

Comparative study of Interleukin-33 in Male with Chronic Obstructive Pulmonary Disease, Asthmatic Patients with Type 2 diabetes mellitus

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Abstract: The aim of this study was to investigate the differences in the levels of IL-33 between healthy control and patients with asthma, patients with COPD, asthmatic patients with type 2 diabetes mellitus, COPD patients with type 2 diabetes mellitus and study the relation of IL-33 in patients with COPD and asthma to development of type 2 diabetes. One hundred and fifty male individuals (age 40-60) were enrolled in this study which was divided into five groups as follows: (C) consisted of 30 healthy individuals as a control group, (AS) consisted of 30 asthmatic patients, (ASD) consisted of 30 asthmatic patients with diabetes mellitus type 2, (COPD) consisted of 30 patients with chronic obstructive pulmonary disease, (COPDD) consisted of 30 chronic obstructive pulmonary disease patients with diabetes mellitus type 2. IL-33, hs-CRP, TAC, MDA, MDA/TAC, insulin, insulin resistant and HbA1c% were evaluated. The results in this study revealed that mean of serum IL-33 level was significant increase in patients with (AS) and (ASD) and non-significant increase in patients with (COPD) and (COPDD) compared with control group, whereas significantly decrease in patients with (AS) compared with (ASD) and significantly decrease in patients with (COPD) compared with (COPDD). Our findings suggest that low IL-33 levels most possibly reflect that the patients with COPD are associated with a higher risk of developing type 2 diabetes mellitus than patients with asthma.

Keywords: IL-33, antioxidant, asthma, COPD, diabetes mellitus type 2

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma is a chronic inflammatory disease classically characterized by airway hyper-responsiveness, allergic inflammation [1].

The cellular infiltrate in asthma contains prominent numbers of eosinophils and type 2 helper (Th2) CD4 T-cells and associated cytokines, interleukins (IL-4, -5, and -13) and is elevated serum immunoglobulin-E (IgE) levels [1,2].

By contrast, the cellular infiltrate in COPD is dominated by neutrophils, macrophages, and an increased number of lymphocytes thought to be type 1 helper (Th1) or CD8 T-cells [3], and the neutrophil-associated cytokines, tumor necrosis factor- α (TNF- α), IL-6, and IL-8 predominate [4].

Interleukin-33 (IL-33) is a recently described as a new member of the IL-1 family [5], and has attracted attention because, uniquely among IL-1 cytokines family, is expressed by many cell types following pro-inflammatory stimulation and is thought to be released on cell lysis. The IL-33 receptor, consisting of ST2 and IL-1 receptor accessory protein, is also widely expressed, particularly by (Th2) cells and has a role in mast cells development and function. IL-33 stimulates the production of IL-5 and IL-13. It enhanced cytokine production by invariant natural killer T cells and human natural killer cells [6-8]. IL-33 is also a potent activator of the innate immune system and has potent effects on this cell type including induction of superoxide anion production [9].

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IL-33 is suggested to function as an alarmin that is released upon endothelial or epithelial cell damage and may not enhance acquired immune responses through activation of inflammasome[10]. Thus, IL-33 profoundly enhances allergic inflammation through increased expression of proallergic cytokines and chemokines. Indeed, IL-33 and its receptor genes are recognized as the most susceptible genes for asthma by several recent genomewide association studies. It has also recently been shown that IL-33 plays a crucial role in innate eosinophilic airway inflammation rather than acquired immune responses such as IgE production [11].

IL-33 binds to the acidic pocket of dimeric histone H2A-H2B at the surface of nucleosomes, resulting in the suppression of the gene transcription at least in the in vitro reporter assay system[12]. Also, intraperitoneal or intranasal administration of IL-33 in mice leads to the induction of inflammation accompanied by eosinophils in mucosa of lung and intestine through the IL-13. The levels of soluble ST2 protein and IL-33 mRNA are increased in sera and/or lungs in a murine asthma model of airway inflammation induced by ovalbumin [13-16].

Chronic inflammation has emerged as a new risk factor for the development of type 2 diabetes. Inflammation plays a key role in patients with (COPD) and asthma increasing evidence points toward a role of asthma and (COPD) in the pathogenesis of type 2 diabetes[17-19].

