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Clinical usefulness of cytokines as diagnostic and follow up markers in patients with stable angina pectoris

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Abstract---Background and aims: Angina pectoris is the discomfort felt when the heart muscle does not receive enough oxygen. The definition of stable angina is the presence of symptoms only with exertion. Chest pain, or its angina equivillant, is a defining feature, and it is relieved by rest or nitroglycerin when exercise is ceased. Often, this is one of the first symptoms or warning indications of underlying coronary disease. The proinflammatory state is believed to aggravate endothelial dysfunction by activating endothelial cells, releases cytokines and chemokines, which may be crucial in the atherosclerotic plaque formation which is the primary cause of angina pectoris. We studied the value of some cytokines and cardiac markers as a diagnostic and follow up markers in patients with stable angina. Methodology: The study was carried out on 50 patients diagnosed with stable angina pectoris, who visited Nasiriya Heart Center throughout the period from December 2021 to April 2022, and 20 age matched healthy person. IL-1β, IL-5, IL-6, IL-8 were assayed at baseline (hospital admission), 1 day and 1 week post-PCI by an enzyme-linked immunosorbent assay (ELISA). In addition, Troponin I (cTnl) was determined by using monoclonal cTnI-specific antibody. D- dimer by electro-chemiluminescence method. CK-MB by monoclonal CK-MB-specific antibody. Myoglobin by monoclonal MYO-specific antibody. Results: The current study showed that cytokines especially IL-1β, IL-6, IL-8 were significantly elevated in both male and female patients with stable angina pictoris compared with age matched healthy

controls, and they are declined to the normal limits one week post PCI. Conclusions: From our results we can conclude that some inflammatory cytokines such as (IL-1β, IL-5, IL-6 and IL-8) have a value in diagnosis and follow up of patients with stable angina.

Keyword---stable angina, inflammatory cytokines, biomarkers, ischemic heart disease.

Introduction

Cardiovascular diseases cause almost one-third of deaths worldwide (Mozaffarian et al., 2015). The most common form of cardiovascular disease is ischemic heart disease (IHD), also known as coronary artery disease (CAD) and atherosclerotic cardiovascular disease (ACD). (Roth et al., 2017). The most frequent sign of ischemic heart disease is chest discomfort, often known as angina, which may be further subdivided into stable and unstable angina. Atherosclerosis of the coronary arteries and coronary vasospasm are generally thought to be the underlying causes of chest discomfort caused by myocardial ischemia (Balla et al., 2018). This disorder results in an imbalance between myocardial oxygen supply and demand. In unstable angina, the increased demand also arises even at rest, unlike stable angina where it only happens during effort. Exercise increases myocardial oxygen demand through increasing heart rate, blood pressure, and myocardial contractility (Ferrari et al., 2018).

Atherosclerosis, an inflammatory disease of the arteries marked by lipid accumulation and metabolic changes as a result of several risk factors, is the main pathological process that results in IHD. More than 70% of at-risk individuals have multiple risk factors for IHD, and only 2%-7% of the general population have no risk factors (Sampasa-Kanyinga & Lewis, 2015). Inflammation has long been recognized as being closely related to CVD and specifically to the atherosclerotic process (van Hout & Bosch, 2018).Inflammatory cytokines such as interleukin 1β (IL-1β), interleukin 5 (IL-5), interleukin 6 (IL-6) and interleukin 8 (IL-8) are linked to a number of heart disorders, including atherosclerotic heart disease and coronary heart disease (CHD). These cytokines play a crucial part in the development of atherosclerotic plaque. (Tian et al., 2014). In order to treat patients with stable angina, percutaneous coronary intervention (PCI) was developed. More than 500,000 PCI procedures are performed each year around the globe for patients with stable angina (Al-Lamee et al., 2018).

