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THE IMPACT OF ATORVASTATIN RELOAD IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION AND ITS CORRELATION WITH THE TOLL-LIKE RECEPTORS

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ABSTRACT

The present study aims to evaluate the effect of pre percutaneous coronary intervention (PCI) atorvastatin reload on peripheral monocyte of toll-like receptor 2 and toll like receptor 4 expression and their correlation with cardiac injury markers (troponin I and creatine kinase Muscle brain isoenzyme) in a patient with stable angina. A double-blind randomized prospective trial in which 60 stable angina patients scheduled for an elective PCI were randomly allocated into two groups after, control group: 30 patients who received low dose atorvastatin 40 mg daily without reload. Atorvastatin reloads group: 30 patients who were already on the usual dose of atorvastatin with further 80 mg and 40 mg at 12 & 2 hrs. before PCI, respectively. TLR2 and TLR4 levels were assayed in peripheral monocyte by flow cytometry and cardiac troponin I, CK-MB, MCP-1 and HMG-box-1 protein were also measured before and at 4 hrs, 12 hrs after PCI. Stent implantation was associated with an elevation in TLR2 and TLR4 expression in peripheral monocyte in both study groups after stenting but significantly higher expression level was observed among the control group ($P < 0.05$) at 4 hr and 12 hr post PCI. Inflammatory cytokine (HMG Box-1 protein MCP-1) were remarkably elevated after stenting in both. study groups ($P < 0.005$) but significantly higher in control group as compared to the atorvastatin reload group ($P < 0.05$) also myocardial injury markers (CKMB, troponin I) were significantly higher in control group than atorvastatin reload group ($P < 0.05$).there is a positive correlation between TLR2 and TLR4 expression with serum level of cardiac troponin I and CK-MB

Atorvastatin reload before coronary artery interventions attenuate toll-like receptor 2 and 4 expressions on peripheral monocyte and significantly reduce serum level of HMG-box-1protein, MCP-1 and cardiac injury markers (CK_MB and cardiac troponin I) and Increase peripheral monocyte expression of TLR2 and TLR4 associated with elevated serum level of cardiac injury markers (CK_MB and cardiac troponin I).

Key words: Atorvastatin, percutaneous coronary intervention

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INTRODUCTION

Coronary artery disease (CAD) is the main cardiovascular diseases affectingthe population all over the world. This disease has been found to be a critical cause of mortality and morbidity in developing and developed cities. environmental factors, Lifestyle, and genetic factorsinclude hypertension, diabetes mellitus, hyperlipidemia, smoking, obesity, homocysteine urea, and psychosocial stressare critical risk factors for the initiation of cardiovascular disease and itsdevelopment [1]. PCI with stent implantation has been widely used and has been proved effective for the treatment of symptomatic ischemic heart disease. However, stenting causes severe damage to the vascular wall and induce inflammatory reaction by a combination of plaque fracture and deployment of the stent [2]. The inflammatory process shows a vital role in atherosclerotic disease of coronary artery Inflammatory cytokines enhance reactive oxygen species productionthat has a fundamental role in the cardiovascular disease pathogenesis of atherosclerosis and cardiovascular disease [3]. TLRs are well-known innate immunity system barriers in present on many immune and non-immune cells, plays a fundamental role in the atherosclerotic plaques formation and subsequentarterial remodeling and plaqueinstabilityby releaseof several inflammatory cytokines found to be associated with cardiovascular disease [4]. Many ligands(exogenous and endogenous) such as lipopolysaccharide (LPS), lipoprotein, heat shock protein (HSP) 60, fibrinogen,mm LDL, and High mobility group box 1 protein have been identified [5]. HMG-box-1protein is a novel pro-inflammatory cytokine in coronary artery disease. So, increased level of it in case of atherosclerosis is associated with a high risk of inflammation and subsequent complication following interventional processes (PCI and CABG) in patients with stable and unstable coronary heart diseases [6]. Atorvastatin first synthesized by Bruce Roth in 1985 [7], is an inhibitor of HMG-CoA reductase thatblocks the biosynthesis ofcholesterol and its associated precursorswhich are isoprenoid products of mevalonate [8]. Atorvastatin is an appropriate first-line lipid-lowering therapy in many subjects with high and low to high-risk CAD. It is an effective drug for patients requiring greater decreases in LDL-cholesterol level [9]. Atorvastatin expresses a dose-dependent effect on serum level of LDL-C with reductions of about 21% to 60%. and so better improvement in cardiovascular diseases. In addition to the effects on serum lipid, improving endothelial function, stabilizing atherosclerotic plaques, anti-oxidant, modulation of immune response and attenuating inflammatory response may also account for the clinical benefits of statins therapy.

