

## IL-17 level in patients with acute myocardial infarction and its effect on lipid profile

Ammal Esmaeel Ibrahim <sup>a,\*</sup>, Hiba Ali Hasan <sup>b</sup> and Alaa Hussein Jawad <sup>a</sup>

<sup>a</sup> Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, 10072, Iraq

<sup>b</sup> Department of Clinical Laboratory Science, Collage of Pharmacy, Al-Mustansiriya University, Baghdad, 10052, Iraq

\*Corresponding author at: Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, 10072, Iraq.  
 Tel.: +964.0790.1566784. Fax: +964.0790.1566784. E-mail address: [dr.ammalalobaidi@yahoo.com](mailto:dr.ammalalobaidi@yahoo.com) (A.E. Ibrahim).

### ARTICLE INFORMATION



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### ABSTRACT

Myocardial infarction (MI) is considered as the major cause of death and disability worldwide, and despite considerable advances in diagnosis and treatment, continues to be a major public health problem. Interleukin-17 (IL-17) is leukocyte-derived cytokine with effects especially on epithelial cells in various tissues. This study designed to investigate the level of IL-17 and its effect on lipid profile in patients with Acute Myocardial Infarction. The study included 50 patients with acute myocardial infarction forty healthy subjects as control group. The levels of IL-17 were significantly elevated in all patients groups ( $p < 0.001$ ), total cholesterol, LDL, VLDL were significantly elevated ( $p < 0.001$ ) in all patients as well. There was positive correlation between IL-17 with HDL, while there was negative correlation with total cholesterol and LDL. The results show significant increase in levels of IL-17, in acute myocardial infarction patients. IL-17 positively correlated with HDL and negatively correlated with total cholesterol and LDL, which lead to consider it as cardio protective factor.

### 1. Introduction

Interleukin-17 is a member of polypeptides family with six different homodimeric cytokines (IL-17A-F) and the heterodimeric IL-17A/F. Their interactions with IL-17 receptors A-E (IL-17RA-E) mediate host defenses while also contributing to inflammatory and autoimmune responses. IL-17A and IL-17F both preferentially engage a receptor complex containing one molecule of IL-17RA and one molecule of IL-17RC. More generally, IL-17RA appears to be a shared receptor that pairs with other members of its family to allow signaling of different IL-17 cytokines. Binding to IL-17RA at one side of the IL-17A molecule induces a conformational change in the second, symmetry-related receptor site of IL-17A. This change favors, and is sufficient to account for, the selection of a different receptor polypeptide to complete the cytokine-receptor complex. The structural results are supported by biophysical studies with IL-17A variants produced by site-directed mutagenesis [1].

A unique intracellular signaling domain was identified within all IL-17Rs, termed similar expression to fibroblast growth factor genes and IL-17R (SEFIR). SEFIR is also found in NF- $\kappa$ B activator 1. However, the ligand specificities of many of these receptors have not been established. The IL-17 signaling system is operative in disparate tissues such as articular

cartilage, bone, meniscus, brain, hematopoietic tissue, kidney, lung, skin and intestine. Thus, the evolving IL-17 family of ligands and receptors may play an important role in the homeostasis of tissues in health and disease beyond the immune system. This survey reviews the biological actions of IL-17 signaling in cancers, musculoskeletal tissues, the immune system and other tissues [2].

Interleukin 17 is cytokine which acts as a potent mediator in delayed-type reactions by increasing chemokine production in various tissues to recruit monocytes and neutrophils to the site of inflammation, similar to Interferon gamma. IL-17 is produced by T-helper cells and is induced by IL-23 which results in destructive tissue damage in delayed-type reactions [3]. Interleukin 17 as a family functions as a proinflammatory cytokine that responds to the invasion of the immune system by extracellular pathogens and induces destruction of the pathogen's cellular matrix. Interleukin 17 acts synergistically with tumor necrosis factor and interleukin-1 [4].

Atherosclerosis is a lipid-driven, chronic inflammatory disease of the vessel wall in which both innate and adaptive immune responses play a role [5]. Immune cells and their mediators directly cause the chronic arterial inflammation that is a hallmark of atherosclerosis. Macrophages, T lymphocytes and mast cells contribute to the smoldering inflammatory response in the vessel wall [6].

