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CORRELATION BETWEEN ADIPONECTIN LEVEL AND OBESITY AS A RISK FACTOR FOR ALLERGY DISEASE

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Much research has focused on the connection between two inflammatory conditions, allergic reactions and obesity which has led to a focus on adiponectin, hormone with anti-inflammatory properties secreted by adipose tissue. The aim of this study was to determine the association of adiponectin with obesity, as a risk factor for the development of allergic condition in order to rationalize approach to its treatment. Research methods for inflammatory markers and biochemical parameters involve immunoassay technique. Statistical analysis was performed with Student's t-test, Wilcoxon T-test and coefficient of correlation. The study included apparently healthy subjects and patients with allergy conditions with confirmed presence of specific IgE, classified into 2 groups according to their body mass index (BMI). The obtained data showed negative correlation (cor = - 0.6), between adiponectin levels and BMI values. Thus, decreased level of adiponectin is associated with increased BMI. The mean values of adiponectin in the studied population, with high statistical differences between the groups (19.1 ± 1.5; 17.7 ± 0.9), (18.8 ± 1.1; 16.6 ± 1.0) demonstrated the relationship between low adiponectin level and development of obesity, and what, in turn, increasd risk of developing allergic conditions. The assumption was made that adiponectin may be used as a sensitive biochemical marker for early diagnostics of allergic reactions.

K e y w o r d s: adiponectin, obesity, allergy reactions, specific IgE.

Adiponectin is a protein with 244 amino acids, mainly secreted by the adipose tissue with molecular weight of 30 kDa [1,2]. Adiponectin exists in five configurations and six forms: the globular adiponectin (gAPN), the full-length adiponectin (fAPN), the low molecular weight adiponectin (MMW), the high molecular weight adiponectin (HMW), and the serum albumin bounded LMW form (ALB-LMW) [2].

Three receptors for adiponectin have been identified: Adiponectin receptor 1 (AdipoR1), Adiponectin receptor 2 (AdipoR2) and T-cadherin [3]. The first two were abundantly synthesized in the skeletal muscles and the liver, respectively, and are ubiquitously expressed, while the last one is expressed on vascular endothelial cells and smooth muscles [1]. AdipoR1 is the high-affinity receptor for gAPN and AdipoR2 is the intermediate-affinity receptor for gAPN and fAPN. However, these two kinds of monomeric forms had not yet been detected in the circulation [2]. Several recent studies have demonstrated that adiponectin inhibits the growth and peritoneal metastasis of gastric cancer, modulates inflammatory reactions, inhibits leptin-stimulated esophageal adenocarcinoma cell proliferation, mediates action in the hypothalamus, regulate appetite, and has insulin-sensitizing effects [2].

Adiponectin showed pro-inflammatory, as well as anti-inflammatory properties [2, 3]. This paradoxical dual effect of adiponectin might be a result of several reasons. First, the biological context, different configurations might express different functions. gAPN, but not fAPN, significantly increased the secretion and mRNA levels of IL-8, GM-CSF, and MCP-1 in HT-29 cells. The HMW and gAPN markedly increased NF-κB activity in U937 and THP-1 monocytic cells which was not observed by MMW and LMW adiponectin. gAPN increased tissue factor (TF) activity and dose dependently induced TF mRNA and protein expression in human umbilical vein endothelial cells which were not observed by fAPN treatment [2]. Therefore, it is im-

portant to make clear which kind of adiponectin was used in certain experiments for pharmacological effect studies.

The pro-inflammatory and the anti-inflammatory effects of adiponectin might be dose dependent. The data from literature sources suggest that the anti-inflammatory effect of adiponectin may be due to an induction of macrophage tolerance [2]. Adiponectin's constant presence in the circulation in high levels renders macrophages resistant to pro-inflammatory stimuli, including its own [2, 3]. Further experiments revealed a strong negative correlation between plasma concentration of adiponectin and body mass index (BMI), waist-to-hip ratio, fasting plasma glucose, insulin, triglyceride, uric acid levels, hyperinsulinemia, and lectin level, but positive correlation with HDL-C in overweight and obese objects [2].