PATIENTS AND METHOD

Study design: Prospective double-blind randomized control trial

Study population

Sixty chronic stable angina pectoris patients on chronic atorvastatin treatment with significant stenosis coronary artery of referred by their special cardiologist to the Al-Najaf center for cardiac surgery and transcatheter therapy for PCI were included in the present study. The patients were divided randomly into two groups after exclusion of the patients who suffered from acute coronary syndromes within the previous 1 month, creatinine ≥ 2mg/ml patients with chronic renal insufficiency, Patient on chronic steroid therapy,

autoimmune diseases, or chronic infection or on antibiotic treatment, patient with any type of cancer or taking chemotherapy, patients with thyroid gland disease, patient with elevated liver enzyme, patients with chronic asthma and pregnant women were excluded.

Control group: 30 patients with stable angina on chronic atorvastatin therapy (40 mg /day) without a loading dose of atorvastatin.

Atorvastatin reload group: include 30 patient with stable angina on chronic atorvastatin therapy (40 mg/day), received further two doses of atorvastatin 80 mg 12 hrs. before elective PCI And 40 mg atorvastatin 4 hr. before the procedure [10]. All randomized patients were enrolled after signing the consent form and the study received prior approval from the Kufa University/Faculty of Medical **Ethics Committees**

Blood sampling and processing

From each patient, three blood samples were obtained. The first sample was taken immediately before the procedure, and the second aspiration about 4 hr. after the PCI, lastly 3rd blood sampling was drawn 12 hr after PCI in each we drew 5 ml of blood from a peripheral vein. The 5ml were divided into 2 ml of aspirated blood put in sterile EDTA tube for flow cytometry analysis (TLR2 and TLR4) and 3 ml of blood put in coagulation enhancer tube and centrifuged at 3000×g for 5 mins to extract serum that's stored in -80°C that to be used for the assay of troponin I, CK-MB, and MCP-1.

Flow cytometric analysis

The peripheral monocyte cells expression of TLR2 and TLR4 was measured by bricyte E6 flowcytometry. a blood sample was stained with fluorescent Phycoerythrin PE (anti-TLR2) antibody and florescent Peridinin chlorophyll protein (PerCP) TLR4 antibody at 4°C and dark environment for 45 minutes. After that the mixture incubated with the RBC lysis buffer, then the mixture was washed with phosphate buffer, irrelevant Isotype-matched control IgG was used as a control. The bricyte E6 (Mandray, China) flowcytometry measured the cell-associated fluorescence of the washed cells and the data were analyzed by MR flow software.

ELISA technique

Sandwich enzyme immune assay was performed for measuring concentrations of serum level of MCP-1 using Elabscience Elisa kits and Calbiotech Elisa kits for troponin I and CKMB serum level. 100µl serum was added to each well and incubate for 1.5 hours at room temperature. After that,100 µl prepared biotinylated detection antibody was added to each well and incubated for 1 hour at room temperature aspirate and wash 3times.Then100µl HRP conjugate solution was added and incubated for 30 minutes at room temperature aspirate and wash 5times. 90 µl substrate reagent was added and incubated for 15mintes at 37C. 50 µl of stop solution was added finally The intensity of the color was measured at 450 nm.

Statistical analysis

Statistical analyses were performed using statistical package for social science (SPSS).categorical variable were presented as number and percentage. Chi-square test was used to express the association between categorical variables, Continuous variables were presented as Mean ±standard error of the mean, a Paired t-test was used for comparison of means at a various time point. The unpaired test used for comparison between 2groups.P value <0.05 was regarded as statistically significant, Spearman's correlation test was performed to correlate between TLR2 and 4 peripheral monocyte expression and cardiac injury markers.