The objectives of this study were to investigate the differences in the levels of IL-33 between COPD and asthmatic patients, asthmatic patients with diabetes mellitus type 2, COPD patients with diabetes mellitus type 2 and healthy control, study the relation of IL-33 in patients with COPD and asthma to development of type 2 diabetes and determine the correlation of IL-33 with oxidant-antioxidant status, hc-CRP, insulin, insulin resistant and HbA1c.

II. METHODS

One hundred and fifty male individuals (age 40-60) were enrolled in this study which was divided into five groups as follows:

- First group (C) consisted of 30 healthy individuals as a control group.
- Second group (AS) consisted of 30 asthmatic patients.
- Third group (ASD) consisted of 30 asthmatic patients with diabetes mellitus type 2.
- Fourth group (COPD) consisted of 30 patients with chronic obstructive pulmonary disease.
- Fifth group (COPDD) consisted of 30 chronic obstructive pulmonary disease patients with diabetes mellitus type 2.

All patients were diagnosed by physicians and other complications or smoking's were excluded. The range of body mass index (BMI) for the patients and control was (30-35)Kg/m², blood was collected from patients attended the center of asthma in Baghdad, Baghdad Teaching Hospital, Al-kendi Hospital and Al-Kadhemia Teaching Hospital from May 2011 to December 2012. Patients and control groups were determined the following parameters:

- Malondialdehyde (MDA) level was determined in serum as a thiobarbituric reactive species according to the method of Buege and Aust [20].
- Total antioxidant capacity (TAC) was measured in serum using Randox Total Antioxidant Capacity (Cat No. Nx 2331) according to the method of Miller [21].
- Serum interleukin-33 (IL-33) level was measured by enzyme-linked immune sorbet assay (ELISA) method [22].
- Fasting insulin was measured in serum using the DRG insulin ELISA kit according to the method of Judzewitsch [23].
- Serum high sensitive c-reactive protein (hsCRP) level was measured by enzyme-linked immune sorbet assay (ELISA) method [24].
- Glycated hemoglobin (HbA1c) level was measured using Bio-Rad VARIANT hemoglobin A1c program utilizes principles of ion-exchange high-performance liquid chromatography (HPLC)[25].

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- Statistical Analysis: Data are presented as mean \pm SD using SPSS program. The differences between two groups were analyzed by t-test. P-value less than 0.05 considered significant. Pearson's correlation coefficient was used to examine between IL-33 and other parameters in patient groups.

III. RESELUTS

This is the first study to document, as far to knowledge, which depict the relation between IL-33 and oxidant-antioxidant status and some inflammation and diagnostic parameters in COPD and asthmatic patients with type 2 diabetes mellitus. Mean \pm SD of IL-33, hsCRP, MDA, TAC, MDA/TAC, Insulin, Insulin resistant, HbA1c for five groups (C, AS, ASD, COPD, COPDD) were shown in table (1) and P-values of previous parameters for the five groups were shown in table (2). The results in table (1) and table (2) revealed that:-

- Mean of serum IL-33 level in AS was significantly difference greater than in the control group $P < 0.05$. Mean of serum IL-33 level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of serum IL-33 level in patients with COPD was no significantly difference greater than in the control group $P > 0.05$. Mean of serum IL-33 level in COPDD was no significantly difference greater than in the control group $P > 0.05$. Mean of serum IL-33 level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of serum IL-33 level in patients with COPD was no significantly difference greater than in the COPDD group $P > 0.05$. Mean of serum IL-33 level in patients with AS was significantly greater than in the COPD group $P < 0.05$. Mean of serum IL-33 level in ASD was significantly difference greater than in the COPDD group $P < 0.05$.
- Mean of serum hsCRP level in AS was significantly difference greater than in the control group $P < 0.05$. Mean of serum hsCRP level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of serum hsCRP level in patients with COPD was significantly difference greater than in the control group $P < 0.05$. Mean of serum hsCRP level in COPDD was significantly difference greater than in the control group $P < 0.05$. Mean of serum hsCRP level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of serum hsCRP level in patients with COPD was significantly difference greater than in the COPDD group $P < 0.05$. Mean of serum hsCRP level in patients with AS was significantly difference greater than in the COPD group $P < 0.05$. Mean of serum hsCRP level in ASD was significantly difference greater than in the COPDD group $P < 0.05$.
- Mean of serum MDA level in AS was significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA level in patients with COPD was significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA level in COPDD was significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of serum MDA level in patients with COPD was significantly difference greater than in the COPDD group $P < 0.05$. Mean of serum MDA level in patients with AS was no significantly difference greater than in the COPD group $P > 0.05$. Mean of serum MDA level in ASD was no significantly difference greater than in the COPDD group $P > 0.05$.
- Mean of serum TAC level in AS was significantly difference greater than in the control group $P < 0.05$. Mean of serum TAC level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of serum TAC level in patients with COPD was significantly difference greater than in the control group $P < 0.05$. Mean of serum TAC level in COPDD was significantly difference greater than in the control group $P < 0.05$. Mean of serum TAC level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of serum TAC level in patients with COPD was significantly difference greater than in the COPDD group $P < 0.05$. Mean of serum TAC level in patients with AS was significantly difference greater than in the COPD group $P < 0.05$. Mean of serum TAC level in ASD was significantly difference greater than in the COPDD group $P < 0.05$.

