore, leukocytosis may indirectly estimate the degree of inflammation during an exacerbation, which reflects the severity of the disease (Rabah *et al.*, 2021).

The results noted an increase in the number of white blood cells in patients with drug allergies compared to the standard sample. White blood cells (WBCs), especially eosinophils, play a major role in the immune response to drug allergies. When a

person is exposed to a drug that he is allergic to, his immune system can produce an allergic response that includes the activation of eosinophils and T cells. In some cases, the immune response to a drug allergen can also involve the production of antibodies, particularly immunoglobulin IgE, which can bind to mast cells and basophils and cause the release of histamines and other mediators that cause allergic symptoms such as itching and swelling. In severe cases, the immune response can be so strong that it causes anaphylaxis, a life-threatening condition that can cause difficulty breathing and low blood pressure.

The results shown in Table 1, indicated an increase in the concentration of eosinophilic blood cells in patients with asthma and drug, and this result corresponds to what was obtained by (Yang *et al.*, 2012; Ciprandi and Silvestri, 2019). Eosinophils play a key role in allergic reactions and were revealed to be a hallmark of asthma and link inflammation to remodeling. These cells contain inflammatory enzymes, produce leukotrienes and express a wide range of pro-

inflammatory cytokines. Increases in eosinophils are often associated with increased severity of asthma and play an important role in airway remodeling. Drug reactions with eosinophilia are severe T-cell-mediated hypersensitivity reactions resulting in rash, fever, eosinophilia, lymphadenopathy, hepatitis, and other organs such as the kidneys, heart, lungs, pancreas, bone marrow, or sometimes brain regions are affected (Jörg-Walther *et al.*, 2015).

The results showed an increase in the concentration of monocytes in patients with asthma and rhinitis compared with the standard sample. Asthma syndrome is characterized by airway inflammation of various types of cells, including neutrophils, eosinophils, mast cells, monocytes, and macrophages. Many of these cells have a characteristic blood monocyte phenotype, indicating active recruitment of these cells from the bloodstream to the airways. Monocytes are precursors of connective tissues, and they are important in inflammatory and immune responses. This result is consistent with what was obtained by (Chow *et al.*, 2011; Lambrecht and Hammad, 2012). It was recently found that circulating monocytes were rapidly activated (within hours) in the nasal mucosa after a local allergen challenge and the major APC subset remained in the nasal mucosa within 1 week with daily exposure to the allergen. This finding is consistent with (Eguíluz-Gracia *et al.*, 2016). The results indicate that the proportions of monocytes are normal in patients with drug allergy. Monocytes play a role in drug allergy by releasing inflammatory cytokines, which can trigger an allergic reaction. They also help activate other immune cells at the site of the reaction. We note in the current study that the proportions are normal for basophils, this result does not.

It agrees with (Mukai *et al.*, 2005; Obata *et al.*, 2007). Mast cells and basophils are the primary effector cells of allergens,

which directly respond to allergen challenge through either immunoglobulin-dependent or independent mechanisms (Marone *et al.*, 2005). Upon activation, mast cells and basophils release three main groups of inflammatory mediators that cause pathological damage and clinical manifestations. Allergy symptoms appear after activation of mast cells or basophils (Kalesnikoff and Galli, 2010). Theoretically, lysis of mast cells and basophils is the final event in allergy, while IgE only functions as one of the main messengers. Although mast cells and basophils play a critical role in allergy, the cell types involved in sensitizing primary effector cells are also necessary for allergic reactions. For example, an individual allergic reaction to alcohol, grass pollen, or certain foods requires a lengthy process to develop sensitivity to that specific type of allergen and not to other allergens. This natural phenomenon indicates that mast cells or basophils must be primed prior to activation (Bradding *et al.*, 2006). Activated mast cells or basophils are certainly involved, but whether activated mast cells or basophils undergo glycolysis remains unknown. Mast cells release three families of mediators, including preformed granule products such as histamine, tryptase, chymase, and heparin; newly synthesized arachidonic acid products such as leukotriene and prostaglandins; and cytokines such as IL-4 and IL-13. These products contribute significantly to pathological damage in various tissues (Munitz *et al.*, 2006).