**Table 1.** Comparison between groups for Age, BMI, IL-17, and lipid profile.

Parameters	AMI	Control
Age	63.0±8.7	60.00±6.36
BMI	28.22±2.31	27.67±3.04
IL-17 pg/mL	8.86±3.70	3.50±1.01
Total cholesterol	200.34±22.50	157.98±9.16
LDL	186.9±25.4	177.87±15.11
Triglyceride	175.38±11.03	155.53±24.09
VLDL	35.13±19.22	31.14±12.10
HDL	36.08±5.41	49.11±5.32
LDL/HDL	5.16	3.61
Total cholesterol/ HDL	5.55	3.30

The array of cytokines implicated in atherosclerosis is strikingly similar to those used by immune effector cells to kill foreign pathogens and defective or diseased host cells [7]. Virtually every major cell lineage used in host defense has been identified in human and/or animal plaques [8].

This study designed to investigate the level of IL-17 and its effect on lipid profile in patients with Acute Myocardial Infarction.

## 2. Experimental

This study was performed during the period from December 2011 to April 2012. This study include fifty patients with Acute Myocardial Infarction (AMI) were admitted to Cardiac Care Unit (CCU) at Medical City Teaching Hospital and Ibn-ALbetar Hospital in Baghdad patients, with rang 50-78 years old, were included in this study. Blood samples were taken from the patients after having thoroughly examined after exclusion of subjects with a history an AMI or diabetes mellitus or any chronic diseases. Control groups contain forty subjects matched in: age, sex and BMI, were included in this study as control group (Table 1).

### 2.1. Blood collection and laboratory analysis

From each patient and control, 5 mL venous blood was aspirated from a suitable vein. Samples were collected between 8-9 A.M. after 10 hours fast. Blood samples were transferred to plain tubes for storage to measure IL17. The non-heparinized blood in the plain tubes were left to clot and than centrifuged at 4000 rpm for 5 minutes to separate the serum to measure the lipid profile the remain of serum is dispensed into tightly closed Eppendorf tubes in 1.0 mL and stored at -20 °C until assayed. Each serum sample was analyzed for urea and creatinin to excluded kidney diseases. IL-17 measured by using ELISA kits from United States Biological Company.

### 2.2. Statistical analysis

Statistical analysis was performed by statisticians with the SPSS 15.01 Statistical Package for Social Sciences and also Excel 2003. Data analysis was done using chi-square test for tables with frequencies, while we used independent sample t-test for tables with means and standard deviations. *p* value of  $\leq 0.05$  was used as the level of significance. Correlation coefficient used to find the correlation between studied markers by using Pearson correlation. Descriptive statistics for the clinical and laboratory results were formulated as mean and standard error.

## 3. Results and discussion

The role of IL-17A to atherogenesis remains controversial, with different studies proposing either a pro-atherogenic or an athero-protective contribution for IL-17A. In patients with unstable angina, levels of plasma IL-17A and the Th17-related cytokines IL-6 and IL-23 are elevated [9].

Emily Smith study mention that "the soluble levels of IL-17A are elevated in the onset of acute coronary syndrome compared to stable angina and in a subset of aged patients with coronary atherosclerosis and referent outpatients" [10]. Monocytes express IL-17RA on their surface, and recent data suggests that IL-17A can also directly affect monocyte chemotaxis in vivo and in vitro [11]. There is more than one pathway by which IL-17A might influence in local inflammation. IL-17A enhance the production of cytokines and chemokines in several cell types, including endothelial and vascular smooth muscle cells (VSMCs) [12], also IL-17A with increase in IL-2, IL-6, and TNF- $\alpha$ . Study by Mohsen Ibrahim *et al.* suggested that IL-6 is a pro-atherogenic cytokine [13]. Increased in IL-6 was also associated with reduced collagen content in the plaques, blunted synthesis, and release of IL-10 and diminished recruitment of inflammatory cells into the atherosclerotic plaque. Elevated levels of IL-6 are also a primary stimulant of soluble intercellular adhesion molecule-1 (sICAM-1), which mediates the attachment and migration of leukocytes across the endothelial surface [13] soIL-17A can effect on plaques by indirect way by increase the release of IL-6. IL-17A also synergistically initiate production of CXCL1 and CXCL10 in cultured VSMCs [12]. CXCL1 is a chemokine that causes monocyte capture on endothelium during atherogenesis and therefore, acting a critical role in monocyte recruitment into artery wall [14].