Methodology

The study was carried out on 50 patients diagnosed with stable angina pectoris (29 males and 21 females), who visited Nasiriya Heart Center throughout the period from December 2021 to April 2022, and 20 age matched healthy person as a control group (13 males and 7 females). Patients who had a history of autoimmune or inflammatory disease, cancer, immunosuppression, or prior treatment with statins were excluded from the analysis since these disorders had the potential to independently alter the parameters of our study. Blood samples for the measurement of serum IL-1β, IL-5, IL-6, IL-8, troponin, D-dimer, CK-MB

and myoglobin were drawn as soon as possible after the patient had arrived at the emergency department. IL-1β, IL-5, IL-6, IL-8 were assayed by an enzyme-linked immunosorbent assay (ELISA), according to the operational manual of BTL, China, (https://www.bt-laboratory.com). Troponin I (cTnl) was determined by using monoclonal cTnI-specific antibody. D- dimer by electro-chemiluminescence method. CK-MB by monoclonal CK-MB-specific antibody. Myoglobin by monoclonal MYO-specific antibody, according to the operational manual of Nipigon Health corp. Canada, (https://nipigonhealth.com). All parameters were also determined one day and one week after PCI. The study was approved by the ethical committee of the postgraduate studies of Southern Technical University - Basrah, Training and Human Development Center / Thi-Qar Health Directorate and Nasiriyah Heart Centre. Furthermore, it performed after taking informed, written consent of the participants.

Statistical Analysis

The statistical significant differences were determined using SPSS (version 26).

Results

Table 1 showed that the serum levels of IL-1β ($P<0.001$), IL-6 ($P<0.01$) and IL-8 ($P<0.01$) were significantly elevated in male patients with stable angina pectoris in comparison with age matched healthy male individuals, while IL-5 was significantly declined ($P<0.01$). In addition, troponin ($P<0.001$, D-dimer ($P<0.05$), CK-MB ($P<0.001$) and myoglobin ($P<0.001$) were also significantly elevated in male patients with stable angina pectoris when estimated before PCI, in comparison with age matched healthy male individuals. One day after PCI, IL-1β, IL-5, CK-MB and myoglobin returned to normal limit, while, IL-6, IL-8 and troponin showed more elevation ($P<0.001$), and troponin still revealed the same level of significancy ($P<0.001$) compared with healthy control. One week after PCI, IL-1β, IL-5, IL-6, IL-8, CK-MB and myoglobin returned to normal limit, while, troponin and D-Dimer were declined but still above than that recorded in the healthy control ($P<0.01$ and $P<0.05$) respectively.

Table 1
The serum levels of IL-1β, IL-5, IL-6, IL-8, troponin, D-dimer, CK-MB and myoglobin in male patients with stable angina before PCI, one day and one week after PCI compared with healthy control

Parameters	Control group (n=13)	Pre-PCI (n=29)	One day post-PCI (n=29)	One week post-PCI (n=17)
	Mean ± SD	Mean ±SD	Mean ± SD	Mean ± SD
IL-1β (pg/ml)	88.79± 12.36	115.32 ± 18.06***	88.99 ± 17.18 NS	87.56 ± 8.43 NS
IL-5 (ng/L)	10.24 ± 1.11	8.61± 0.95 ***	10.41 ± 1.81 NS	10.16 ± 1.63 NS
IL-6 (ng/L)	4.43 ± 0.62	5.31 ± 0.78 **	6.61 ± 1.16 ***	4.05 ± 0.79 NS
IL-8 (ng/L)	8.20 ± 0.67	9.17 ± 1.03 **	11.20 ± 1.96 ***	8.16 ± 1.04 NS
Troponin(ng/ml)	0.0196 ± 0.0015	0.5617 ± 0.1751***	0.3455 ± 0.1397***	0.0265 ± 0.0051**
D-Dimer (ng/ml)	353.15 ± 84.93	436.48 ± 103.37*	719.10 ± 195.37***	445.38 ± 122.96 *
CK-MB(ng/ml)	3.71 ± 1.47	5.91 ± 1.53 ***	4.35 ± 0.96 NS	3.92 ± 1.30 NS
Myoglobin	53.23 ± 11.41	70.52 ± 13.19 ***	57.66 ± 15.85 NS	56.61 ± 14.33 NS

(ng/ml)				

Compared with healthy control: ***P<0.001 , ** P<0.01 , * P<0.05, NS: Non-significant. As shown by Table 2, the serum levels of IL-1β (P<0.05), IL-5 (P<0.05), IL-6 (P<0.05) were significantly elevated in female patients with stable angina pectoris in comparison with age matched healthy female individuals, while IL-8 showed no significant changes. Furthermore, troponin (P<0.0001, D-dimer (P<0.05), CK-MB (P<0.05) and myoglobin (P<0.01) were also significantly elevated in female patients with stable angina pectoris when estimated before PCI, in comparison with healthy age matched female healthy individuals. However, one day post –PCI, IL-1β, IL-5 and CK-MB were normalized, but the level of IL-6 (P<0.001), IL-8 (P<0.01), troponin (P<0.001), D-Dimer (P<0.001) and myoglobin (P<0.05) revealed more elevation. While, one week post PCI, the serum levels of IL-1β, IL-5, IL-6, IL-8, CK-MB and myoglobin were normalized, while troponin and D-Dimer were declined but still above the healthy limit (P<0.05) for both.