The Concentration of Some Interleukins According to The Type Of Sensitivity:

Interleukins are a group of cytokines (secreted proteins and signaling molecules) that are expressed and secreted by white blood cells (leukocytes) as well as some other cells of the body, and the human genome encodes more than 50 interleukins and related proteins (Brocker *et al.*, 2010).

Table 2: The level of interleukins according to the type of sensitivity.

IL / ng/ml	Asthma	Drug allergy	Control
IL-4	837.6±29.4a	407.8±27.0b	330.9±23.7c
IL-5	568.4±32.1a	323.1±39.7b	146.9±23.4d

The results shown in Table 2, indicated a high concentration of interleukin-4 in patients with asthma, and this result is consistent with (Varga *et al.*, 1999; Nag *et al.*, 2002). Asthma shares many pathological features. Indeed, the same side effects of inflammation, mediators, and adhesion molecules can be observed in allergic diseases of the upper and lower airways. IL-4 plays key roles in stimulating IgE production by plasma cells and regulating the expression of FcRI and MHC class II molecules in mast cells, basophils, monocytes, macrophages, and B (Yamanishi *et al.*, 2017).

Through the results of the current study, we notice an increase in the levels of interleukin-4 in the serum of patients with drug allergies when compared with the control group, as this result coincided with the researchers (Limsuwan and Demoly, 2010). The mechanism underlying the role of IL-4 in drug sensitivity includes the activation of mast cells. When an allergen drug enters the body, it triggers an immune response that includes the production of IL-4 by T cells. IL-4 promotes the growth and activation of mast cells, which release histamine and other chemicals that cause inflammation and tissue damage. The most effective strategy for managing drug sensitivity is to avoid or discontinue the offending drug. When available, alternative drugs with unrelated chemical structures should be substituted.

The results of the analysis showed an

increase in the concentration of IL-5 in patients with asthma. This result is consistent with the results obtained by (Bartemes *et al.*, 2014; Chen *et al.*, 2017; Sohn *et al.*, 2008).

Asthma is mainly triggered by adaptive immune responses. Several studies showed that type 2 cytokines, including IL-5 were associated with allergic inflammation and that these cytokines were elevated in the sputum and blood of patients with asthma and rhinitis, we noticed an increase in the concentration of IL-5 in drug-allergic patients. This result is consistent with the researcher's findings (Limsuwan and Demoly, 2010). The mechanism underlying the role of IL-5 in drug allergy involves the activation of eosinophils. When an allergen enters the body, it triggers an immune response that includes the production of IL-5 by T cells. IL-5 promotes the growth and activation of eosinophils, which release chemicals that cause inflammation and tissue damage. This response can trigger allergic symptoms (Bergmann *et al.*, 2019; Bernstein *et al.*, 2020).

The Concentration Level of Antibodies According to The Type of Allergy:

Immunoglobulins, also known as antibodies, are glycoprotein molecules produced by plasma cells (white blood cells). They act as an important part of the humoral immune response by recognizing and binding to specific antigens, such as bacteria or viruses, and helping to destroy them.

