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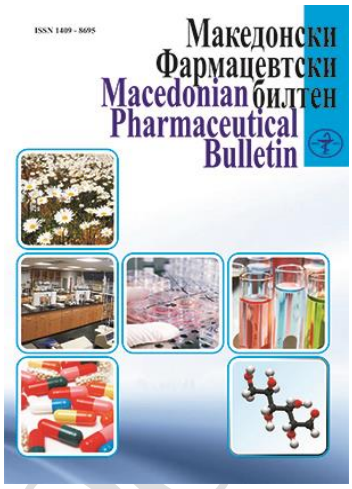
Accepted Manuscript



Title: Adiponectin as anti-inflammatory marker in development of allergic asthma

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DOI:

Received date: October 2022

Accepted date: December 2022

UDC:

Type of paper: Original scientific paper

Mac. Pharm. Bull. Vol. 68(1) 2022

Please cite this article as:

*Corresponding author e-mail: spasovskamilena@yahoo.com

doi: *Original scientific paper*

Adiponectin as anti-inflammatory marker in development of allergic asthma

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Abstract

Factors that could contribute to the pathogenesis of asthma in obese include low-grade inflammation, impaired metabolism and dysfunctional adipose tissue secretion. Because adiponectin (ADPN) is involved in the mechanisms of asthma inflammation, the aim of the study is to evaluate the correlation between ADPN as inflammatory marker for obesity, with other inflammatory cytokines that have synergistic effect in intensity of airway inflammation in obesity. Methods implemented were immunoassay technique and immunoturbidimetric method. Statistical analysis was performed with SPSS. A total of 90 practically healthy subject and patients with asthma from 20 to 25 years old were evaluated and divided into two subjects using BMI classification. Based on the mean value of IL-6 and CRP in studied population ($p<0.01$), IL-6 can be considered as surrogate marker for obesity and CRP for obesity and asthma. The differences in ADPN ($p<0.01$) between groups show that ADPN produced and released by adipose tissue might be responsible for chronic inflammation related to obesity. Based on the obtained data for positive correlation of IL-6 ($r = 0.470$) and CRP ($r = 0.660$) with BMI, adipose tissue could be a dynamic factor for producing inflammatory markers. Negative correlation of ADPN and BMI ($r = -0.481$) shows that obesity may be a contributor to allergic asthma, because adiponectin as anti-inflammatory protein is decreased. Our study showed that ADPN as early anti-inflammatory marker has the potential to reduce allergy sensitization and CRP and IL-6 have synergistic effect in the intensity of airway inflammation in obesity.

Key words: adiponectin, obesity, asthma, inflammatory markers, CRP, IL-6

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Introduction

Obesity, metabolic syndrome and asthma are rapidly increasing globally (Singh et al., 2013). Factors that could contribute to the pathogenesis of asthma in obese include: low-grade inflammation, impaired metabolism and dysfunctional adipose tissue secretion (Otelea et al., 2021). Adiponectin, as adipokine secreted by adipose tissue increases insulin sensitivity, has cardio and vascular protection actions and modulates immune response (Luo and Liu, 2016). Transcription of the ADPN is upregulated by several adipogenic transcription factors such as: nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/enhancer-binding protein (C/EBP)-α and β, forkhead box O1 protein (FOXO1), sirtuin 1 (SIRT1) and SP1 transcription factor (Sp1) (Swarbrick and Havel, 2008). Adiponectin secretion is regulated by SIRT1and the endoplasmic reticulum oxidoreductase Ero2-Lα (Qiang et al., 2007). This transcription factors are regulated by the nutrition status and therefore, nutrition controls the ADPN secretion (Olivares-García et al., 2015). Interleukin 6 (IL-6) and C-reactive protein (CRP) suppress adiponectin gene expression and decrease production of adiponectin (Zhang et al., 2009).

In Mendelian randomization study, ADPN was associated with healthier metabolic profile (low VLDL, high HDL, low TGL, saturated fatty acids and systemic inflammatory markers), but did not show a direct relation between ADPN and any of these metabolic markers. Inflammatory markers (IL-6 and fibrinogen) were the only factors which were not rejected by the analysis (Borges et al., 2018).

