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Atorvastatin Reload Down Regulates TLR-2 Expression and Reduces the Acute Inflammatory Response in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT
Coronary artery disease (CAD) is the single most common cause of morbidity and mortality in developed world. PCI with stent implantation is a widely used, safe and effective technique for the treatment of symptomatic ischemic heart disease. Stenting, however, causes significant injury to the vascular wall, resulting in a repair process that requires inflammatory process activation. This study was done to assess the effect of pre PCI atorvastatin reload on toll like receptor 2 expressions with its downstream signaling**.** A double blind randomized prospective trail in which 60 patients with stable angina pectoris, who are scheduled for an elective PCI at Al-Najaf Center for Cardiac Surgery and Trans Catheter were enrolled and were assigned randomly1:1 into two groups, after an ethical committee of the University of Kufa /Faculty of medicine approval, 30 patients who received low dose atorvastatin 40mg daily without reload (control group). Stent implantation was associated with an elevation in TLR 2 expression in peripheral monocyte in both study groups after stenting but significantly higher expression level was observed among control group than atorvastatin reload group ($p<0.05$) at 4hrand 12hr post PCI. Inflammatory cytokine (MMP9, MCP-1, and IL-6) were significantly increased after stenting in both study groups ($P<0.005$) but higher in control group than atorvastatin reload group ($p<0.05$) also myocardial injury markers (CKMB, troponin I) were significantly higher in control group than atorvastatin reload group ($p<0.05$). We conclude that atorvastatin reload before coronary artery interventions attenuate toll like receptor 2 expression on peripheral monocyte and significantly reduce serum level of MMP9,MCP-1 and IL-6and cardiac injury markers(CK_MB and cardiac troponin I)

Keywords: PCI, ATORVASTATIN RELOAD, TLR2, IL-6, MCP-1, MMP9, myocardial injury markers and percutaneous coronary intervention

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INTRODUCTION

Stable angina pectoris commonly defined as chest discomfort arises due to coronary heart disease (CAD) and gets worsened by exertion or emotional stress and relieved by rest or nitroglycerin. the major reason being the disturbance between myocardial oxygen supply and demand and such condition cause classic angina [1]. The pathogenesis of the disease suggests atherosclerotic coronary artery obstruction as the major reason behind the occurrence of the disease. Statins (HMG-CoA reductase inhibitors) are generally suggested against stable CAD and acute coronary syndrome; this might be due to their lipid lowering activity [2-3]. Such significant activities along with endothelial function restoration activity, anti-inflammatory effect, oxidative stress reduction and thrombogenic inhibition have suggested a potential role of pre-PCI (percutaneous coronary intervention) statin in improvement outcomes for patients [4-7]. Stent implantation as a therapeutic model analyzes the potential interrelation among statin therapy, atherosclerotic disease progression and serum evidence of inflammation, generally resulted by proliferation and migration of vascular smooth muscle cells [8]. Various immune cells express toll-like receptors (TLRs), such as B cells, Neutrophils, microglial cells, dendrite cells, macrophages and also non-immune cells, such as skeletal muscle, fibroblasts, epithelial cells, keratinocytes, myocytes and neurons. However, till now 13 TLRs have been identified in mammals [9-10] TLR2 is a cell surface receptor that binds a wide range of microbial components, such as gram-positive-derived lipoteichoic acid, bacterial lipoproteins. It is present in a number of epithelial cells ,immune cells, and endothelium [11]. TLR2 has a unique ability to form functional heterodimers with either TLR6 or TLR1 and causes relatively broader ligand specificity. TLR2 expression, along with that of TLR1 and TLR4, is markedly increased in endothelial cells overlying atheromas [11-12]. The expression and activation of endothelial TLR2 takes place at of the region of turbulent blood flow, in experiments using human coronary artery endothelial cells under laminar blood flow showed decreased TLR2 expression when compared to endothelial cells exposed to static or turbulent flow [13]. Exogenous TLR2 activation stimulates atherosclerotic plaque formation. TLR2 is involved in the initial intimal lesion formation and development of the occlusive disease. TLR2 promotes migration of vascular smooth muscle cell from tunica media to the intima in an IL-6 dependent manner [14].