Table 2
The serum levels of IL-1β, IL-5, IL-6, IL-8, troponin, D-dimer, CK-MB and myoglobin in female patients with stable angina before PCI, one day and one week after PCI, compared with healthy control

Parameters	Control group (n=7)	Pre-PCI (n=21)	One day post-PCI (n=21)	One week post-PCI (n=13)
	Mean ± SD	Mean ±SD	Mean ± SD	Mean ± SD
IL-1β (pg/ml)	93.72 ± 12.09	109.62± 18.75 *	86.54 ± 11.97 NS	88.02 ± 9.63 NS
IL-5 (ng/L)	10.32 ± 1.27	8.65 ± 1.36 *	10.00 ± 1.96 NS	9.96 ± 0.86 NS
IL-6 (ng/L)	4.81 ± 0.68	5.62 ± 0.85 *	6.66 ± 1.07 ***	4.5.2 ± 0.73 NS
IL-8 (ng/L)	8.04 ± 0.68	9.18 ± 1.79 NS	10.21 ± 1.49 **	8.04 ± 0.84 NS
Troponin (ng/ml)	0.0201 ± 0.0015	0.6134 ± 0.1778***	0.3147 ± 0.1265***	0.0268 ± 0.0049*
D-Dimer (ng/ml)	337.71 ± 65.58	477.47 ± 112.35 *	751.47 ± 182.70***	447.38 ± 116.74*
CK-MB (ng/ml)	4.35 ± 0.46	5.8 ± 1.28**	4.66 ± 0.92 NS	4.08 ± 1.01 NS
Myoglobin (ng/ml)	45.14 ± 9.66	65.95 ± 14.54 **	61.89 ± 15.52 *	51.00 ± 13.95 NS

Compared with healthy control: *** P<0.001 , ** P<0.01 , * P<0.05 , NS: Non-significant.

Discussion

Our study showed that IL-1β significantly elevated in male and female patients with stable angina pictoris, these results were in agreement with Bai et al. (2019) who showed that IL-1β levels in the patient group were significantly higher than those in the control group (14.47±1.73 vs. 26.82±1.56 ng/L) (p<0.05). and also found that the levels of IL-1β before PCI was significant differ in comparison with its level 3 days after PCI (20.62±6.48 vs. 15.98±1.54 ng/L)(P <0.05). The IL-1β level in the treatment group peaked at 0.5 h after PCI and then, gradually

decreased and returned to normal levels after 3 days. It's also agree with Ørn et al. (2012) who found that IL-1β levels (pre-PCI) were elevated as compared to healthy controls, but rapidly declined 2 days after PCI. Ischemia causes damage to heart tissue, which is followed by a healing and remodeling process that is marked by an intensive inflammatory response. When tissue is injured, a macromolecular complex called the cryopyrin inflammasome amplifies the inflammatory response. Caspase-1, the effector enzyme of the inflammasome, cleaves pro-IL-1β once the inflammasome has been triggered to become active by danger- and injury-related moieties. This resulting in the activation of IL-1β. IL-1β induces leukocyte chemotaxis in injured myocardium, promotes cytokine and chemokine production, and enhances systemic inflammatory response (Toldo et al., 2018).

There is insufficient data link of the IL-5 to ischemic heart disease. A study by Ye et al. (2020) aimed to examine the potential pathways of IL-5's involvement in coronary artery disease, they conclude that levels of IL-5 were decreased in CAD patients and inhibited oxLDL Th1 and Th17 differentiation in vitro. Previous research has shown an inverse relationship between the occurrence of CVD and IL-5, Ishigami et al. (2013) found that anti-IL-5 antibodies had a positive association with the development of atherosclerosis. Another study done by Cappuzzello et al., (2011) which revealed that in the patients with chronic heart failure, IL-5 was also decreased and decreased IL-5 levels were related to disease progression. Experimental findings indicating that transplantation of B1 cells specifically reverses the proatherogenic impact of splenectomy and that this effect is reliant on the capacity of B1 cells to generate IgM antibodies have supported the idea that B1 cells and natural antibodies have atheroprotective activities (Ait-Oufella et al., 2010; Kyaw et al., 2011). It is still not completely understood how danger-associated molecular pattern-specific IgM antibodies are produced by B1 cells, but interleukin IL-5 released from type 2 innate lymphoid cells (ILC2) has been identified as one important stimuli (Baumgarth, 2016).