Adiponectin is the linkage between the inflammatory processes of asthma and obesity. (Otelea et al., 2021). Asthma is recognized as a heterogeneous condition for several diseases with distinct mechanistic endotypes and variable phenotypes (Kuruvilla et al., 2019). In allergic asthma, allergens are taken by epithelial cells followed with secretion of cytokines that activate dendritic cells and type 2 innate lymphoid cells (ILC2s). Naïve lymphocytes are promoted to Th_2 cells and together with ILC2c promote secretion of TH_2 biomarkers (IL-4, IL-5, IL-13) and promote eosinophile inflammation. Th_1 functions regulate Th_2 activation (Zhu et al., 2020). In neutrophilic asthma (Th_1 asthma) triggers (endotoxin, ozone, virus infection) release IL-6, IL-8 and LTB4 to attract neutrophiles. Immune cells activate Th_1 and

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Th17 helper responses leading to release of IL-8, Il-17, IL-22, IFNγ and TNFα. Treg cells regulate this mechanism (Sze et al., 2020). ADPN may exert positive effect on both Th_1 and Th_2 phenotypes of asthma. Cellular mechanism in this process is very complex and involves cells from immune response.

In M_1 and M_2 macrophages, effects of ADPN depends on the polarization of the cell and might be the time-dependency response of macrophages to the external stimuli. In M1 macrophages, ADPN induces secretion of proinflammatory cytokines TNFα, IL-6, IL-12 (van Stijn et al., 2015). During the sensitization step, M_1 macrophages prevent an allergy reaction and in later phase they promote eosinophilic inflammation and hyperresponsiveness (Draijer and Peters-Golden, 2017). In M_2 macrophages adiponectin induce expression of IL-10 and IL-1 receptor antagonist. Anti or inflammatory activity of ADPN depends on polarization of macrophages through the receptors $AdipoR_1$ and $AdipoR_2$ (van Stijn et al., 2015). ADPN relayed intra-cellular signal through AMP-activated protein kinase (AMPK), p-38 mitogen -activated protein kinase (p38 MAPK) and PPARα. In airway smooth muscle (ASM) the AMP signal suppresses the smooth muscle proliferation via mTOR pathway and inhibits proliferative effect of transforming growth factor β_1 (TGF- β_1) (Liu et al., 2015). Agonist of PPARα protects against the non-adrenergic, non-cholinergic inhibition of relaxation of ASM induces by irritants (Dellabianca et al., 2020). Activation of PPARα reduces the cell infiltrate and the secretion of proinflammatory cytokines (Elaidy et al., 2018). In mouse models ADPN reduces eotaxin secretion, eosinophil adhesion capacity via $AdipoR_1$, and exacerbation of asthma is prevented (Verbout et. Al., 2013). In adipocyte – conditioned media, adiponectin restrains Th_1 and Th17 cell glycolysis and mitigates inflammation (Surendar et al., 2019). In mice sensitized with ovalbumin exogen, adiponectin inhibits release of IL-13, Il-5 and Th_2 expression so the general effect is attenuation of allergic airway responses (Shore et al., 2006).

Because ADPN is involved in all these mechanisms of asthma inflammation, the aim of the study was to determine the role of adiponectin, as biomarker for obesity, in the processes of development of allergic asthma. Evaluation of biomarkers was made to confirm the anti-inflammatory activity of ADPN. We examined the correlation of adiponectin with

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inflammatory cytokines (CRP, IL-6) and assessed the association of obesity and allergy asthma.

Materials and methods

A total of 40 practically healthy subjects (21 male and 19 female) and 50 patients with asthma (25 male and 25 female) from 20 to 25 years old were evaluated and each were divided into two subgroups using BMI classification (Tschop, 2002). Control lean group had 20 subjects (9 males and 11 females) with BMI < 25.0 kg/m² and control obese group had 20 subjects (12 males and 8 females) with BMI > 30.0 kg/m². Asthmatic lean group had 25 patients (12 males and 13 females) with BMI < 25.0 kg/m² and asthmatic obese group had 25 patients (13 males and 12 females) with BMI > 30.0 kg/m².

The study was performed according to a designed protocol in accordance with the ethical principles of the Helsinki Declaration on Medical Research on Humans (WMA, 2013). Informed consents for all participating individuals were obtained. Patients and controls underwent the following: 1) Specific allergology examination which included the collection of relevant medical history from Department of allergology in internal medicine in Ohrid and 2) Body mass index calculation as weight (kg)/height (m²).