Emily Smith, report that blocking IL-17A in vivo lead to reduced CXCL1 expression within atherosclerosis-prone aortas and weakened aortic macrophage content. Emily Smith also prove that the pro-inflammatory role of IL-17A in the regulation of monocyte migration into the aortas via ex vivo monocyte adhesion assay, thatpoint toIL-17A contributes in the pathogenesis of atherosclerosis through the controlling of monocyte enrollment to the aortic wall at least via CXCL1. IL-17A regulates the levels of G-CSF in circulation and thus, affects neutrophil numbers in the blood. Cultured human T cells isolated from atherosclerotic coronary arteries also produce of IL-17A after polyclonal stimulation compared to T cells extracted from non-diseased vessels [10].

Administration of a rat-anti-mouse IL-17A antibody into Apoe<sup>-/-</sup> mice fed resulted in a 50% reduction in aortic root lesions. IL-17A powerfullystimulates IL-8 and Vcam1 expression in human umbilical vein endothelial cells (HUVEC) and apoptosis in vascular smooth muscle cells (vSMCs), [15]. Gao *et al.*, examined the influence of rat-anti-mouse IL-17A neutralizing or isotype control Abs on rapid carotid stenosis and atherosclerosis in Apoe<sup>-/-</sup> mice. Anti-IL-17A-treated mice showed aobviousreduces in aortic root plaque size, and carotid artery stenosis, and thatagreed with a decrease in immunohistochemical MoMA2 and  $\alpha$ -smooth muscle actin staining within carotid arteries [16]. Thus suggest that IL-17A plays a pro-inflammatory role in atherosclerosis through the induction of aortic chemokines, cytokines, and accumulation of macrophages within atherosclerotic plaques.

In the intact heart in vivo, IL-17 neutralization results in reduced necrotic and apoptotic myocyte death, suggesting that inhibition of the IL-17 pathway may be of therapeutic benefit in human Myocardial Infarction.

**Table 2.** The correlation (*r*) between IL-17 with (lipid profile) for studied group.

Parameters	<i>r</i>	<i>p</i> value
Total cholesterol	-0.453	<0.001
LDL	-0.385	<0.001
Triglyceride	-0.246	<0.001
VLDL	-0.246	<0.001
HDL	+0.351	<0.001

IL-17 involved in the clearance of extracellular pathogens and has been considered as a driving force in many inflammatory diseases [17].

Our study contradicts with the study that found patients with higher IL-17 levels had reduced risk of major cardiovascular, in this study risk factors are the cholesterol and LDL-cholesterol, events may provide further evidence of a beneficial role of IL-17. In mice with myocardial infarction, IL-17 may be used therapeutically for treating MI, considering that it may ameliorate, rather than exacerbate, the disease [18].

The negative correlation between IL-17 A and total cholesterol as well as LDL-C in our study may suggest that the increased level of IL-17 stimulate LDL-C receptor expression in hepatic cell that subsequently lead to increased uptake of LDL particles and decreased LDL-C plasma level [19].

In Table 2 our results show that highly significant negative correlation between IL-17 and all lipid profile except for HDL which show highly significant positive correlation, these findings suggest that increase in IL-17 level is affect myocardial infarction via dyslipidemia so that make us consider it as cardiovascular protective factor. Proinflammatory cytokines are known to contribute to features of the metabolic syndrome, such as: hypertension, dyslipidemia, insulin resistance, endothelial dysfunction, clotting system activation, pro-oxidative stress and pathogenesis of atherosclerosis [15,20].

HDL-C has antioxidant and anti-inflammatory properties also have anticoagulant effect and enhances half-life of post stacyclin. The anti-inflammatory properties of HDL-C may be particularly relevant here, because we observed systematic inflammation and endothelial activation in patients with low HDL-C level [21]. Our result of positive correlation between IL-17 and HDL is may be because several proinflammatory cytokines have been implicated in the overall regulation of plasma HDL concentrations [22]. This finding is disagreement with results from previous studies which reports that IL-17 expression is up regulated under hypercholesterolemia conditions [22-24]. Another study show that cholesterol incubation significantly increases IL-17A production, which is consistent with findings in mice that a high-fat diet leads to increased IL-17A production [25]. Also, IL-17A Ab-treated mice have reduced atherosclerotic lesions in the presence of unchanged serum cholesterol and HDL/LDL ratio, therefore IL-17A is unlikely to affect atherogenesis via changes in hyperlipidemia or production of oxLDL Abs [15].

#### 4. Conclusion

The results show significant increase in levels of IL-17, in acute myocardial infarction patients. IL-17 positively correlated with HDL and negatively correlated with total cholesterol and LDL, so that make us consider it as cardio protective factor.

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