The regulatory effect of adiponectin on innate immunity under physiological conditions may emerge as an important determinant of metabolic adaption [3]. Unlike most other adipokines, levels of circulating adiponectin are higher in individuals with lower body mass index [1, 2].

In prospective observational studies in humans using multivariable regression, higher levels of circulating adiponectin are associated with lower risk of type 2 diabetes mellitus, hepatic dysfunction, and metabolic syndrome, but higher mortality in patients with kidney disease, heart failure, previous cardiovascular disease, or general elderly cohorts; this different direction of effect between risk of incident disease and mortality among high-risk groups has been called the adiponectin paradox [4]. The complex metabolic disorders involved in compensatory changes that might occur in response to human diseases and the association between adiponectin levels and consequential disease might be explained by reverse causality (where disease status could alter adiponectin concentration) or residual confounding (where adiponectin could be a marker of another causal factor, such as adiposity or insulin resistance). Classical multivariable regression studies cannot distinguish causal from noncausal associations, and randomized controlled trials specifically targeting adiponectin are not possible in the absence of a specific therapeutic targeting adiponectin concentration or function. Mendelian randomization uses genetic variants (mostly single-nucleotide polymorphisms (SNPs) that are robustly related to the risk factor of interest as tools to assess its role in causing disease [5].

Previous Mendelian randomization studies indicate that circulating adiponectin is a consequence of low insulin sensitivity, but whether adiponectin concentration is also a cause of insulin sensitivity is uncertain [5]. Using Mendelian randomization in a study of 63,746 coronary heart disease cases and 130,681 controls, Borges et al., in 2016 show that adiponectin may not be causally related to coronary heart disease. Although multivariable analyses show that higher adiponectin concentration is associated with lower glycated hemoglobin, insulin, triglycerides (TG), and higher high-density lipoprotein cholesterol (HDL-C), using Mendelian randomization, they found little evidence that these were causal. Whether adiponectin is associated with systemic metabolic profile, and, if it is, what aspects of these associations are causal is unknown. A broader interrogation of the metabolic effects of adiponectin through high-throughput profiling of metabolic status could provide valuable insights into whether adiponectin is a non-causal biomarker or causally important in the pathophysiology of some human diseases [6]. Adiponectin acts as a key regulator of the innate immune system and plays a major role in the progression of inflammation and metabolic disorders [3]. Until recently, it was associated only with obesity, a condition that can cause other diseases (allergic diseases, type 2 diabetes, cardiovascular disease). Increasing evidences now, indicates that obesity is causally linked to a chronic low-grade inflammatory state which contributes to the development of obesity-linked disorders, in particular to metabolic dysfunction [7]. The association between obesity and respiratory allergy may, at least partly, depend on decreased immunological tolerance to the allergen as a consequence of immunological changes induced by adipokines, such as adiponectin and leptin, and some pro-inflammatory cytokines secreted by WAT [3].

Therefore, an increase in WAT is characterized by a chronic inflammation that pushes the immune system toward a Th2 polarization. Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathological factors that induce, maintain and amplify allergic inflammation. IL-4 and IL-13 orchestrate this inflammation by promoting IgE synthesis, upregulating adhesion molecules selective for eosinophil recruitment, and causing increased mucus production and airway hyperreactivity.

Proliferation and polarization of macrophages and monocytes as components of an innate immune system are important part of metabolic adaption.

Members of the innate immune system innate-like lymphocytes such as group 2 innate lymphoid cells (ILC2s), natural killer T (NKT) cells, and gamma delta T (γδ T) cells play important roles in the development of obesity and its related diseases [3].

Obesity is a risk factor for the development of allergic and respiratory diseases [8].