PATIENT AND METHODS

From 680 patients admitted to the Al-Najaf center for cardiac surgery and Tran's catheter therapy from July to September 2017. Full medical and drugs history were taken from those patients and full relevant investigation were made before the start of the study , Only 60 patient were fill field the inclusion criteria which are (chronic stable angina on chronic atorvastatin treatment 40mg/day

for more than 1month with significant coronary artery stenosis (50-99%) in luminal diameter of coronary arteries that diagnosed by angiography and provided written informed consent) Those patients were referred by their cardiologist to the Al-Najaf center for cardiac surgery and trans catheter therapy for PCI. patients with acute coronary syndromes (ACS) such as unstable angina pectoris or myocardial infarction, within the previous 1 month and creatinine ≥ 2 mg/ml in patients with chronic renal insufficiency ,all patients on chronic steroid therapy, autoimmune diseases or chronic infection or on antibiotic treatment, with any type of cancer or taking chemotherapy, those with thyroid gland disease, with elevated liver enzyme and with chronic asthma, advanced age and pregnancy were excluded from the this study. The enrolled patients were divided randomly 1:1 into two groups: The control group included 30 patients with stable angina on chronic atorvastatin therapy (40 mg/day) without a loading dose of atorvastatin. Atorvastatin reload group included 30 patient with stable angina on chronic atorvastatin therapy (40 mg/day). They received further two doses of atorvastatin 80 mg, 12 hrs before elective PCI and 40 mg atorvastatin 2 hrs before the procedure [29]. All randomized patients that were enrolled in the study provided written informed consent and the study protocol were approved by the Kufa University\faculty of medicine ethics committees. From each patient three blood samples were taken the first sample was taken immediately before the procedure, the second aspiration about 4 hr after the PCI, and lastly the third blood sampling was drawn 12 hr after PCI. From each patient, a volume 5 ml of blood was taken from the peripheral vein. The 5 ml blood samples were further divided into 2 ml of aspirated blood and poured in sterile EDTA tube for immediate flow cytometry analysis (TLR2) and 3 ml of blood poured in coagulation enhancer tube and centrifuged at 3000 ×g for 5 mints to extract serum. The serum was stored at -80°C and subsequently used for the assays of troponin I, CK-MB, MMP9, MCP-1 and IL-6.

Flow cytometry Analysis

Peripheral blood monocyte Cells were stained with florescent Phycoerythrin PE (anti-TLR2) antibody at 4°C and dark environment for 45 minutes. After that the mixture incubated with the RBC lysis buffer, and then the mixture was washed with phosphate buffer. Isotope-matched irrelevant control IgG was used as a control, the peripheral monocyte cells -associated fluorescence was determined with bricyteE6 (Mandray, China) flow cytometry. Data were assessed by the MR-flow software.

ELIZA technique

Sandwich enzyme immune assay was performed for measuring concentrations of serum level of IL-6, MMP9 and MCP-1 using Elabscience kits and Calbiotech Elisa kits for troponin I and CKMB serum level. A volume of 100 µl serum, in microtiter, was incubated for 2.5 hours under room temperature. Furthermore, a volume of 100 µl prepared biotin antibody was pipette into each well with 1-hour incubation under room temperature. Streptavidin solution (100 µl) was added to the wells followed by an incubation period of 45 minutes and then the color intensity was determined at 450 nm.

Flow cytometry Analysis

Cells were stained with florescent Phycoerythrin PE (anti-TLR2) antibody at 4°C and dark environment for 45 minutes. PE-conjugated non-specific mouse IgG2a antibodies were used for isotope controls. Cells were washed and cell-associated fluorescence was measured by using bricyteE6 (Mandray, china) flow cytometry data were analyzed by MR flow software.

