Role of CD14 Gene polymorphism and IgE in pathogenesis of Acute Bronchial Asthma

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Abstract: Acute bronchial asthma is characterized by acute episodes of obstruction relateded to airway inflammation mostly in response to respiratory tract infection. CD14 play a key role in inflammatory pathways. The aim of this study is to determine the influence of CD14 gene polymorphism and its plasma levels on the predisposition to develop asthma and its severity. This study was conducted on 20 patients during acute attack of asthma (group I) and in convalescence (after 6 weeks of treatment of the same patients, group II). Asthma severity scoring system was preformed to all patients according to (Martin et al; 2006). Arterial blood gases, plasma levels of sCD14 and serum total IgE were measured by ELISA. CD14 gene polymorphism was detected by restriction fragment polymorphism (PCR). During acute asthma, plasma levels of sCD14 were higher than during convalescence: sCD14, 3.23±0.48 versus 2.64±0.24 µg/ml, (p= 0.001). Higher plasma levels of sCD14 were present during the acute attack in those with 159TT and 159TC (p= 0.002 & p= 0.001, respectively), whereas in 159CC homozygous, sCD14 levels were insignificantly increase during the acute attacks (p= 0.119). A significant negative correlation was found between sCD14 and asthma score (r= 00.58, p= 0.001). There was a significant positive correlation between IgE and plasma level of sCD14. These results suggest that in acute **asthma** production of sCD14 is increased in an attempt to control airway inflammation, and for subjects whose genotype limits or prevents these increases, the ability to control airway inflammation is impaired resulting in more severe **asthma**.
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Introduction:

Acute asthma is characterized by acute episodes of obstruction related to loss of control of airway inflammation mostly in response to a viral respiratory-tract infection ***(Martin et al., 2006)***. Many genetic variations associated with asthma and asthma phenotypes have been reported ***(He et al., 2001)***. Polymorphisms in several candidate genes have been identified and associated with asthma***(Pinto et al., 2009)***. CD14 is important in clearly defined immunologic and inflammatory pathways ***(Antal-Szalmas 2000)*** Single nucleotide polymorphisms in the promoter regions of their genes alter the amount of expressed protein***(Ohchi et al., 2004)*** and have been extensively studied in adults and children***(Koppelman et al., 2001)***. Differences in gene expression have been identified among individuals with stable asthma, yet dysregulation of pro - or anti-inflammatory processes is likely to have the most critical influence during the early stages of an acute asthma attack, when the loss of control of inflammation could be expected to be maximal***(Smit et al., 2008)***.

CD14 is a key component of the innate immune system and its gene is located on chromosome 5q31.1***(Isabel et al., 2008)***. It is expressed on monocytes and macrophages, functions as a receptor for lipopolysccharide receptor***(Ulevitch and Tobias 1995)***, and exists in a membrane-bound form and a soluble form (sCD14). CD14 plays a critical role in determining the balance of Th1:Th2 cytokines, with activation promoting the release of interleukin 12 and deviation of immune responses towards an antiviral T-helper type 1 (Th1) response ***(Macatonia et al., 1995))***. A C-T polymorphism at position 159 in the promoter of CD14 (C-159T) modulates the cellular response to endotoxin and significantly influences total IgE levels***(Kowal et al., 2008)***. The effect of this genetic variant on the cytokine response of the inflammatory cells is incompletely understood***(Keskin et al., 2006)***. This polymorphism has been shown to be associated with increased levels of sCD14 and decreased serum immunoglobulin E (IgE)***(Buckova et al., 2006)*** and the expression of a more severe atopic phenotype in previous studies***(Smit et al., 2007)***.

CD14 gene may have had age-dependent effects on asthma-related phenotypes, including atopy and airway hyper responsiveness ***(Kiley et al., 2007)***. The CD14 protein is part of the receptor complex for endotoxin ***(O'Donnell et al., 2004)*** which is a potent

inflammatory agent and may contribute to the high prevalence of respiratory disorders ***(Vercelli 2004)***. Genetic variation in the CD14 gene may modify the interaction between endotoxin exposure, allergic diseases, and asthma severity ***(Hasday et al., 1999)***. The aim of this study is to determine the influence of CD14 gene polymorphism and its plasma levels on the predisposition to develop asthma and its severity.