Allergic inflammation and obesity have a common inflammation pattern, therefore their association is justified. The connection between respiratory allergies and obesity may let believe that the two conditions are simply different expressions of a general inflammation as a response of the immune system. Lifestyle factors, such as food quality and type, physical activity, and alcohol consumption, seem to have a role in such a relationship. Even though a strong association between obesity and allergy-related diseases has been reported in several studies, no published data show a scientific and firm link between the two conditions [9].

While the associations of obesity with cardiovascular, endocrine, and rheumatologic diseases are well described, the respiratory effects of obesity and interactions with adipokines are less well known. Healthy adipose tissue is highly vascularized, and each adipocyte is nourished by an extensive capillary network. However, the hypertrophic expansion of adipose tissue in obesity is often accompanied by inadequate angiogenesis leading to reduced capillary density and local hypoxia. Hypoxia is one of the first pathological changes occurring in adipose tissue during obesity and is thought to be a main driver of fibrosis via the activation of hypoxia-inducible factor 1 (HIF1α). This contributes to local inflammation and dyslipidemia. Adipose tissue dysfunction in obesity results in a shift from an anti-inflammatory toward a pro-inflammatory profile. Obesity-associated inflammation starts in adipose tissue and liver with elevated macrophage infiltration and expression of pro-inflammatory cytokines [10].

A better understanding of the physiological role of adiponectin in the regulation of innate immunity may provide a basis for the development of adiponectin-based therapeutic strategies [3].

Research strategies, therefore, need to determine the role and correlation of adiponectin with pathological obesity, as a risk factor for developing a variety of allergic inflammations, which can lead to their rational approach and treatment, based on scientific evidence. Evaluation of bibliographic references is important for better understanding of their close association with therapeutic options for different types of allergic conditions.

Materials and Methods

The study involved 80 people, of which 40 were healthy subject and 40 were patients with confirmed allergic inflammation based on IgE levels.

The inclusion criteria for this study were either male or female patients with normal body weight and with pathological obesity.

Exclusion criteria. Individuals older than 60 years of age were excluded from study because this age group experiences the greatest burden of chronic kidney disease (CKD), cardiovascular disease, and malignancy on the basis of their age alone, each of which may be exacerbated by obesity [11]. Patients below 20 years of age were also excluded from the study because classification of body mass index is not appropriate for children in whom the 50th centile for body mass index shows profound changes from birth through to early adulthood [12].

Patients with infectious diseases, cardiovascular rheumatic, malignant, liver disease, kidney disease, pregnant women and nursing mothers were also excluded, as well as patients in whom obesity has developed as a secondary factor [13].

All procedures performed in the study were generally in accordance with the appropriate ethical standards of the Declaration of Helsinki for medical research on humans, modified for the purposes of our study [14].

All persons were subjected to full clinical examination: 1) BMI was calculated according to their weight, which was measured in kg, and height, which was measured in meters (weight and height were self-reported); 2) Full conventional laboratory tests were performed (CBC, specific IgE (sIgE) for inhalator allergens, and inflammatory marker adiponectin). Serum sIgE was detected with immunoblotting assay on nitrocellulose membrane coated with 20 selected allergens using RIDA qline allergy kit (R-Biopharm, Germany). Eosinophils were measured with fluorescence flow cytometry on 5part differential counter Sysmex XS-800. Measurement of adiponectin serum level was done in all cases and control group by ELISA technique using Abcam.

Fasting venous blood samples were collected at 9.00 AM. After centrifuging at 4°C, the blood was stored at -70°C until analyzed [13].

The National Institute of Health (NIH) uses BMI to define a person as underweight (BMI un-

der 18.5 kg/m^2), normal weight (BMI greater than or equal to 18.5 to 24.9 kg/m^2), overweight (BMI greater than or equal to 25 to 29.9 kg/m^2) or obese (BMI greater than or equal to 30 kg/m^2) [15].