ELIZA technique

Sandwich enzyme immune assay was performed for measuring concentrations of serum level IL-6, MMP9and MCP-1 using Elabscience kits and Calbiotech Elisa kits for troponin I and CKMB serum level .100µlserum was added to microtiter plates. The incubation time was 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. 90µl 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 analyses

Statistical package for social science (SPSS) version 20 analyzed the obtained data and the categorical variables were presented as numbers and percentages. The association among the variables was measured using Chi-square test. A continuous variable was expressed as the Mean ± standard error of mean; a Paired t-test was used for comparison of means at the various time points. The unpaired test used for comparison between 2groups.P value <0.05 was regarded as statistically significant.

RESULT

All the baseline parameters of both groups are statistically similar regarding gender, age, and smoking, history of diabetes mellitus, hypertension, drug intake, total cholesterol, and renal function test. The demographic characteristic of participated patients summarized in table 1

Effect of PCI on myocardial injury markers at different time point

After the stent implantation, a remarkable improvement ($p<0.05$) in the CK-MB and cardiac troponin I level at 4 and 12 hrs was observed against the 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 are summarized in Figures 1and 2

Effect of PCI and atorvastatin reload on 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 (4-12) hrs. Respectively in both 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 (4-12) hrs after PCI. This finding summarized in Figures 3, 4 and 5.

Effect of PCI and atorvastatin reload on MMP9 serum level at different time points

In our study, there is no baseline difference between the two study groups while its level elevated in both group (4-12) hr post coronary intervention but more elevation in the control group than high dose atorvastatin group. Figure 6 summarized this finding.

Effect of PCI and atorvastatin reload on MCP-1 serum level at different time point

There was no baseline difference in the MCP-1serum level in both study groups but was significantly elevated ($p>0.05$) after 4-12 hr. post-stenting in both groups with a higher level in the control group these findings are expressed in Figure 7.

Effect of PCI and atorvastatin reload on IL-6 serum level at different time points.

In the present study there is no baseline difference in IL-6 serum level in both study groups but significantly elevated ($p<0.05$)(4-12) hr. post stenting in both groups with higher level in the control group these finding are expressed in figure 8

Table 1: Demographic characteristic of participated patients

Patients characteristics	Control group (n=30)	Atorvastatin reload group (n=30)	P-value
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 blockers	13 (43.3%)	17 (56.7%)	N.S
Nitrates	30 (100%)	30 (100%)	N.S
Investigation			
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 (mg/dl)	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 ± 19.3	197.5 ± 24.3	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

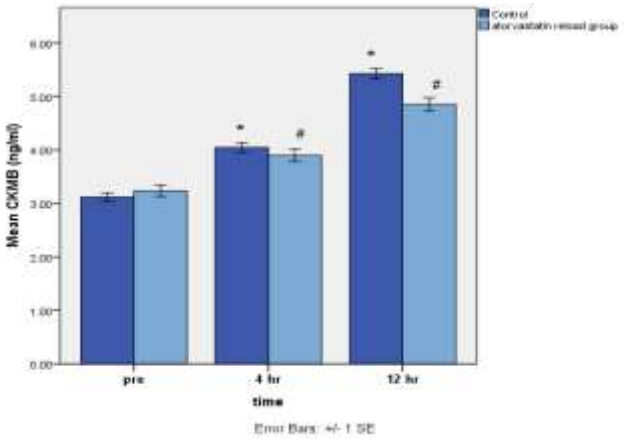


Figure 1: Effect of atorvastatin reload on CK_MB ng/ml pre PCI and at 4 hr, 12hrs after PCI in comparison to the control group

*Control groups at (4, 12) hrs vs. pre-stent ($p<0.05$)
Atorvastatin reloads groups at (4, 12) hrs vs. control groups ($p<0.05$)