RESULT

All the baseline parameter of both groups are statistically similar regarding gender, age, smoking, history of diabetes mellitus, hypertension, drugs intake, total cholesterol, renal and liver function test. The demographic characteristic of participated patients presented in Table 1

Table 1. Demographic characteristic of participants of this study

Patients characteristics	Control	Atorvastatin	P
Male	20(66.7%)	20(66.7%)	N.S
Age (years)	60.1 ± 5.2	62.3 ± 4.3	N.S
Smoking	14 (36.7%)	12 (66.7%)	N.S
Diabetes	12 (40%)	15 (50%)	N.S
Insulin	5 (16.7%)	4 (13.3%)	N.S
Oral hypoglycemic	9 (30%)	11(36.7%)	N.S
Hypertension	19(63.3%)	22(73.3%)	N.S
Aspirin	30 (100%)	30 (100%)	N.S
Clopidogrel	30 (100%)	30 (100%)	N.S
B-blockers	18 (80%)	14 (46.7%)	N.S
ACE inhibitors	18 (60%)	21 (70%)	N.S
Calcium channel	13 (43.3%)	17 (56.7%)	N.S
Nitrates	30 (100%)	30 (100%)	N.S
HbA1C	6.9±0.1	7.2±0.4	N.S
Blood Urea (mg/dl)	28.6 ± 4.7	26.8 ± 4.8	N.S
Serum Creatinine	0.8 ± 0.2	0.9 ± 0.2	N.S
WBC (count)	8.5± 0.7	7.9± 0.9	N.S
TC mg/dl	192.7 ±	197.5 ±	N.S
INR	1.07±0.06	1.09±0.09	N.S
APTT(sec)	26.4±1.2	26. 8±1.4	N.S
PT(sec)	14.2± 0.02	14.2±0.02	N.S
ALT (IU/l)	27±1.4	26±1.6	N.S
AST(IU/l)	24±1.6	24±0.9	N.S

Data presented as Mean ± SE; N.S Not significant; P-value <0.05

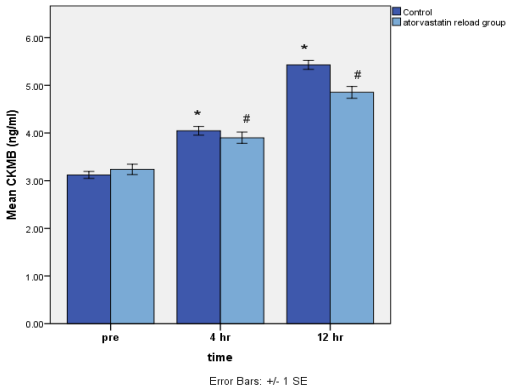


Figure 1. Effect of atorvastatin reload on CK_MB ng/ml pre PCI and at 4 hr, 12hrs after PCI . in comparison to the control group
***Control groups at (4, 12) hrs. vs. pre-stent (p<0.05).**
 # Atorvastatin reloads groups at (4, 12) hrs. vs. control groups (p<0.05).

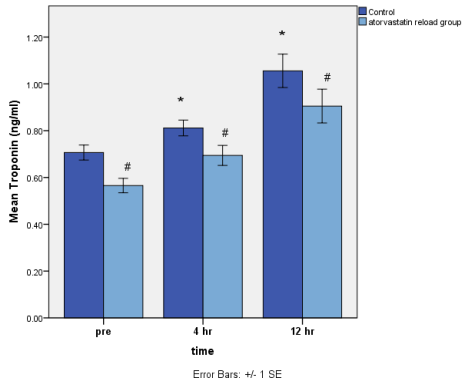


Figure 2. Effect of atorvastatin reload on Troponin I (ng/ml)pre PCI and at 4 hr, 12hrs after PCI . in comparison to the control group
***Control groups at (4, 12) hrs vs. pre-stent (p<0.05).**
 # Atorvastatin reloads group at (4, 12) hrs vs. control groups (p<0.05).