Subjects and methods:

This study included 20 patients who attending Chest Disease Unite, Internal Medicine Departments, Mansoura University Hospital during acute attack of asthma (group I) and in convalescence (after 6 weeks of treatment of the same patients, group II). The patients were subjected to the following: Full history taking and complete clinical examination with stress on duration and severity of the disease; Arterial Blood Gases; Asthma severity scoring system was preformed to all patients according to ***(Martin et al., 2006)***; Plasma levels of sCD14 was measured by ELISA using commercially available ELISA kits (*R&D systems, Minneapolis, MN)*; Serum total IgE was measured by ELISA *(Biomerieux Vitek Inc., Marcy, France)* ***(Panhuysen et al., 1995)***; CD14 gene polymorphism by restriction fragment polymorphism (PCR).

Extraction of genomic DNA:

Blood was collected in EDTA-tubes and stored at room temperature until the genomic DNA was extracted using QIA amp DNA Mini Kit from QIAGEN according to the manufacturer` s instructions .

Determination of CD14 polymorphism *(Ouburg et al., 2005)*:

The C-T substitution in the proximal **CD14** promoter GC box at position -260 from the translation start site results in a **Hae** III restriction site. The primers, 5' TCA CCT CCC CAC CTC TCT T 3' (sense) and 5' CCT GCA GAA TCC TTC CTG TT 3' (antisense) (Invitrogen Life Technologies, Breda, The Netherlands), flanking this restriction site. Amplification was performed using a thermal cycler (Biometra). The parameters were an initial denaturation at 95°C for 5 min, followed by 35 cycles: denaturation at 95°C for 30 s, annealing at 59°C for 30 s, and elongation at 72°C for 1 min. The final elongation was at 72°C for 7 min followed for a cooling to 4°C. Then digested overnight at 37°C with **Hae** III (Invitrogen, The Netherlands). These fragments were analyzed by electrophoresis on 4% low melting agarose gels stained with ethidium bromide. The assay thus yields one 497-bp band for the CC genotype , three bands of 144, 353, and 497 bp for CT heterozygotes, and two bands of 144 and 353 bp for TT homozygotes**.**

Table (1) Scoring system of asthma severity

	1 Point	2 points	3 points
oxygen saturation	>90 %	90-95 %	<90%
Auscultation	Nil to mild end expiratory wheeze	expiratory wheezing	Inspiratory and expiratory wheezing or diminshed breath sounds
Retractions	None or intercostal	Intercostal and substernal	Intercostal and substernal and supraclavicular
Dyspnoea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts
Respiratory rate: (/min)	2 – 6 years <36 7 – 9 years <31 10 – 13 years <27 >13 years <24	36 – 39 32 – 35 28 – 30 25 – 27	>39 >35 >30 >27

Statistical analysis:

The data was collected, presented and statistically analyzed with the computer program SPSS version 9 using the following tests, ANOVA test, Fisher Exact test, Chi–square test, unpaired test and linear regression test. Probability (p) values of less than 0.05 were considered significant.

Results:

During acute asthma, plasma level of sCD14 was higher than during convalescence: CD14, 3.23±0.48 µg/ml versus 2.64±0.24 µg/ml (p=0.001);. Genotype percentages in acute asthma, the CC, CT& TT genotypes percentages for CD14 C-159T were (25%,42%,32.5% respectively) [Table 2]. During the acute episodes of asthma, a plasma level of sCD14 was significantly related to genotype for CD14 C-159T. Mean plasma sCD14 levels were highest in subjects with CD14–159TT (3.64±0.21 µg/ml), followed by heterozygous (3.2±0.36 µg/ml), and lowest for those with CD14-159CC (2.61±0.1 µg /m) p< 0.05 [Table 3]. While, IgE concentration was higher in CD14-159 CC genotype than both CT and TT genotypes respectively (p<0.05) [Table 5]. Higher plasma levels of CD14 were present during the acute attack than convalescence in those with 159TT and 159TC (p=0.002 and p=0.001, respectively), whereas in 159CC homozygous, CD14 levels there was insignificant increase during the acute attacks than convalescence (p=0.119). [Table 4] CD14-159CC genotypes had significant higher mean asthma severity scores compared with the other genotypes (CD14 C-159T, CC 11.4 vs. CT 9.1 vs. TT 9.6, p <0.05, [Tables 6]. A significant negative correlation was found between sCD14 and asthma score (r=00.58, p=0.001). As regard IgE level, there was a significant positive correlation between IgE and plasma level of sCD14, and asthma score [Table 7].

Table (2) plasma sCD14 and CD14 genotype frequencies

	Group I (acute asthma)	**Group II (Convalesence)**	**t**	**P**
sCD14 Range (µg /ml) Mean ±SD	2.5-4.1 3.23±0.48	2.1-3.2 2.64±0.24	9.46	0.001*
Genotypes				
CD14 C-159T n (%)	**CC**	**CT**	**TT**	
	10 (25)	**17 (42.5)**	**13 (32.5)**	

* Significant (p < 0.05).

Table (3) plasma concentration of sCD14 in relation to its corresponding genotypes:

CD14 C-159T	**CC**	**CT**	**TT**
Range(µg/ml)	2.5-2.8	2.9-3.5	3.3-4
Mean	2.61	3.27	3.64
SD ±	0.1	0.36	0.21
F (P)	40.24 (0.000*)		
Tukey's test			
CC &	CT	0.003*	CT & TT 0.002*
	TT	0.001*	

Table (4): plasma sCD14 concentrations in relation to corresponding genotypes during acute asthma attack and convalescence

Genotypes	**Acute asthma**	**Convalescence**	**t**	**p**
CD14 C-159T				
TT Range Mean±SD	3.3-4 3.64±0.21	2.4-3.1 2.74±0.21	14.02	(0.002)*
TC Range Mean±SD	2.9-3.5 3.27±0.36	2.2-2.9 2.55±0.21	9.04	(0.001)*
CC Range Mean±SD	2.5-2.8 2.61±0.1	2.3-2.7 2.5±0.12	1.72	(0.119)

Table (5): Serum IgE concentrations among CD14 genotypes in all studied groups

Serum IgE	CD14genotypes C-159T		
	CC	**CT**	**TT**
Range(µg/ml)	100-260	130-250	55.3-125.6
Mean±SD	198.5±49	191±41.1	87.9±24.2
F (P)	32.7 (0.000*)		
Tukey's test			
CC &	CT	0.82 NS	CT & TT 0.000*
	TT	0.000*	