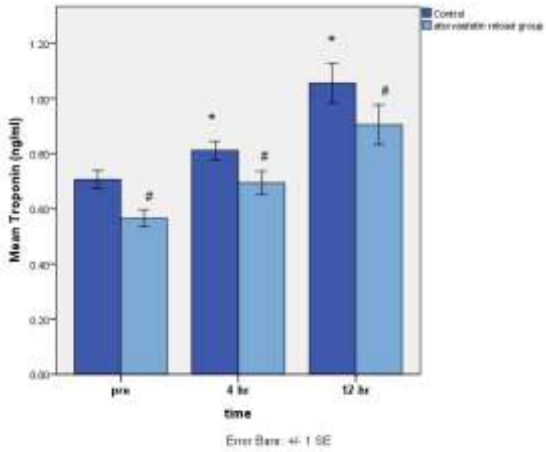


Figure 2: Effect of PCI and atorvastatin reload on Troponin I ng/ml level pre PCI and at 4 hr, 12hrs after PCI in comparison to the control group

*Control groups at (4, 12) hrs vs. pre stent ($p<0.05$)
Atorvastatin reloads groups at (4, 12) hrs vs. control groups ($p<0.05$)

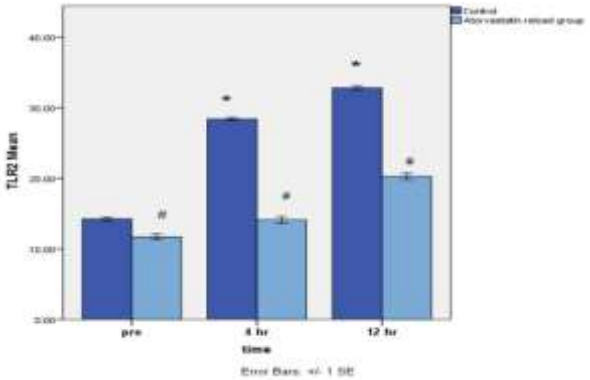
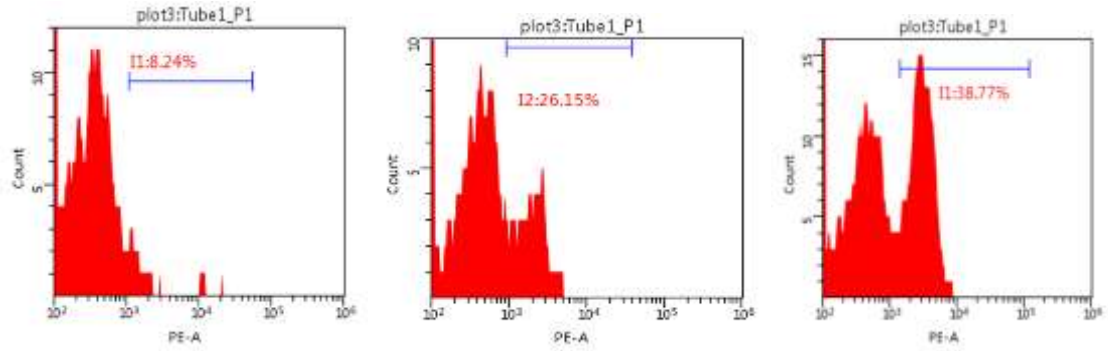


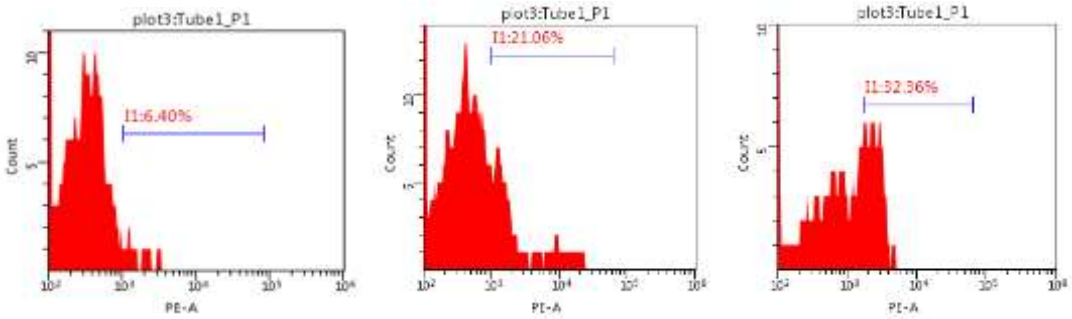
Figure 3: Effect of PCI and atorvastatin reload on peripheral blood monocyte pre PCI and at 4 hr, 12hrs after PCI in comparison to the control group expression of TLR2