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- Mean of serum MDA/TAC and Insulin levels in AS were significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in ASD were significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in patients with COPD were significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in COPDD were significantly difference greater than in the control group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in patients with AS were significantly difference greater than in the ASD group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in patients with COPD were significantly difference greater than in the COPDD group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in patients with AS were significantly difference greater than in the COPD group $P < 0.05$. Mean of serum MDA/TAC and Insulin levels in ASD were significantly difference greater than in the COPDD group $P < 0.05$.
- Mean of serum homeostasis model assessment for insulin-resistance (HOMA-IR) level in AS was significantly difference greater than in the control group $P < 0.05$. Mean of serum HOMA-IR level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of serum HOMA-IR level in patients with COPD was significantly difference greater than in the control group $P < 0.05$. Mean of serum HOMA-IR level in COPDD was significantly difference greater than in the control group $P < 0.05$. Mean of serum HOMA-IR level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of serum HOMA-IR level in patients with COPD was significantly difference greater than in the COPDD group $P < 0.05$. Mean of serum HOMA-IR level in patients with AS was significantly difference greater than in the COPD group $P < 0.05$. Mean of serum HOMA-IR level in ASD was no significantly difference greater than in the COPDD group $P > 0.05$.
- Mean of HbA1c level in AS was no significantly difference greater than in the control group $P > 0.05$. Mean of HbA1c level in ASD was significantly difference greater than in the control group $P < 0.05$. Mean of HbA1c level in patients with COPD was no significantly difference greater than in the control group $P > 0.05$. Mean of HbA1c level in COPDD was significantly difference greater than in the control group $P < 0.05$. Mean of HbA1c level in patients with AS was significantly difference greater than in the ASD group $P < 0.05$. Mean of HbA1c level in patients with COPD was significantly difference greater than in the COPDD group $P < 0.05$. Mean of HbA1c level in patients with AS was no significantly difference greater than in the COPD group $P > 0.05$. Mean of HbA1c level in ASD was significantly difference greater than in the COPDD group $P < 0.05$.

Table(3) showed the correlation between IL-33 and hsCRP, MDA, TAC, MDA/TAC, Insulin, Insulin resistant, HbA1c for the pathological groups (AS, ASD, COPD, COPDD). The results in table (3) revealed that:-

- A significant positive correlation between IL-33 and hsCRP in patients with AS and ASD, significant negative correlation in patients with COPDD and no significant positive correlation in patients with COPD.
- A significant positive correlation between IL-33 and MDA in patients with AS, ASD, COPD and COPDD.
- A significant negative correlation between IL-33 and TAC in patients with AS, ASD, COPD and COPDD.
- A significant positive correlation between IL-33 and MDA/TCA in patients with AS, ASD, COPD and COPDD.
- No significant positive correlation between IL-33 and insulin in patients with AS, ASD, COPD and COPDD.
- No significant positive correlation between IL-33 and HOMA-IR in patients with AS and ASD, significant positive correlation in patients with COPD and COPDD.
- No significant positive correlation between IL-33 and HbA1c in patients with AS, COPD, significant positive correlation in patients with ASD and COPDD.