Full conventional laboratory test was performed: specific IgE (sIgE), inflammatory marker adiponectin, hsCRP and IL-6. Serum sIgE was detected with immunoblotting test on nitrocellulose membrane coated with 20 selected allergens using RIDA qline allergy kit (R-Biopharma, Germany). Measurement of adiponectin serum level was done for all cases and control group by Indirect Elisa ”Enzyme-linked immunosorbent assay technique” (user Abcam, United Kingdom). Immunoturbidimetric method was used for measure hsCRP and Electrochemiluminescence immunoassay (ECLIA) for IL-6 serum concentration.

Fasting venous blood samples were collected at 9.00h. After centrifuging at 4 °C, the blood was stored at – 70 °C until analyzed (Salah et al., 2015).

Statistical analysis was performed with Statistical Package of Social Science (Version 15; SPPS). Normality tests were presented as mean ± standard deviation (SD). ANOVA test was used to compare the four groups followed by pairwise comparisons using least

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significant difference (LSD) test. Correlation matrix and coefficient of correlation were done using Pearson's correlation coefficient. A p-value less than 0.05 was taken as the threshold of statistical significance.

Results and discussion

Because increased adipose tissue is associated with low-grade chronic inflammation and pro-inflammatory factors inhibit ADPN production, the assumption is that chronic inflammation such as allergic asthma, associated with visceral obesity inhibits production of ADPN, perpetuating inflammation.

Table 1.

Demographic characteristics of the study groups are shown in Table 1. In the study of demographic profile, study groups were matched for age, sex and mass index.

In order to evaluate the relationship of the groups, variances and significance between inflammatory markers were determined. Analysis of serum level of IL-6 in the 4 studied groups revealed significantly higher levels ($p < 0.01$) in obese subgroups whether asthmatic or control compared to the lean subgroups. The clinical importance is that IL-6 could be considered a surrogate marker for obesity. Serum level of IL-6 showed significant positive correlation with BMI in 4 studied subgroups (Table 3), so IL-6 concentrations were positively correlated with obesity. Zedan et al. (2015) reported significant positive correlation with IL-6 and obese state. IL-6 may play pivot role in metabolic diseases, including obesity, through impairing insulin signaling and suppressing adiponectin production. Communications with adipose tissue and other organs are through releasing mediators produced by macrophages and adipocytes including IL-6, TNFα, leptin, ADPN. Therefore, adipose tissue could be a dynamic factor for producing inflammatory markers like IL-6 that leads to low grade systemic inflammation. The primary cytokine involved in hepatic CRP synthesis is IL-6, an important adipocyte-signaling molecule released from visceral and fat stores. High levels of IL-6 are signal for increased synthesis of CRP which exacerbates the inflammatory response

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(Bahceci et al., 2007). It stimulates IL-4 and IL13 production by promoting the differentiation of Th_2 cells which causes mucus hyper secretion by airway epithelial cells and Th17 differentiation (Sideleva et al., 2012). IL-6 contributes to decreased adiponectin levels in HFD-fed mice (Wueest et al., 2021).

CRP is an established marker of inflammation. Serum CRP showed significant increase ($p < 0.01$) in asthmatic obese group compared to the other 3 subgroups (asthmatic lean, control lean and control obese). CRP was found to be significantly higher in the asthmatic lean when compared with lean controls. The clinical importance is that CRP could be considered a surrogate marker for both obesity and asthma. CRP levels were strongly associated with obesity and obesity-related diseases (Festa et al., 2000). Furthermore, serum level of CRP showed significant positive correlation with BMI in 4 studied subgroups (Table 3), so there is positive correlation between the size of adipose tissue and CRP. Hence, hypoadiponectinemia can be responsible for low-grade systemic chronic inflammation states, which is closely related to an increase in CRP level. Par et al. (2015) found positive associations of obesity with elevated cytokine CRP and IL-6. In the study of Menezes et al. (2018), direct association between adiposity and IL-6 and CRP and inverse association with adiponectin was reported.

Table 2 presents the registered higher adiponectin level in control lean group compared to control obese and asthmatic obese. The clinical importance of difference between control lean and control obese group is that adiponectin produced and released of the adipose tissue might be responsible for chronic inflammation related to obesity. Serum level of adiponectin showed significant negative correlation with BMI in 4 studied subgroups (Table 3). Obesity may be a contributor to allergic asthma, because adiponectin as anti-inflammatory protein is decreased. Low levels of adiponectin evidenced pathogenesis of asthma in children (Ma et al., 2019).