*Control groups at (4 and 12) hrs vs. pre-stent ($p<0.05$)
Atorvastatin reloads group at (4 and 12) hrs vs. control groups ($p<0.05$)



A B C

Figure 4: Toll like receptor 2 expression in peripheral monocyte in the control group. A before, B and C (4 and 12) hr. after PCI



A B C

Figure 5: Expression of TLR2 in peripheral monocyte in atorvastatin reload group A before PCI, B and C (4-12) hr. after PCI

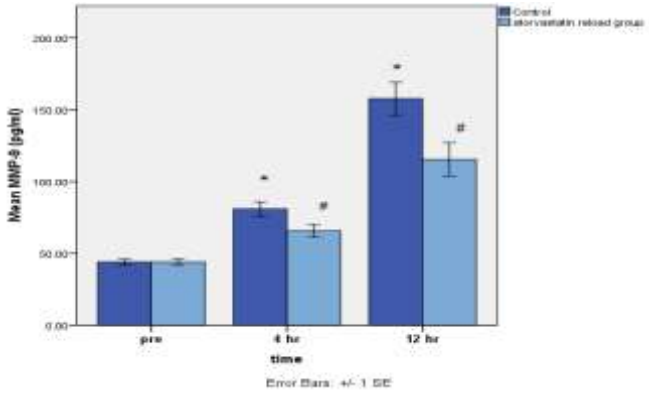


Figure 6: Effect of PCI and atorvastatin reload on MMP9pg/ml pre and (4 -12) hrs. In comparison to the control group
*Control groups at (4, 12) hrs vs. pre-stent (p<0.05)
Atorvastatin reloads groups at (4, 12) hrs vs. control groups (p<0.05)

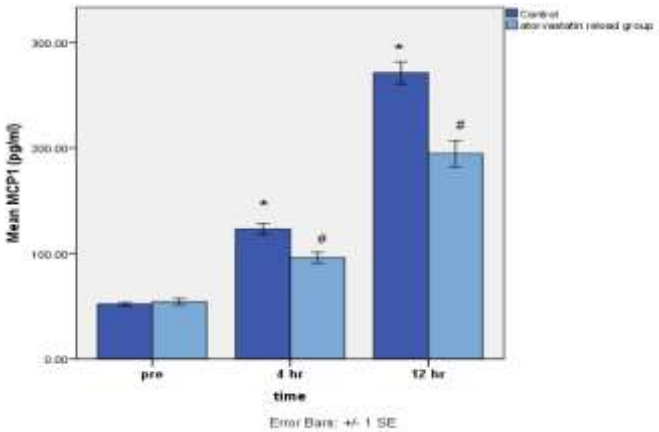


Figure 7: Effect of PCI and atorvastatin reload on MCP-1pg/ml pre and (4 -12) hrs in comparison to the control group
*Control groups at (4, 12) hrs vs. pre-stent (p<0.05)
Atorvastatin reloads groups at (4, 12) hrs vs. control groups (p<0.05)

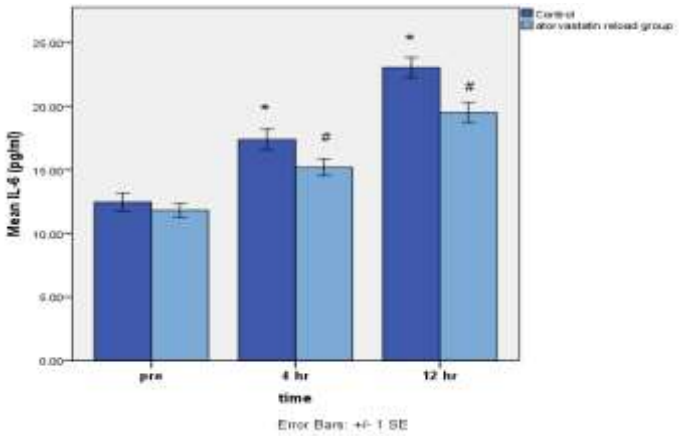


Figure 8: Effect of PCI and atorvastatin reload on IL-6 per and (4, 12) hrs as compared with the control group
*Control groups at (4, 12) hrs vs. pre-stent ($p<0.05$)
Atorvastatin reload groups at (4, 12) hrs vs. control groups ($p<0.05$)