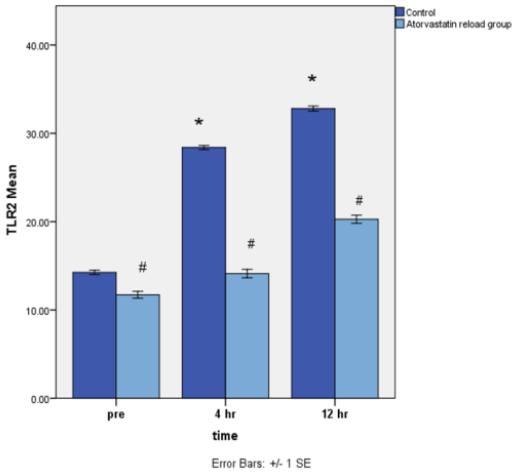


Figure 3. Effect of PCI and atorvastatin reload on peripheral blood monocyte expression of TLR2 pre PCI and at 4 hr, 12hrs after PCI in comparison to the control group
***Control groups at (4, 12) hrs vs. pre-stent (p<0.05).**
 # Atorvastatin reloads group at (4, 12) hrs vs. control groups (p<0.05).

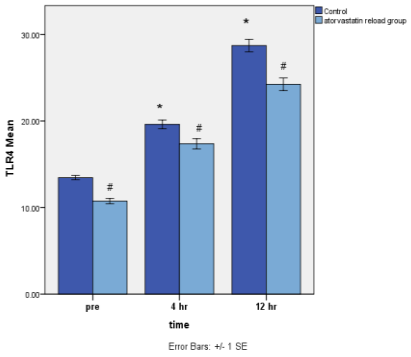
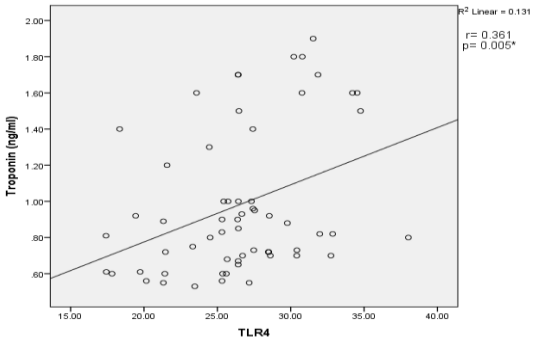


Figure 4 .Effect of PCI and atorvastatin reload on peripheral blood monocyte expression of TLR4 pre PCI and at 4 hr, 12hrs after PCI in comparison to the control group
***Control groups at (4, 12) hrs vs. pre-stent (p<0.05).**
 # Atorvastatin reloads group at (4, 12) hrs vs. control



groups (p<0.05).

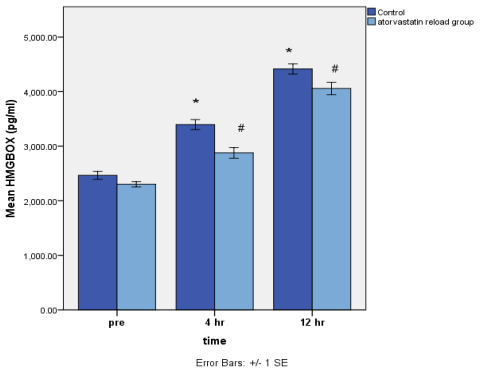


Figure 5. Effect of PCI and atorvastatin reload on HMGBox-1protein pg/ml pre and (4 ,12)hrs post intervention.
***Control groups at (4, 12) hrs vs. pre stent(p<0.05).**
 # Atorvastatin reload groups at (4, 12) hrs vs. control groups (p<0.05)

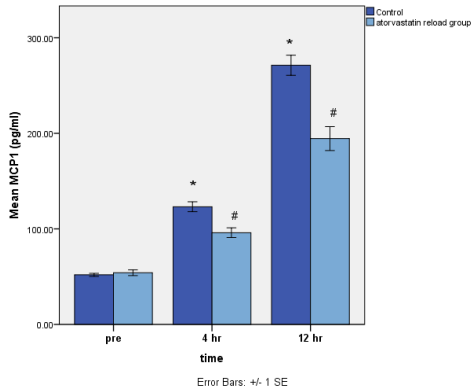


Figure 6. Effect of PCI and atorvastatin reload on MCP-1pg/ml pre and (4 -12)hrs. in comparison to the control group
***Control groups at (4, 12) hrs. vs. pre-stent (p<0.05).**
 # atorvastatin reloads groups at (4, 12) hrs. vs. control groups (p<0.05).