Increased levels of inflammatory parameters are well correlated with progression and severity of the metabolic disorders (Donath and Sheolson, 2011). It can be assumed that in healthy population, change in proinflammatory markers should be compensated by altered anti-inflammatory markers; any deviation from this profile would lead to systemic disorder. ADPN, IL-6 and CRP are important regulators in relation to metabolic disorder.

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Under normal conditions, adipose tissue released low levels of proinflammatory cytokines (IL-6, IL-8, TNFα, leptin) and increased level of anti-inflammatory adipokine adiponectin. In obese state, adipose tissue hypertrophies and becomes infiltrated with proinflammatory macrophages. Proinflammatory cytokines and adipokines are increased and level of adiponectin is decreased (Salah et al., 2015).

Adiponectin actions are mediated trough adiponectin receptors: AdipoR1, AdipoR2, T-catherdin, which are expressed on airway epithelial cells. ADPN interacts trough AMPK, which regulates cellular metabolism (and obesity) and inflammatory functions of macrophages. ADPN downregulates the levels of eotaxin and MPO which are responsible for neutrophilic and eosinophilic infiltrations (Otelea et al., 2021). Adiponectin has a protective effect of inflammation and antioxidant processes, especially in obesity-related asthma.

Table 2.

Table 3.

Since chronic inflammation plays a key role in pathogenesis of asthma, we examined the association for ADPN with CRP and IL-6. Serum adiponectin has a negative significant correlation compared to IL-6, but there is no correlation with CRP (Fig. 1) As adiponectin decreases, IL-6 increases and causes inflammation in obesity by impaired metabolism and represses adiponectin production. ADPN agonist reduce IL-4, TNFα, IL-17 and IL-23 expression in the lung, and this effect may be reduced by the negative effect of IL-6 (Vargas-Sánchez et al., 2020). CRP may be associated with overweight, but not with adiponectin as marker for obesity.

The results presented in our study showed that decreased production of ADPN contributes to the systemic and allergy inflammation found in obesity. It indicates that decreased levels of adiponectin may serve as marker of increase metabolic and inflammatory risk.

Fig. 1

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Conclusion

There is a positive association between asthma and obesity in regard to inflammation. Adiponectin as early anti-inflammatory marker has the potential to prevent the asthma sensitization, which can occur as a consequence of obesity. The intensity of airway inflammation could be relatively greater on obese asthmatic patients through increased levels of CRP and IL-6, suggesting a synergistic effect of obesity in existing airway inflammation. CRP can be considered as a predictive marker for obesity and asthma, while adiponectin and IL-6 can be regarded as obesity marker. The proinflammatory effect of IL-6 and anti-inflammatory effect of adiponectin resulted in negative correlation. Further studies are required in order to clarify the implication of adiponectin in inflammatory process of asthma.

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Резиме

Улогата на адипонектин како антиинфламаторен маркер во развој на алергиска астма

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Клучни зборови: адипонектин, патолошка дебелина, астма, инфламаторни маркери, CRP, IL-6

Нарушениот инфламаторен процес и променета секреција на адипоцитите се фактори кои ги поврзуваат патолошката дебелина и астма. Бидејќи адипонектинот е вклучен во воспалителните процеси на астма, целта на оваа студија е да се одреди поврзаноста на адипонектин, како маркер за патолошка дебелина со инфламаторни цитокини, кои имаат синергистички ефект врз воспалението на дишните патишта.

За испитување на инфламаторни маркери користени се имуноензисмки и имунотурбидиметриски метод. Статистичка анализа е направена со SPSS.

Беа вклучени 90 навидум здрави испитаници и пациенти со астма од 20 до 25 годишна возраст, кои беа поделени на поддгрупи според класификација на БМИ. Разликата во средните вредности на IL-6 и CRP ($p < 0,01$) во испитуваната популација ни укажува дека IL-6 може да се смета за важен маркер за патолошка дебелина додека CRP како маркер и за патолошка дебелина и за астма. Разликата на адипонектин помеѓу групите ($p < 0,01$) посочува дека адипонектин ослободен од адипоцитите може да биде одговорен за инфламаторните процеси поврзани со патолошка дебелина. Позитивната корелација на IL-6 и CRP со BMI ($cor = 0,470; 0,660$) го вкрстува адипозното ткиво како динамичен фактор, од каде се ослободуваат инфламаторни цитокини.