DISCUSSION

Percutaneous coronary intervention (PCI) is a commonly used strategy for revascularization of coronary arteries in a patient with coronary heart diseases [16]. Coronary artery lumen is here widening by a combination of plaque fracture and that associated with vessel dilatation that caused by stent insertion. Although its successful in relieving ischemia and restoring coronary arteries patency and, this technique may induces the release of multiple inflammatory markers that associated with inflammation and induce myocardial injury [17] which was observed in about 20-30% of patients after stent implantation [16]. The 3 important reasons to recommend myocardial revascularization are to ameliorate myocardial ischemia symptoms, to decrease mortality risks in the future and to treat myocardial infarction and to prevent morbidities such as arrhythmias, or heart failure. In the present randomized prospective blinded trial we evaluate the effect atorvastatin reload on myocardial injury markers (CK-MB, Troponin I) and we found that high dose atorvastatin significantly decreased cardiac necrosis markers. cardiac injury markers elevation after elective PCI in patients with stable angina have been associated with an increased risk of peri-procedural myocardial necrosis [18]. The level of myocardial injury markers was remarkably decreased instable angina patients who underwent a higher dosage of atorvastatin 1-day prior to PCI [19]. The attenuation in the level of myocardial injury markers in the present study may be attributed due to ability of the atorvastatin in influencing the phosphorylation of the prosurvival kinases PI3K/AKT and finally its downstream effect or, endothelial nitric oxide synthase (eNOS), and p44/42 MAPK, p38 MAPK, and its downstream signaling [20-21]. Atorvastatin administered at a single high dosage before 24 hr of elective coronary angioplasty in a patient with stable angina on chronic statin therapy reduced the chances of per procedural my necrosis after elective PCI [22-23]. Early statin treatment in acute myocardial infarction might improve endothelial progenitor cell mobilization and decrease the myocardial infarction area by causing angiogenesis [24]. These benefits of statin may result from short-term pleiotropic effects and long-term low-density lipoprotein cholesterol lowering the effect of statin [25]. The atorvastatin shows a protective effect on myocardial injury and this may reduce with longer treatment, however, it can be restored by "reloading" [26]. Saha et al determined the significant potential of a loading dose of atorvastatin in reducing the myocardial injury markers that follow percutaneous coronary intervention [27]. Leoncini et al reported that Two concepts about statin administration: earlier is better considering the time and higher is better considering the dose [28]. In the present study, we found that TLR2 expression in human monocyte was increased remarkably after stent implantation in both treated and control groups at 4hr and 12hr .but the increment was higher in control patients than in patients who received higher loading atorvastatin TLR2 activation causes intimal hyperplasia and stimulates atherosclerotic plaque formation also. TLR pathway influences the nuclear localization of the NF-kB transcription factor and gene expressions of pro-inflammatory cytokine [29]. TLR-2 deficiency resulted in decreased production of pro-inflammatory cytokines including TNF-a, IL-1b, IL-6, and MCP-1, furthermore, several polymorphisms of toll like receptor 2 has been correlated with higher cardiovascular disease risk [29-30]. In the present study high dose atorvastatin attenuate MMP9 level in the atorvastatin reload group than control group the level of MMP9 at 4hr and 12 hr. Post intervention significantly higher in control group than atorvastatin reload group. Over expression of matrix metalloproteinase-9 (MMP-9) (gelatinase) occurs due to mechanical injury after intracoronary stent placement and after balloon inflation and its level highly associated with post interventional vascular remodeling in human blood vessels [31-35]. Post coronary artery intervention associated with increased expression and activity of MMP9 which play a fundamental role in the evolution of arterial rest enosis by modulating collagen content in the retinoic vessels [36]. It is also known that the plasma level of MMP-9 is an important marker of inflammation associated with cardiovascular disease progression in patients with stable angina pectoris and it's a novel predictor of cardiovascular mortality in patients with ischemic heart disease [37]. Reduction in MMP9 expression observed in high dose atorvastatin treated group may have resulted from a reduction in the level of total cholesterol, oxidized LDL and also a decrease in the number of macrophages and other inflammatory cells that secrete MMP9(34).