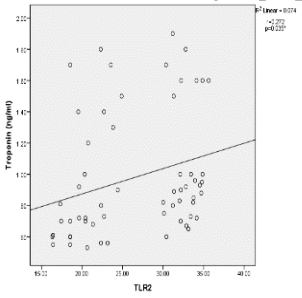


Figure 7.Correlation between A TLR2 expression on peripheral monocyte and cardiac Troponin I

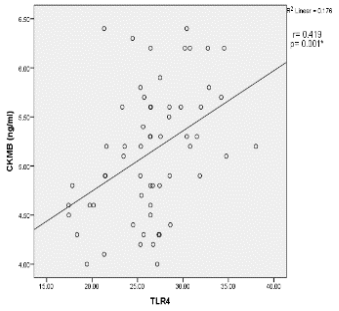
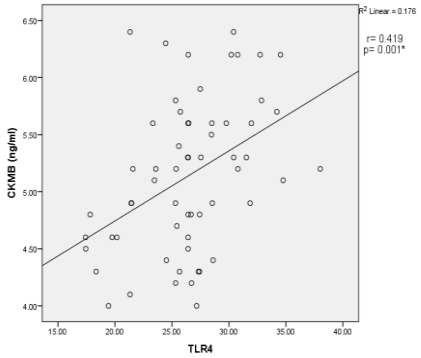


Figure 8. Correlation between A TLR2 expression on peripheral monocyte and CK-MB

Figure 9. Correlation between A TLR4 expression on peripheral monocyte and cardiac Troponin I



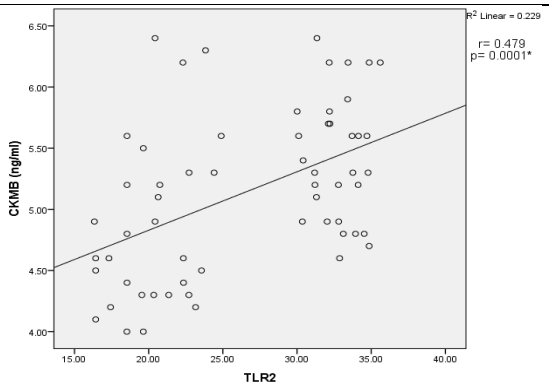


Figure 10. Correlation between A TLR4 expression on peripheral monocyte and CK-MB

Effect of PCI on myocardial injury markers at different time point

After the stent implantation, a remarkable elevation ($p<0.05$) in the CK-MB and cardiac troponin I level at 4 and 12 hrs. was observed against pre-stent level in both study groups. But this increment in myocardial injury markers was remarkably reduced ($p<0.05$) in the atorvastatin reload group than the control group. This change in serum level of myocardial injury markers isshown in Figures 1and 2. Effect of PCI and atorvastatin reloadon peripheral blood monocyte expression of TLR 2 at different time points. There was a notable increase in the TLR2 expression on peripheral blood monocyte after stent implantation at (4 and 12) hrs. respectively inboth groups ($p<0.05$) but the Monocyte expression of toll-like receptors 2 was remarkably higher ($p<0.05$) in control group than in atorvastatin reload group at (4 and 12) hrs. after PCI. This finding presented in Figures 3. Effect of PCI and atorvastatin reload on peripheral blood monocyte expression of TLR 4 at different time points. There is a significant increase in the TLR4 expression on peripheral blood monocyte after stent implantation at (4-12) hrs. respectively in control and atorvastatin reload group ($p<0.05$). Furthermore, Monocyte expression of toll-like receptors 4 was remarkably higher ($p<0.05$) among control group than in the atorvastatin reload group at (4 and 12) hrs. after PCI as shown in Figure 4. Effect of PCI and atorvastatin reload on MCP-1 serum level at different time point. In the current study there is no baseline difference in MCP-1serum level in both study groups but significantly elevated ($p<0.05$)(4 and 12) hr. post-stenting in both groups with a higher level in the control group than atorvastatin reloads group these findings are shown in figure 5.