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Table(1): Mean±SD of IL-33, hsCRP, MDA, TAC, MDA/TAC, insulin, insulin resistant and HbA1c for the five groups (C, AS, ASD, COPD, COPDD).

groups parameters	C(30) Mean±SD	AS(30) Mean±SD	ASD(30) Mean±SD	COPD(30) Mean±SD	COPDD(30) Mean±SD
IL-33(pg/ml)	132.4±50.12	676.5±224.3	458.3±189.8	163.2±70.1	142.6±62.8
hsCRP(g/L)	2.25±0.42	4.17±1.21	6.12±2.32	7.15±2.87	8.2±3.11
MDA(μmol/L)	0.88±0.3	1.64±0.11	2.42±0.23	2.00±0.61	2.88±0.81
TAC(mmol/L)	0.8±0.16	0.50±0.08	0.31±0.03	0.38±0.06	0.22±0.02
MDA/TAC	1.18±0.41	5.24±2.32	10.87±2.72	13.11±4.13	15.43±3.82
Insulin(μIU/ml)	12.5±1.3	18.2±2.5	33.5±7.1	20.6±6.3	36.8±8.2
HOMA-IR	2.61±0.08	5.93±1.1	18.12±5.2	8.22±3.3	20.23±4.1
HbA1c%	4.32±0.51	4.81±1.7	7.99±2.3	5.2±2.1	9.76±3.6

Table(2): P-value between C and AS, ASD, COPD, COPDD, between AS and ASD, COPD between COPD and COPDD, and between ASD and COPDD

P-values parameters	C-AS	C-ASD	C-COPD	C-COPDD	AS-ASD	COPD-COPDD	AS-COPD	ASD-COPDD
IL-33(pg/ml)	S	S	NS	NS	S	NS	S	S
hsCRP(g/L)	S	S	S	S	S	S	S	S
MDA(μmol/L)	S	S	S	S	S	S	NS	NS
TAC(mmol/L)	S	S	S	S	S	S	S	S
MDA/TAC	S	S	S	S	S	S	S	S
Insulin(μIU/ml)	S	S	S	S	S	S	S	S
HOMA-IR	S	S	S	S	S	S	S	NS
HbA1c%	NS	S	NS	S	S	S	NS	S

S: Significant NS: Non-significant

Table(3): -correlation between IL-33 and other parameters for the patient groups.

groups IL-33(pg/ml)	AS		ASD		COPD		COPDD	
	r	p-value	r	p-value	r	p-value	r	p-value
hsCRP(g/L)	0.65	S	0.53	S	0.34	NS	-0.47	S
MDA(μmol/L)	0.55	S	0.75	S	0.68	S	0.88	S
TAC(mmol/L)	-0.48	S	-0.39	S	-0.61	S	0.64	S
MDA/TAC	0.51	S	0.44	S	0.52	S	0.82	S
Insulin(μIU/ml)	0.02	NS	0.05	NS	0.23	NS	0.33	NS
HOMA-IR	0.13	NS	0.2	NS	0.41	S	0.52	S
HbA1C%	0.03	NS	0.49	S	0.27	NS	0.66	S

r: correlation coefficient S: Significant NS: Non-significant

IV. DISCUSSION

IL-33 appears to be a crucial cytokine for Th2-mediated host defense and plays a central role in controlling immune response in tissues. It is able to activate cells of both the innate and adaptive immune system, and depending on the disease can either promote the resolution of inflammation or drive disease pathology[1].

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Tissue damage caused by factors such as high free fatty acids, oxidative stress, and inflammation can lead to necrosis of cells and release of biologically active IL-33. This can interact with its receptor ST2 on a number of cell types within adipose tissue[1]. ST2 was initially shown to be selectively expressed on Th2, but not Th1 [26,27]. Th2 cells and fat-associated lymphoid cluster cells leading to the production of protective Th2 cytokines (IL-5, IL-10 and IL-13). IL-33 can polarize macrophages towards an alternatively activated (M2) phenotype and reduce lipid uptake in adipocytes and macrophages via the down-regulation of several metabolic genes[1,27].

IL-33 reduced lipid storage and decreased the expression of several genes associated with lipid metabolism and adipogenesis. IL-33 lead to protective metabolic effects with reduced adiposity, reduced fasting glucose and improved glucose and insulin tolerance [28].

IL-33 expression was found in higher levels in endobronchial biopsies from human asthmatic subjects compared to controls. IL-33 expression was particularly evident in patients with severe asthma. Recently some studies found that expression of IL-33 is associated with chronic inflammatory condition[1,29,30].