Bellosta et al demonstrated that Statins do not only inhibit the macrophage infiltrate in the vascular wall, but also decrease the production of MMP9 from the inflammatory cells [38]. Atorvastatin treatment may inhibit gene transcription activation of MMPs (by its effect on toll-like receptor expression and its downstream pathways which include NF-KB) this finding is in agreement with Post et al who found attenuation of MMP9 level after primary PCI in patients who received atorvastatin before PCI [24]. Crisby et al alobserved that 40 mg/d pravastatin 3months before carotid endarterectomy ameliorate plaque MMP9, macrophage, in and lipid. And elevate collagen and tissue inhibitors of MMP9 [39]. In the present study, the level of MCP-1 in the systemic circulation after atorvastatin reload was significantly less compare to the control group (at 4-12) hrs post intervention and this results was in agreement with Munk et al who observed that endothelial damage and trauma to the vessels wall that associated with PCI cause increase in MCP-1 level immediately post intervention [40]. Grzesk et al found that high monocyte chemo attractant protein-1 level after coronary intervention acts as strong predictor for future rest enosis [41]. High monocyte chemo attractant protein-1 serum level have been found after myocardial reperfusion , patients with heart failure and patients with myocardial infarction [42]. Oxidized-LDL (ox-LDL) which is a powerful stimulant for monocyte chemo tactic protein expression from macrophages, vascular smooth muscles cell and endothelial cells this expression of MCP-1 that induced by oxidized-LDL is level and time dependent manner. [43]. Statins, by its well-known lipid-lowering effect will attenuate oxidized lipid which is one of the stimulants for monocyte/macrophage for inflammatory cytokine and chemokine production and through its anti-inflammatory effects by its effects on (NF-kB) activity, decrease expression of monocyte chemo attractant protein-1 in endothelial cells, SMC and monocyte/ macrophages. Romano et al showed that 1day treatment with statin induces inhibition of MCP-1 synthesis in endothelial and mononuclear cells in vitro [4]. Unfortunately there is no research study the effect of pre PCI atorvastatin reloading on MCP-1level in patients with stable angina In the present study there is significant increase in IL6 level at (4–12) hrs after coronary intervention in both study groups but the higher increment in the control group as compared with atorvastatin reload group. This finding is in agreement with Kang et al and Goldberg et al who observed that IL-6 elevation after coronary intervention is frequently attributed to the inflammatory stimulus resulted from vascular injury, plaque disruption, stent insertion and inflation of the balloon [37,44]. NF-kB that stimulated by various factors after PCI play a fundamental role in inflammatory response. This stimulation of NF-KB will increase expression of different inflammatory cytokine for example IL-6 that are involved in the systemic inflammatory reactions [45]. Production of IL-6 after percutaneous coronary interventions stimulated hepatocytes production of acute phase reactant (that is associated with increased blood viscosity and increased platelet number and activity) and C-reactive protein, the levels of which correlate directly with the occurrence of arterial rest enosis. High level of IL-6 is positively correlated with plaque vulnerability and its inflammation [37,46-48]. IL-6 is a highly sensitive marker during myocardial ischemia and reperfusion than CK-MB and CRP furthermore elevated level of IL-6 is strongly associated with all-cause and cardiovascular mortality than CRP [49-50]. Lubrano [47] observed that increased level of IL-6 in healthy men are associated with high risk of myocardial injury in the future life and this correlation was independently from hsCRP serum level. Atorvastatin loading decrease IL6 level in systemic circulation by inhibiting the mevalonate pathway and consequently inhibit inflammatory process, macrophage activation and decrease MMP9 production [51-52].

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