Our study included 80 subjects who were classified into 4 groups according to BMI and sIgE: Group 1 (20 subjects) control none obese, consists of apparently healthy subjects; Group 2 (20 subjects) control obese, consists of apparently healthy subjects; Group 3 (20 patients), non-obese patients with allergy; Group 4 (20 patients) obese patients with allergy.

Statistical analysis was performed with RStudio Data Visualization version 4.0.4. Data were presented as mean ± SD. For time point differences, a two-sample t test and Wilcoxon T test were used. P value < 0.05 was considered significant.

Results and Discussion

The study follows a previous study of 180 patients with allergic symptoms from 3 to 81 years old (116 women and 64 men) to determine the evaluation of adiponectin in allergy conditions.

The patients were divided into two groups according to positive or negative sIgE for inhalator allergens (the presence or absence of allergy), in order to see if adiponectin is directly involved in allergic inflammation (Table 1). Forty five patients (19 men and 26 women) displayed an IgE concentration of ≥ 0.35 IU/ml. In one hundred thirty-five patients (45 men and 90 women) the IgE concentration was < 0.35 IU/ml.

A significant correlation was established between valuable diagnostic parameters (hallmark sign of allergy) of allergy, IgE and eosinophils (P = 0.03). According to the analyses, the level of adiponectin in patients with elevated IgE is higher and statistically different than in patients without allergies. The study concluded that adiponectin as an anti-inflammatory protein, reduces the intensity of the reaction caused by the allergen and is an early and sensitive marker in allergic reactions. The cut-off value of serum adiponectin as an indicator for development of an allergy condition is 16.7 μg/ml.

The research continued in order to see how pathological obesity associated with allergic inflammation affects the concentration of adiponectin.

Elevated levels of adiponectin in allergic conditions, regardless of BMI are probably due to the anti-inflammatory properties of this protein. The protein is released during the inflammatory response, as an endogenous protective agent from allergic reactions [9]. The presumed underlying mechanism is inhibition of genes responsible for expression of inflammation [16].

This study was conducted in order to determine how obesity, as a risk factor for the development of allergic inflammation, affect adiponectin levels. Based on their medical condition, patients were examined in groups (group of healthy subject and patients with allergy disease) with P > 0.05, meaning that the groups are equal.

The demographic data are shown in Table 2.

The mean values of BMI in the studied population are demonstrated in Table 3, where there are statistical differences between group 1 and group 2, and between group 3 and group 4 with P < 0.05.

Higher adiponectin level in none obese control compared with obese control, with P < 0.01, was noted. This is in harmony with Hosny et al., who found that serum adiponectin was higher among the lean subgroup than the obese and overweight subgroups [15]. The study of Salah et al., represented lower adiponectin serum level in obese control compare to non-obese control [13]. The clinical importance of this finding is that adiponectin produced and released by WAT might be responsible for the chronic inflammation related to obesity.

Moreover, there was a higher adiponectin serum level in none obese allergy patients compared with obese allergy patients with P < 0.01. The study Hosny et al., documented that serum adiponectin was significantly higher in asthmatic patients compared with control group [15]. This significant dif-

Table 1. Statistics of adiponectin serum level in patients with/without allergy

Patients	N	Adiponectin serum level, μg/ml (mean ± SD)	Wilcoxon T test
Patients with allergy, with sIgE ≥ 0.35 IU/ml	45	18.2±1.5	P = 0.0008281
Patients without allergy with sIgE < 0.35 IU/ml	135	17.3±1.2	P = 0.0008281

T a b l e 2. Demographic data of survey population

Parameters	Group 1, control none obese subjects	Group 2, control obese subjects	Group 3, none obese allergy patients	Group 4, obese allergy patients	*P* value
Age, mean ± SD	36.3 ± 9.9	38.6 ± 10.2	34.9 ± 11.8	37.7 ± 9.7	> 0.05
			Male		
N	9	9	11	10	
%	45	45	55	50	
			Female		
N	11	11	9	10	
%	55	55	45	50	