Effect of PCI and atorvastatin reload on HMGBox-1protein serum level

In the present study, there is a significant elevation ($p<0.05$)in the serum level of HMG-box-1protein (4 and12)hr. as a response to stenting in both study groups and this increment significantly higher in control group than atorvastatin reload group at (4 and 12)hr. and these results are shown in Figure 6. Correlation between peripheral monocyte TLR 2 expression and cardiac troponin I and CK-MB. There is positive relationship between TLR2 and cardiac troponin I ($p=0.035$and $r=0.272$) and Ck-MB ($p= 0.0001$and $r =0.479$) as shown in Figure 7and 8.

Correlation between peripheral monocyte TLR 4 expression and cardiac troponin I and CK-MB

There is positive relationship between TLR4 and cardiac troponin I (p=0.005and r=0.361) and Ck-MB (p= 0.001and r=0.419) as shown in Figure 9 and 10

DISCUSSION

Despite modern advances in technology and widespread use of antiplatelet and other therapy at the time of intervention, troponin I and creatine kinase (CK-MB) elevation still elevated in many patients after the percutaneous coronary intervention [11]. A peri-procedural increase of myocardial injury markers is frequently found, in up to 40% following PCIof patients, even when the procedure uncomplicated and seems successful, this elevation in myocardial injury markers depends on the complexity of the lesion and underlying clinical conditions [12]. In this prospective randomized study, there was a significant increment in myocardial injury markers (CK-MB, troponin I) after PCI in both study groups but more in the control group than atorvastatin reload group. The incidence of periprocedural myocardial injury isstrongly associated with systemic inflammation and endothelial injury that results from implantation of the stent and balloon inflation [13]. Saha et al. observed that the atorvastatin loading dose significantly reducesmarkers of myocardial injury that follow percutaneous coronary intervention. A single high dose of atorvastatin administered 24 h before elective PCI in patients with stable angina on chronic statin therapy is able to decrease the occurrence of peri procedural myonecrosis after elective PCI. These benefits of statin may result from short-term pleiotropic effects [14]. During PCI technique(in a patient on chronic atorvastatin treatment) breakthrough inflammation precipitated by injury to the blood vessels and plaque and this inflammation is suppressed by atorvastatin reload before PCI [15] short-term high-dose pretreatment with atorvastatin before PCI in a patient with NSTE-ACS can attenuate cardiac injury marker by its anti-inflammatory effect and microvascular function improvement [16]. Cardioprotectiveeffect of Statin are lost over longer treatment period due to activation of Phosphatase Tensin homolog (PTEN)which is a potent inhibitor of PI3\AKT signaling pathway so reloading of statin will inhibit PTEN and stimulate PI3\AKT signaling pathway which increase gene expression of endothelial nitric oxide synthase, enhance angiogenesisdecreased vascular inflammation, inhibition migration and proliferation of VSMC, enhances macrophages and VSMCs apoptosis in the atherosclerotic plaques and increased stability of the plaque and improve endothelial function by increasing endothelial progenitor cells. In the current study, we assessed the effect of atorvastatin reload before PCI on HMG box-1 protein and we found that there was a significant reduction in HMGBox1protein level in atorvastatin reload group in comparison with the control group before and after the intervention. The distension ofthe arterial wall, placement of the stent, and the vascular lesion caused by the balloon angioplasty act as a strong stimulus for the inflammatory process and HMGB1 released. HMGB1 released into the extracellular compartment in two different ways: active secretion from activated innate immune cells such as monocytes and macrophages or Released passively from necrotic cells Once it's released from necrotic cells and it will upregulate IL-1, IL-6, TNF-α, CRP [17]. HMGB1 isnon-chromosomal nuclear protein, present in different cell types with a highly similar sequence among species. HMGB1 acts as an intracellular regulator of transcription, such as p53 and nuclear factor-κB (NF-κB), and plays a crucial role in the maintenance of DNA functions [18]. Elevated HMGB1 serum level before PCI acts as a predictor of myocardial injury after the percutaneous coronary intervention. HMGB1 acts as a pro-inflammatory cytokine and act as an endogenous ligand for toll-like receptors two and four. HMGB1 is an important proinflammatory cytokine that playsa vital role in the myocardial ischemia\reperfusion injury, the pathogenesis of atherosclerotic CAD, heart failure, and peripheral artery disease. There significant correlation between coronary heart disease severity and HMGB1 level In patients with coronary artery disease, hsCRP, TNF-α and IL-6 [19], cTnI andin-stent restenosis. HMGB1is an endogenous ligand for TLR2 and TLR4 after its release from necrotic or inflammatory cells activate the release of various inflammatory cytokine and chemokine that cause myocardial cells damage and release of CK-MB and cardiac troponin I and it may reflect the degree of coronary artery stenosis in patients with SAP. HMGB1 expressed abundantly in atherosclerotic plaques is derived from human autopsy specimens. Patients with hyperlipidemia have high HMGB1 serum levels and atorvastatin treatment decrease serum HMGB1 levels by its lipid-lowering effect. In the current study, we found that atorvastatin by its pleiotropic effects as anti-inflammatory, anti-oxidant and immunomodulatory will decrease HMGBox1 protein in systemic circulation and so inhibit other inflammatory cytokine releases. In the present study, we found that TLR2 and TLR4 expression in human monocytes increased significantly in both atorvastatin reload group and control groups at 4hr and 12hr after stent implantation .but the increment was higher in control patients than in patients who received atorvastatin loading dose. monocyte expression of TLR4 elevated after PCI in patients with stable angina pectoris(1). Oxidative stress and the inflammatory process associated with ischemia/ reperfusion resulted from stenting and balloon inflation increase monocyte expression of toll-like receptors and further activation of NF-kB. Chronic atorvastatin Pretreatment with more than 1month and further loading dose 80mg and 40mg 12 and 2hr before stenting will decrease cell expression of toll-like receptors by inactivation of IKK which activate IKB that inhibit NF-kB [20]. TLR2 and TLR2 activations act as a potent stimulant for intimal hyperplasia and acceleration of atherosclerotic plaque formation. TLR4 is necessary for the oxLDL-induced macrophage differentiation into foam cells so TLR4 is a critical mediator in oxLDL-induced inflammatory cytokine expression in vascular smooth muscle cells. Statins have a direct regulatory effect on TLR4 expression in human monocytes that influences cellular activation. Statins reduce CD14 monocytes surface expression of TLR4 in vivo and ex vivo in a dose-dependent way which leads to reduced expression of pro-inflammatory cytokines. Atorvastatin exerts its anti-inflammation effect through inhibition of LPS-induced upregulation of TLR4 mRNA and its downstream NF-kB, p38, and ERK signaling pathways in human aortic endothelial cells and human umbilical-vein endothelial cells [21]. High TLR2 and TLR4 expression on peripheral monocyte have a positive