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Негативната корелација на адипонектин и БМИ (*p = -0,481*) го потврдува дека адипонектин е намален при патолошка дебелина, со што се потврдува неговото антиинфламаторно дејство.

Од резултатите се сугерира дека адипонектин како ран антиинфламаторен маркер има потенцијал да превенира инфламаторни процеси при астма, а CRP и IL-6 имаат синергистички ефект врз воспалителните процеси на астма при патолошка дебелина.

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Table 1. Demographic characteristics of studied groups

	Control lean		Control obese		Asthmatic lean		Asthmatic obese	
	N	%	N	%	N	%	N	%
Sex								
Male	9	45	12	60	12	48	13	52
Female	11	55	8	40	13	52	12	48
BMI classification								
Underweight <18.5	0	0	0	0	3	12	0	0
Healthy weight (18.5-24.9)	20	100	0	0	22	88	0	0
Overweight (25-29.9)	0	0	7	35	0	0	6	24
Class 1 obesity (30-34.9)	0	0	7	35	0	0	15	60
Class 2 obesity (35-39.9)	0	0	5	25	0	0	3	12
Class 3 obesity ≥40	0	0	1	5	0	0	1	4

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Table 2. Comparison of biochemical parameters of the studied population

		hsCRP (mg/L)		IL 6 (pg/mL)		Adiponectin (µg/mL)	
		Mean difference	*P*	*Mean difference*	*P*	*Mean difference*	*P*
Asthmatic lean	Asthmatic obese	-6.560	<0.01	-2.788	<0.01	0.665	0.033
	Control lean	0.685	0.156	0.369	0.258	-1.909	0.558
	Control obese	0.005	0.992	-2.306	<0.01	1.560	<0.01
Asthmatic obese	Control lean	7.245	<0.01	3.157	<0.01	-0.854	<0.01
	Control obese	6.565	<0.01	0.482	0.141	0.896	<0.01
Control lean	Control obese	0.680	0.182	-2.675	<0.01	1.753	<0.01

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Table 3. Pearson's correlation coefficient of BMI and serum cytokine levels in all studied subjects

		hsCRP (mg/L)	IL- 6 (pg/mL)	Adiponectin (µg/mL)
BMI	Pearson's Correlation	0.470	0.660	-0.481
	Significance (2-tailed)	<0.01	<0.01	<0.01

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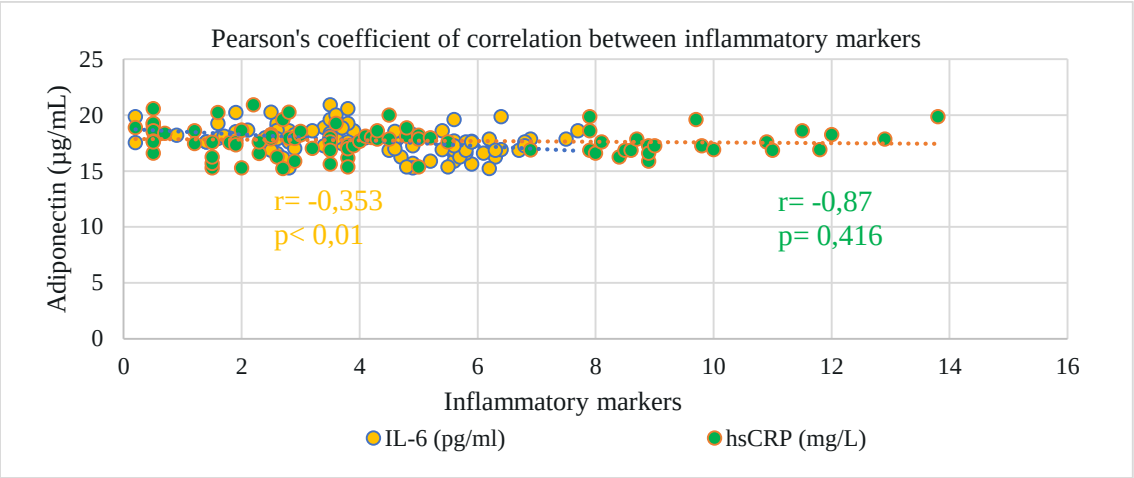

Fig. 1. Correlation between inflammatory markers.

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