T a b l e 3. BMI and concentration of adiponectin serum level with the studied

Parameters	Group 1, control none obese subjects	Group 2, control obese subjects	Group 3, none obese allergy patients	Group 4, obese allergy patients	*P* value
BMI, (mean ± SD)	21.6 ± 1.6	32.5 ± 1.3	22.1 ± 1.7	32.4 ± 1.6	< 0.05
Adiponectin serum level μg/ml, (mean ± SD)	19.1 ± 1.5	17.7 ± 0.9	18.8 ± 1.1	16.6 ± 1.0	< 0.01

ference between patients with allergies indicates that obesity may be a contributor to allergic inflammations, because adiponectin as anti-inflammatory protein is decreased.

It is still unknown whether reduced physical activity associated with obesity can result in allergy reactions, or only obesity as a factor causes allergy reactions [17]. Cytokines are released from adipose tissue, contributing to allergy inflammation. In obesity, visceral adipose tissue is a key factor in reducing the process of chronic inflammation [7]. Over 50 different adipokines that regulate various body processes are secreted from adipocytes. Adipokines leptin and adiponectin are adipokines that are closely associated with allergic inflammation [13]. Adipose tissue is an active endocrine organ that releases cytokines and hormones regulating metabolic processes and the immune response. Under normal conditions, adipose tissue secretes low levels of pro-inflammatory cytokines (IL-6, IL-8, TNFα), leptin and increased level of the anti-inflammatory adipokines, adiponectin [7].

In the obese state, adipose tissue hypertrophy becomes infiltrated with pro-inflammatory macrophage. Pro-inflammatory cytokines and adipokines are increased, and the level of adiponectin is decreased. Complications of obesity, such as type 2 diabetes, steatohepatitis and the metabolic syndrome most likely occur because of this “metabolic inflammation” [7].

The negative correlation between BMI and adiponectin serum level is shown in Figure, (pearson correlation coefficient (r) = - 0.6 and $P < 0.01$).

Salah et al., found that increased visceral fat is associated with decreased total adiponectin levels [18]. The clinical importance is that low level of anti-inflammatory protein adiponectin that occurs in obese state contributes to the increasing prevalence of allergy inflammation in patients. Other adipokines are increased during obese state, but the level of adiponectin decreases [7]. Allergy and obesity as inflammatory processes trigger the immune response through the activation of Th2 cells, which leads to a reduction of the release of adiponectin as an anti-inflammatory protein [3].

In vivo animal studies of lean mice suggests that exogenous administration of adiponectin attenuates allergen-induced airway hyperactivity and eosinophilic influx [19]. The simplest method to elevate the adiponectin is to administer the protein

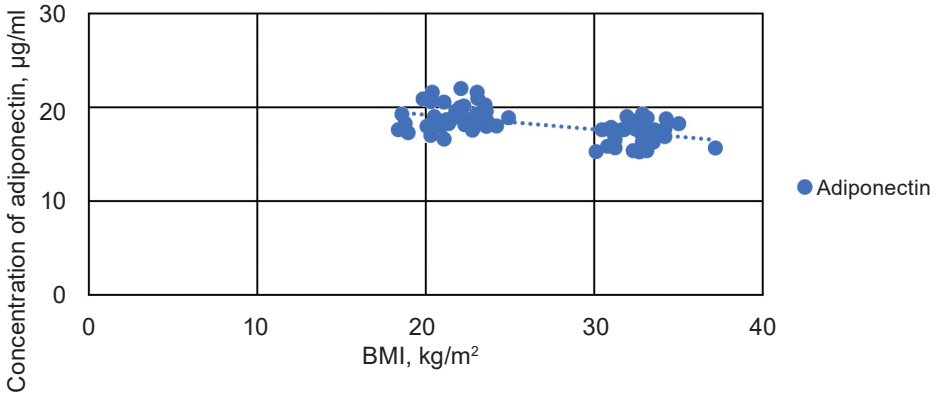

Fig. Correlation between adiponectin serum level and BMI

itself. But several scientific and technical problems need to be solved. Because adiponectin is a protein hormone, parenteral administration might have the risk of allergic reactions and other problems specific for adiponectin are likely to emerge, and this has to be considered also [2].