NS: non significant

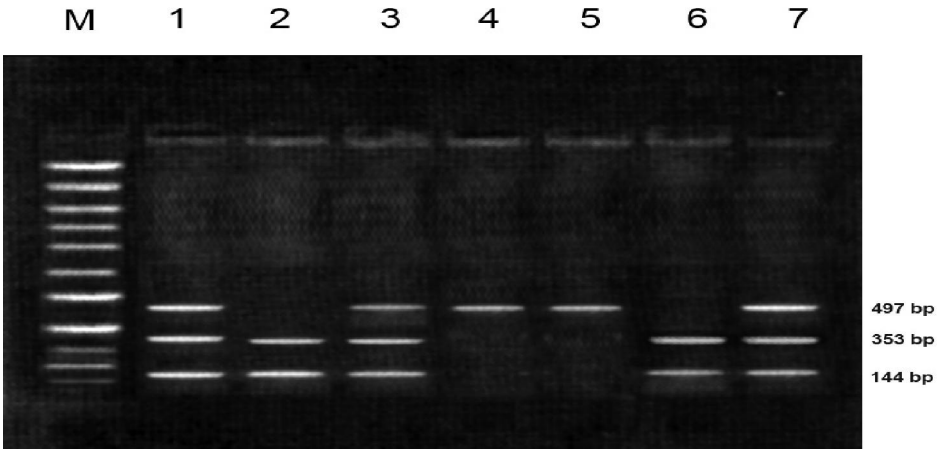

Fig (1): Agarose gel electrophoresis for PCR products stained with ethidium bromide detecting Polymorphism at 159 bp of flanking region of the CD14 gene by restriction fragment assay. CC homozygotes are in lanes(4 and 5) with single band of 497 bp, TT homozygotes are in lanes(2 and 6) with two bands of 144 and353 bp: and CT

Table (6): Asthma severity score and its relationship to CD14 genotypes:

Asthma severity score	CD14genotypes C-159T		
	CC (n=10)	**CT (n= 17)**	**TT (n= 13)**
Range	8-15	5-11	6-10
Mean ±SD	11.4±2.0	9.1±1.8	9.6±2.0
F (P)	5.98 (0.005*)		
Tukey's test			
CC &	CT	0.004*	CT & TT 0.53 NS
	TT	0.003*	

Table (7): Correlation between asthma score and CD14 and IgE:

	Asthma score		IgE	
	r	**p**	**r**	**p**
sCD14	-0.58	0.001	0.517	0.002
IgE	0.436	0.005		

Discussion:

Bronchial asthma is a complex disease caused by a combination of genetic and environmental factors ***(Hammad and Lambrecht 2008)*** and exposure to various environmental stimuli can effect on the pathogenesis of the disease ***(Tamari et al., 2009)***. Many genetic variations associated with asthma and asthma phenotypes have been reported ***(Cookson 2004)***. Although a large number of studies have identified possible genetic loci and chromosomal mutations that may be involved in the development of asthma or these related phenotypes with stable disease ***(Schwartz 2009)***, additional researches are needed to clarify the influence of genetic differences in acute asthma and asthma exacerbation, as transcription of genes involved in asthmatic inflammation is likely to be maximal during acute exacerbation. CD14 is a multifunctional receptor expressed in the surface of monocytes, macrophages and neutrophils or serum soluble ***(Ulevitch and Tobias 1995)***. It is the main receptor of lipopolysaccharides (LPS) or inhaled endotoxins, which are potent inducers of pulmonary inflammation and may activate the immune system and cause Th1 differentiation and/or Th2 suppression***(Isabel et al., 2008)***. It has been proposed that altered CD14 expressions, more increased in asthmatics after LPS inhalation, can change the balance of Th1-Th2 cells, influencing IgE levels and inflammations in allergic diseases such as asthma ***(Alexis et al., 2001)***. Thus changes in CD14 expression seem to be important, especially in allergic asthma, and functional polymorphic variants of the CD14 gene modulate the response to LPS ***(Simpson et al., 2006)***. The most prevalent single nucleotide polymorphism in CD14 is the C-159T polymorphism, which is associated with changes in serum IgE level ***(William et al., 2006)***. The genetic variants of the CD14 promotor region affect both monocyte expression of CD14 and serum concentration of soluble CD14 ***(Kowal et al., 2008)***. In order to investigate the influence of genetic difference in acute asthma to elucidate the underlying mechanisms of acute exacerbation, we study genetic polymorphism for CD14 and its t plasma level during acute asthma and during convalescence. However the association between the C-159T CD14 polymorphism and asthma has been demonstrated in some but not all studies ***(Sharma et al., 2004; Kedda et al., 2005; Zambelli-Weiner et al., 2005 and Tan et al., 2006)***. In the present study, we found that acute asthma, plasma level of sCD14 was higher than during convalescence($p<0.001$) and this higher level were present in one genotype than others. During the acute episodes of asthma, plasma levels of sCD14 were significantly related to genotype for CD14 C-159T. Mean plasma sCD14 levels were highest in subjects with CD14–159TT, followed by heterozygous and lowest for those with CD14–159CC. These results are in agreements with studies of ***Martin et al., 2006*** and ***Kowal et al., 2008***, they found that sCD14 were higher only in subjects with CD14-159 TT and159CT but not in those with 159CC. This study demonstrated that genotype-specific differences in plasma levels of sCD14 during acute exacerbation was even more pronounced than during convalescence, a higher plasma levels of CD14 was present during the acute attack in those with 159TT and 159TC ($p=0.002$ and $p=0.001$, respectively), whereas in 159CC homozygous, CD14 levels there was insignificant increase during the acute attacks ($p=0.119$). Although ***Kedda et al., 2005*** found that C-159T polymorphism has been associated with increased sCD14 in children and there were no difference in CD14 serum levels in adults with different genotypes for CD14.Enhanced expression of CD14 and increased sCD14 levels that seen in subjects carrying the TT genotype leads to increased activation of cells involved in the immune response and increased secretion of proinflamatory mediators including TNF-α, IL-1B, IL-12 and IFN-γ skewing the immune response towards Th1***(Keskin et al., 2006; Renckens et al., 2006 and Hong et al., 2007)*** . Serum level of IgE concentration was higher in CD14 -159 CC genotype than both CT and TT genotypes respectively ($p1=0.002$, $p2=0.003$). These results are in accordance with ***Baldini et al., 1999*** who found that CD14/-159 TT homozygous showed significantly lower levels of total serum IgE than did both CC and CT subjects and they explain this by their finding that an association between sCD14 levels and low IL14 and high IFN-γ, which intern may regulate IgE responses and consequently IgE levels***(He et al., 2001; Pinto et al., 2009; Buckova et al., 2006 and Williams et al., 2006)***. In this study, CD14–159CC genotypes had significant higher mean asthma severity scores compared with the other genotypes (CD14 C-159T, CC 11.4 vs. CT 9.1 vs. TT 9.6, $p<0.05$). Those subjects who was CD14 –159CC was over three times more likely to have moderate or severe attacks of acute asthma compared with the other genotypes ***(Zambelli-Weiner et al., 2005)***. The preferential transmission of the C allele to children with severe atopic asthma was demonstrated in an Indian population ***(Sharma et al., 2004)*** and an association between the T allele and lower asthma severity scores was found in population from Barbados***(Zambelli-Weiner et al., 2005)***. Thus analysis of the frequency of the C allele in our patients provides further support for the association between that polymorphism and asthma severity as the increased frequency of the C allele was found in patients with moderate to severe asthma but not in mild asthmatics, linking the C allele of CD14 with increased risk of asthma severity and exacerbation. A potential mechanism in determining severity of an acute attack is impaired ability to increase sCD14 ***(Kowal et al., 2008)***. The effect of CD14

C-159T on asthma severity was partly dependent on plasma sCD14 levels, with higher levels associated with a milder asthma attack, possibly because of increased Th1 cytokine release ***(Keskin et al., 2006 and Kedda et al., 2005)***. A significant negative correlation was found between sCD14 and asthma score (r= 00.58, p=0.001). Consistent with this reports, ***Martin et al.,2006***, found that during acute asthma attacks in children, plasma sCD14 levels were inversely correlated with severity, suggesting a protective role for sCD14. Plasma sCD14 levels have been directly correlated with IFN-γ and inversely correlated with IL-4, suggesting that in children with acute asthma, the beneficial effect of greater CD14 activity may result from increased Th1 and decreased Th2 responses ***(He et al., 2001 and Isabel et al., 2008)***. A relative predominance of Th1 over Th2 cytokines assists in the elimination of viral infections ***(Ramshaw et al., 1997 and Hoebee et al., 2003)***, thus lower levels of sCD14 may allow ongoing viral replication and inflammation. These results suggest that in acute asthma production of CD14 is increased in an attempt to control airway inflammation, and for subjects whose genotype limits or prevents these increases, the ability to control airway inflammation is impaired, resulting in more severe asthma Therefore, this study supports the concept that sequence variations in the CD14 gene are likely to play a role in the development of asthma.

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