Table- 3 The level of immunoglobulins according to the type of allergy

Antibodies. ng/ml	Asthma	Drug allergy	Control
IgE	18.1±2.8a	11.2±2.6b	5.6±1.2d
IgG	47.9±5.3a	30.3±3.4b	12.0±3.9c
IgM	50.2±8.6a	26.1±4.6b	18.5±3.7c

The results shown in Table 3, indicated a significant increase in the concentration of immunoglobulin IgE in patients with asthma, and drug allergies. This result is consistent with (Murrison *et al.*, 2019 ; Baldo and Pham, 2020). Allergic diseases, including asthma, are characterized by increased levels of IgE in the blood. A hypersensitivity reaction initiated by immune mechanisms mediated by IgE antibodies occurs in allergic asthma. IgE plays a central role in the initiation and spread of inflammatory and thus allergic responses. Indeed, recent studies have revealed that IgE, through its high-affinity IgE receptor, is an important regulator of TH2 responses Peng, 2009). In primary drug allergy, drug-specific IgE is formed during the transformation of plasma cells from activated B cells that interact with Th2 cells. In an allergic reaction, allergens bind to mast cells or basophils with high-affinity Fc receptors, to which drug-specific IgE binds, causing degeneration of the granules of mast cells or basophils, leading to the release of several mediators (histamines, leukotrienes, and prostaglandins) (Fatangare *et al.*, 2021).

In the current study, we notice a high concentration of IgG in patients with asthma, and drug, and this is consistent with what was obtained by each of (Stokes and Casale, 2011 ; Hamid and Tulic, 2009; Jiménez *et al.*, 2020), although the mechanisms by which IgG contributes to the pathogenesis of The incidence or tolerance of allergic responses remains controversial, and evidence from both studies indicates an important role for IgG in regulating allergic phenotypes. Clinical studies have shown that in addition to elevated levels of allergen-specific IgE, allergic individuals also have elevated levels of allergen-specific IgG. The result showed that the activating receptor Fc γ RIII was essential for efficient induction of Th2 responses (Bandukwala *et al.*, 2007).

In drug allergy, the mechanism of IgG involvement can vary depending on the specific drug and the individual's immune response. In some cases, IgG can recognize

and bind to drugs or drug metabolites as foreign, forming immune complexes that activate complement. In other cases, IgG can bind to specific cells in the body, such as platelets, causing them to activate and release inflammatory mediators. The exact mechanism of IgG involvement in drug allergy can depend on many factors, including the specific drug, the individual's immune system, and the mode of exposure.

The study indicates a high concentration of IgM in patients with drug and asthma, and this result is consistent with (Rahnama *et al.*, 2013). Where a direct and significant relationship was observed between the level of serum IgM and IgE in patients suffering from both asthma and allergic rhinitis.

The Level of Immunoglobulin Concentration According to Age Groups:

The results shown in Table 4, indicated an increase in the concentration of IgE compared to the standard sample, and there were no significant differences according to age groups. IgE plays an essential role in the first type of immediate allergic response. IgE binds to allergens and sends signals to other cells to release substances and chemicals, such as histamine, that cause symptoms of an allergic reaction. The results showed a rise in the concentration of IgG compared to the standard sample, where there were significant differences in the concentration height, where the age group <46 (42.8 \pm 12.0) found the highest concentration of the rest of the groups. Allergens play an important protective role because they compete with allergen-specific IgE antibodies for binding to given allergens and can inhibit CD4 and T-cell activation by inhibiting IgG-mediated antigen presentation (Flicker and Valenta, 2003). The results noted a rise in the concentration of IgM compared to the standard sample, where there are significant differences in height, and the age group 5-25 years (40.4 \pm 7.3) was found to have a higher concentration than the rest of the groups.

Table 4: The level of antibodies of allergic patients according to age groups.

Parameters Levels	Categories	Control	Patients
IgE ng/ml	25_5	6.7±1.8b	14.3±3.1a
	45_26	3.1±1.5b	13.7±2.0a
	<46	6.4±1.3b	14.9±3.2a
IgG ng/ml	25_5	11.6± * b	36.6±13.6a
	45_26	17.2± * b	38.1±10.9a
	<46	10.6±2.8b	42.8±12.0a
IgM ng/ml	25_5	15.3±2.7b	40.4±7.3a
	45_26	18.1±3.1b	33.2±7.5a
	<46	20.3±3.1b	39.1±8.2a

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