Oxidative stress as seen in patients with chronic inflammatory disease results in injury to the airspace epithelium such as asthma and COPD, increased influx of neutrophils and eosinophils into the lungs, and activation of transcription factors, including nuclear factor- κ B, which switches on the genes for TNF- α , IL-8, and other inflammatory mediators, and production of reactive oxygen species ROS [31].

Excessive reactive oxygen species ROS production leads to alteration in key enzymatic as well as nonenzymatic antioxidants such as glutathione, vitamins C and E, beta-carotene, uric acid, thioredoxin, superoxide dismutases, catalase, and glutathione peroxidases leading to oxidant-antioxidant imbalance in airways, and such oxidative stress leads to pathophysiological effects associated with asthma and COPD and has been implicated in insulin resistance [32].

Reactive oxygen species play a key role in initiation as well as amplification of inflammation in asthmatic and COPD airways interfere with insulin signaling at various levels and are able to inhibit the translocation of glucose 4 (GLUT4) in the plasma membrane, leading to insulin resistance. Moreover, an increase in insulin or glucose levels further increases reactive oxygen species production and oxidative stress, impairing both insulin action and secretion and accelerating the progression to overt type 2 diabetes[31,33].

Induction in TAC levels in groups (ASD and COPDD) suggest the imbalance between oxidant and antioxidant systems and the depletion of the protective antioxidant system may be associated with an increase in risk of complications from COPD and asthma.

Some studies have suggested that a reduced lung function could be a risk factor for the development of insulin resistance or diabetes [34–36]. Other study demonstrated neutrophils and eosinophils activation through activation of nuclear factor- κ B and kinases enzymes by IL-33 are connected to increased oxidative stress, which inducer of ST2 expression and inhibitor of IL-33 signaling through kinases enzymes [37].

C-reactive protein (CRP) is a major inflammatory cytokine that functions as a nonspecific defense mechanism in response to tissue injury or infection. Elevated levels of CRP, IL-6, and TNF- α have been shown to predict the development of the insulin resistance syndrome and type 2 diabetes, supporting a role for inflammation in the pathogenesis of diabetes. Circulating TNF- α levels have been found to be elevated in COPD patients with chronic hypoxemia, TNF- α , a central inflammatory mediator in the process of muscle wasting, promotes cachexia by reducing peripheral insulin action. Muscle loss fat gain, and decreased fat oxidative capacity lead to elevated circulating TNF- α , escalating insulin resistance and muscle loss [31].

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V. CONCLUSION

Although both asthma and COPD are chronic inflammatory conditions, the findings of the present study that COPD but not asthma may be associated with a higher risk of developing type 2 diabetes mellitus. This could be due to differences in the type of inflammation in asthma versus COPD. The cellular infiltrate in asthma contains prominent numbers of eosinophils and Th2 cells and cellular infiltrate of COPD is dominated by neutrophils, macrophages, and Th1 cells. IL-33 receptor is ST2 which is selectively expressed on Th2, but not Th1. Therefore, level of IL-33 in patients with COPD less than patients with asthma. IL-33 reduced lipid storage and decreased the expression of several genes associated with lipid metabolism and adipogenesis. IL-33 lead to protective metabolic effects with reduced adiposity, reduced fasting glucose and improved glucose and insulin tolerance. Therefore, patients with COPD are associated with a higher risk of developing type 2 diabetes mellitus than patients with asthma.

Other finding of the present study that, IL-33 levels in patients groups most possibly reflects the inflammatory component of diabetes and oxidant-antioxidant status, the imbalance between oxidant and antioxidant systems and the depletion of the protective antioxidant system and production of reactive oxygen species ROS were higher in patients with COPD than patients with asthma. Reactive oxygen species interfere with insulin signaling at various levels leading to insulin resistance. And an increase in insulin or glucose levels further increases reactive oxygen species production and oxidative stress, impairing both insulin action and secretion and accelerating the progression to overt type 2 diabetes. Therefore, patients with COPD are associated with a higher risk of developing type 2 diabetes mellitus than patients with asthma.

In spite of anti IL-33 can be used therapeutically for management of asthma but may be increased risk of diabetes mellitus type 2. Therefore, we suggest that possible antioxidant strategies that can be used therapeutically for better management of asthma and COPD.

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