Elevation of serum level of IL-6 in the current study was in agreement with the results of Kumar Mahesh et al. (2018) in their study performed on 36 consecutive patients with chronic stable angina who underwent Bare Metal Stent (BMS) angioplasties, IL-6 also showed a more significant elevation (4.45 ± 2.45pg/ml) post PCI in comparison to baseline levels (1.30 ± 0.19 pg/ml) ($p<0.05$). Our results were also in agreement with the results of Groot et al. (2019) who show that the median baseline IL-6 level was (3.7 pg/ml) and it was increased a threefold to (10.3 pg/ml) ($p<0.001$) after 24 h and subsequently decreased to (1.8 pg/ml))($p<0.001$) at 2 weeks to remain stable. Furthermore, the study of Tøllefsen et al. (2021) carried out on 269 individuals who had undergone STEMI revealed that circulating IL-6 levels rose from the day of admission to the first day after, and then dropped to levels lower than those at the time of admission at the 4-month follow-up ($p<0.001$). Sun et al. (2020) concluded that the pre-operative expression of IL-6 ($P<0.001$) was increased in restenosis patients compared with non-restenosis patients. Reperfusion of the myocardium following cardiac ischemia might promote cardiomyocyte apoptosis. Various studies have shown that one of the most important aspects of ischemia-reperfusion (I/R) damage is the induction of myocardial apoptosis, which is caused by inflammation (Arslan et al., 2011; Boros & Bromberg, 2006). After cardiac I/R injury, IL-6 promoted the

development of infarction, while IL-6 deficiency reduces I/R injury. However, alteration of other inflammatory mediators, activation of the coagulation system, or neutrophil influx cannot account for the positive effects (Jong et al., 2016).

Chronic inflammation is a hallmark of atherosclerosis. IL-8 is one of the inflammatory chemokines that contributes to atherogenesis and the destabilization of atherosclerotic plaque. IL-8 promotes monocytes into the subendothelial space, has mitogenic and chemotactic effects on vascular smooth muscle cells, and promotes plaque vulnerability by unbalancing metalloproteinases and metallopeptidases. At the same time, in ischemic tissues, IL-8 seems to be beneficial by accelerating neovascularization and promoting angiogenesis (Diakos et al., 2014; Moreno Velásquez et al., 2019).

Correia et al. (2010) declare that individuals who developed cardiovascular events during hospitalization had greater levels of IL-8 (37 pg/ml vs. 10 pg/ml, P=0.003) compared with those free of events. Qi et al. (2003) showed that the preprocedural plasma concentrations and the postprocedural differentials of IL-8 in the complication group were significantly higher than those in the noncomplication group. A study carried out by Shetelig et al. (2018) on 258 patients with STEMI, revealed that the elevated level of IL-8 was significantly drop during PCI and then rise on day 1 after PCI. Atherosclerosis is a chronic inflammatory disease involving both innate and adaptive immune responses (Spitz et al., 2016). Neutrophils, which is a part of the innate immune system, attach to atherosclerotic plaques principally via creating neutrophil extracellular traps (NETs). An et al., (2019) revealed that the IL-8/CXCR2 signaling pathway caused neutrophils to produce NETs in response to the pro-inflammatory cytokine IL-8. Furthermore, activated NETs induced the production of IL-8 from macrophages via the toll-like-receptors/nuclear factor-kappa B (TLR9/NF-κB) pathway, thereby exacerbating atherosclerosis development.