correlation with cardiac injury markers(Troponin I and CK-MB) so increase peripheral monocyte expression cause more inflammatory cytokine release and more cardiac damage. Atorvastatin was the most potent statin which could exert acute and rapid response on the inflammation within 5 minutes after administration. And a part of pleiotropic actions of atorvastatin is the modulation of TLR expression and activation on peripheral monocytes through immunomodulatory effects. In ourstudy, the level of MCP-1 in the systemic circulation after atorvastatin reloads was significantly less ($p<0.05$)compared to the control group (at 4-12) hrs post-intervention. Vascular Endothelial damage and trauma associated with PCI cause increase in MCP-1 level immediately post-intervention. MCP-1 level detected in peripheral blood after endothelial cell injury induced by balloon inflation has a fundamental effect on activation and recruitment of monocytes and other inflammatory cells and in the evolution of atherosclerosis and its higher level reflect the atheromatous plaques instability [22], and acts as a strong predictor for future restenosis. High serum levels of MCP-1 have been found after myocardial reperfusion, patients with myocardial infarction and patients with heart failure [23]. Oxidized-LDL (ox-LDL) is a powerful stimulant for monocyte chemotactic protein expression from macrophages, vascular smooth muscles cell, and endothelial cells. This expression of MCP-1 induced by oxidized-LDL is level and time-dependent manner. Statins, by its well-known lipid-loweringeffect, will reduce oxidized lipid which is one of the stimulants for monocyte/macrophage for inflammatory cytokine and chemokine production and through itsanti-inflammatory effectsby its effects on (NF-kB) activity, decrease expression of monocyte chemoattractant protein-1 in endothelial cells, SMC and monocytes/ macrophages.

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