Due to limited data available on the pharmacokinetics of adiponectin in humans, the control of the dose, the blood concentration and the monitoring of side effects will be difficult to deal with. A self-regulating manner of adiponectin has been observed. There is a feedback loop by which adiponectin downregulated its own production and expression of AdipoR2 receptor. Similar to insulin, adiponectin resistance also exists [2].

Although there is a lack of human studies, adiponectin has the potential for use in the treatment of pathological obesity. Administration of adiponectin slightly, but not significantly, reduces weight gain induced by a high-fat diet in mice [20].

Daily administration of a very low dose of globular head domain of gAd to mice consuming a high-fat/sucrose diet caused profound and sustainable weight reduction without affecting food intake. The effect of gAd on weight reduction may reflect its ability to stimulate lipid oxidation or some other mechanism that should be described in future.

Adiponectin, adiponectin receptors and signal transduction may be potential targets for drug development. Adiponectin can be used as a therapeutic strategy due to its exogenous anti-inflammatory, anti-atherogenic and anti-diabetic properties, in order to directly or indirectly increase the plasma or tissue concentration of adiponectin [20]. For testing pharmacology treatment of adiponectin for obesity and for safe uses and administration. Regulation of the pathways controlling its production represents a promising target for managing obesity, inflammatory response, metabolic processes and type 2 diabetes.

Conclusion. Adiponectin as an anti-inflammatory marker is closely associated with obesity-linked complications, including allergic conditions. Because of correlation between adiponectin and obesity, adiponectin may be used as sensitive and early biochemical marker for allergic reactions. Adiponectin can be a potential therapeutic target for allergic inflammation, which can occur as a consequence of obesity.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

КОРЕЛЯЦІЯ МІЖ РІВНЕМ АДИПОНЕКТИНУ ТА ОЖИРІННЯМ ЯК ФАКТОР РИЗИКУ РОЗВИТКУ АЛЕРГІЧНИХ ЗАХВОРЮВАНЬ

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Існує багато досліджень, щодо зв'язку між двома запальними станами – алергічними реакціями та ожирінням, які зосередженні на адипонектині, гормоні з протизапальними властивостями, що виділяється жировою тканиною. Метою цього дослідження було визначення зв'язку адипонектину з ожирінням як фактором ризику розвитку алергічного стану, щоб покращити його лікування. Маркери запалення та біохімічні показники досліджували за допо-

могою імуноензимного аналізу. Статистичну обробку результатів проводили за допомогою *t*-критерію Стьюдента, Т-критерію Вілкоксона та коефіцієнту кореляції. У дослідженні брали участь здорові особи та пацієнти з алергічними станами з підтвердженою наявністю специфічних IgE. Досліджених осіб було розділено на 2 групи відповідно до індексу маси тіла (ІМТ). Одержані дані показали негативну кореляцію (кор = - 0,6) між рівнем адипонектину та значенням ІМТ. Так, знижений рівень адипонектину асоційовано з підвищеним ІМТ. Середні значення рівня адипонектину у досліджуваних осіб із статистичними відмінностями між групами (19,1 ± 1,5; 17,7 ± 0,9), (18,8 ± 1,1; 16,6 ± 1,0), демонстрували взаємозв'язок між низьким рівнем адипонектину та розвитком ожиріння, що в свою чергу підвищувало ризик розвитку алергічних станів. Зроблено припущення, що адипонектин може бути використаний як чутливий біохімічний маркер для ранньої діагностики алергічних реакцій.

Ключові слова: адипонектин, ожиріння, алергічні реакції, специфічний IgE.

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