Elevation of serum level of troponin in the patients of stable angina pectoris in the current study was similar to many studies performed to investigate the relationship between serum troponin and CAD. Buturak et al. (2016) mentioned that 304 patients with stable angina pectoris showed high hsTnT level (9.7 ng/L), and the level was further elevated ($p < 0.001$) to 19.4 ng/L 12 h after PCI. A study by Nageh et al. (2005) on 316 patients with stable angina concluded that in one-third of the patients performed PCI, cTnI increased post-procedurally and was independently and substantially predictive of an elevated risk of adverse events at 18 months. In the study of Tricoci et al. (2013) performed on 10,199 patients with early ACS had PCI during the initial hospitalization; 4,198 (41.2%) of the patients had rising cTn levels pre-PCI, 4,276 (41.9%) experienced a new rise in cTn level within 24 hours after PCI, and 1,496 (14.7%) experienced no new rise in post-PCI cTn level. Contrary to the CK-MB level, the prolonged rise of of cTn was caused by the continued release of cTn from the contractile apparatus. (Aydin et al., 2019). Cardiac-TnI has become the most sensitive marker for the diagnosis of serious problems in individuals undergoing PCI. It provides accurate cardiac injury diagnosis that is sometimes not evident by visual inspection alone. After PCI, the adjunctive measurements of cardiac markers may help identify certain populations with high cardiac marker concentrations who might benefit from long-term antiplatelet therapy. Measurements of cTnI 16–24 hours post-PCI

should be part of the work-up management of patients following elective PCI (Alhadi & Fox, 2010).

As in our study D-dimer levels elevation, may reflect a systemic prothrombotic state and focal vessel wall-related fibrin formation with unstable atherosclerotic plaque activity (Türkoğlu et al., 2020). In observational study performed on 3972 consecutive patients with ACS treated by PCI by Chen et al. (2021), they reported that D-dimer level was an independent predictor of adverse outcomes for ACS patients undergoing PCI, and it added predictive value when paired with clinical risk variables and risk scores. A prospective follow-up study by Gong et al. (2016) on 2410 patients with angiographic-proven CAD enrolled, they concluded that plasma D-dimer levels appeared to be a useful predictor for the severity of CAD and the subsequent major clinical events.

Elevation of CK-MB in male and female patients with stable angina pectoris in our study was in agreement with Montaser et al. (2016) who mentioned that CK-MB in ischemic heart diseases was significantly higher 6.5 ng/L than the respective concentrations in the control group 1.4 ng/L ($P < 0.001$). A modern study by Wu et al. (2020) confirmed that stable CHD patients with a higher serum hsCK-MB level (≥4.730 ng/mL) have a higher risk of all-cause mortality. A meta-analysis study by Jang et al., (2013), including 48,022 subjects, clarified the clinical implication of CK-MB elevation, even a small increase of CK-MB was associated with a significant increase in the risk of long term mortality. CK-MB elevation 1 to <3 upper limit of normal (ULN) increase the risk of death by 48 percent. The risk was increased by 71% with CK-MB elevation 3 to <5 ULN and was tripled with CK-MB elevation >5 ULN. CK-MB elevation correlates with a greater atherosclerotic plaque burden. CK-MB elevation after intervention may be a marker of diffuse atherosclerotic disease or a consequence of catheter-based intervention in more diseased arteries or both (Mehran et al., 2000).

Elevated myoglobin level in our study was in agreement with the result of Sun et al. (2017), who concluded that serum myoglobin level was significantly higher in the CAD patients compared with the non-CAD patients (25.6±13.6 vs. 123.6±450.7 μg/L, $P<0.001$). It is also agree with Montaser et al. (2016) who showed that the level of myoglobin in the MI group were significantly higher 151.46 ng/L than the respective concentrations in the control group 19.61 ng/L (IQR: 21.10) ($P < 0.001$). Macdonald & Nagree (2008) have shown that serial myoglobin measurements are very useful markers in the early discharge from hospital and follow-up of out-patients after discharge in ACS patients. (Jaffery et al., 2008), in their study on 955 patients with chest pain, they mentioned the high values of myoglobin in diagnosis and follow up. The role of myoglobin in I/R is not fully clear. Previous study suggested that the reactions between myoglobin and hydrogen peroxide are a key factor in oxidative damage in the ischemic and then reoxygenated heart (Witting et al., 2006). These reactions result in generation of ferryl myoglobin (MbFeIV = O) and the globin radical (·MbFeIV = O) (35, 37). Both species are strong oxidants, which may induce lipid and protein peroxidation (B. et al., 2008).

Conclusion

From our results we can conclude that some proinflammatory cytokines (IL-1β, IL-5, IL-6 and IL-8) and some cardiac markers (Troponin, CK-MB, myoglobin and d-dimer) have a value in diagnosis and follow up in stable angina patients.

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