Interleukin 1β And Interleukin-6 and Some Oxidants in Patients With Stable Angina

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ABSTRACT
ROS play an essential physiological roles in the cellular homoeostasis and cell signaling under normal circumstances. The overexpression of ROS was involved in the pathological events of several diseases, including cardiovascular, because they cause damage to many cell structures.This study aims to evaluate the levels of inflammatory biomarkers, [interleukin-6 (IL-6) and interleukin-1beta (IL-1β)] in stable angina patients and their relationship with oxidative stress. The current study is a case-control one performed on 88 patients with stable angina and 44 people as a control group attending the Nasiriyah Heart Center from August 2023 to March 2024. All cases were diagnosed by cardiologists and confirmed by laboratory investigations. Blood samples (10 ml) were collected from patients. Serum was isolated after centrifugation and stored at -20°C. Serum CK-MB, MYO and Trop I were determined by electro-chemiluminescence immunoassay. While, the ELISA was employed to assess the levels of human IL-6, human IL-1 β, SOD, (GSH-Px/ GPX), total cholesterol, triglycerides, LDL, VLDL and HDL, using the kits from Solarbio, China. The patients with stable angina didn't show significant variation in the serum level of troponin I and CK-MB in comparison with control, while serum myoglobin level was significantly increased in patients with stable angina compared to control. Although the level of total cholesterol was insignificantly increased, but the levels of triglyceride (TG), VLDL-C and LDL-C were significantly increased, while the serum level of HDL-C was significantly declined in comparison with control. The serum levels IL-6 and IL-1β, in addition to activities of SOD and GPx were increased significantly in patients of angina compared to control. We could conclude that IL-1β, IL-6, SOD and GPx are increased in stable angina. Inflammatory events and oxidative stress could play an important roles in initiation of atherosclerosis and subsequent angina.

1. Introduction

One third of all deaths was caused by cardiovascular diseases worldwide. Coronary artery disease (CAD) is the highest prevalent among all cardiovascular diseases according to the records of The American Heart Association [1]. It is the major cause of death and its mortalities are elevated steadily [2]. In addition, to increased percent of patients with poor life quality and disability [3]. Angina pectoris is the most common feature of CAD, 112 million people globally complain of angina pectoris [4]. It caused by myocardial ischemia, which occurs as a result of coronary arteries fixed stenosis or vasospasm of the coronary arteries [5-6]. A subset of patients presented with non-obstructive coronary disease, which may be attributed to vasospasm [7], endothelial dysfunction [8-9], and oxidative stress [10-11]. ROS play an essential physiological roles in the cellular homoeostasis and cell signaling under normal circumstances [12]. The overexpression of ROS was involved in the pathological events of several diseases, including cardiovascular, because they cause damage cell structures, such as nucleic acids, proteins, carbohydrates and lipids, and alters their functions [13-14].

Antioxidants in the body protected against the damaging effect of ROS. The scavenging activities of excess free radicals are achieved by the non-enzymatic and enzymatic antioxidants [15]. Recent researches showed that the atherosclerosis is an inflammatory disease. Inflammatory cytokines participated in initiation and development of ischemic heart disease, and their serum levels strongly predict coronary artery disease [16-18]. The inflammatory mediators released by injured endothelium will enhance the interaction of circulating leukocytes with endothelium and enhancing the process of initiation and development of ischemic heart disease [19]. Interleukin 1 family was participated in the platelet and inflammatory cells aggregation, which accelerated the plaques formation, ventricular remodeling and apoptosis of myocardial cell [20-21].

2. Methodology

This study is a case-control one performed on 88 patients with stable angina, visited Al-Nasiriya Heart Center, in addition to 44 persons as control group. The patients were diagnosed by cardiologists, throughout the period from August 2023 to March 2024. Five milliliters of venous blood were obtained from all participants, the samples were centrifuged at 3000 rpm for 15 minutes and the sera was then isolated and stored at (-20 ^{0}C) until analyzed. Patients with cancer, autoimmune or inflammatory illnesses, immunosuppression, and the use of statin medicine were excluded. Serum CK-MB, MYO and Trop I were determined by electro-chemiluminescence immunoassay. While, the ELISA was employed to assess the levels of human IL-6, human IL-1 β, SOD, (GSH-Px/ GPX), total cholesterol, triglycerides, LDL, VLDL and HDL, according to the company's kits Solarbio, China.

The ethical committee at Thi-Qar Health Directorate gave agreement to carry out the work, and a written consents were taken from all participants.

Statistical analysis

Student t test (SPSS, version 26) was performed to determine the statistical differences between the studied groups. The statistical variations between percentages were detected by Chi-square test. If the p-value is 0.05 or lower, the result was considered as significant.

3. Results and Discussion

The mean age of the patients with stable angina (55.13 ± 8.27 y) was significantly (P<0.001) more than the mean age of the control group (49.70 ± 6.25 y). BMI in patients was also significantly (P<0.05) more than control (27.31 ± 4.73 VS. 25.29 ± 3.48), however, the variation between the patients and control group in the sex distribution was insignificant (P=0.44). While, a significant more incidence of diabetes (13.63% VS. 39.77%, P<0.01), hypertensive (29.54 VS 72.72%, P<0.001), smokers (15.90% VS. 32.95%, P<0.03) and positive family history (20.45% VS40.90%, P<0.01) were recorded in patients with stable angina in comparison with control (table 1).

Table (1) : The studied population characteristics.

Variables		Control group (n = 44)	Stable angina group (n = 88)	P. value
Age (years)		49.70 ± 6.25	55.13 ± 8.27	<0.001
BMI (kg/m^2)		25.29 ± 3.48	27.31 ± 4.73	<0.05
Sex	Male	26 (59.09%)	58 (65.91%)	0.44 ^{NS}
	Female	18 (40.91%)	30 (34.09%)	

Table 2 showed that in comparison with control group, the patients with stable angina didn't show significant variation in the serum level of troponin I (0.0122 ± 0.0082 VS. 0.0107 ± 0.0035 ng/ml in control, P=0.29) and CK-MB (3.22 ± 0.82 VS. 3.02 ± 0.18 in control ng/ml, P=0.13), while serum myoglobin level was significantly elevated in patients with stable angina (42.60 ± 18.16 ng/ml) compared with control (26.27 ± 8.87 ng/ml, P<0.001).

Table (2): Troponin, myoglobin, and CK-MB levels in the stable angina and control groups

Parameters	Control group (n = 44)	Stable angina group (n = 88)	P. value
Troponin I (ng/ml)	0.0107 ± 0.0035	0.0122 ± 0.0082	0.29^{NS}
Myoglobin (ng/ml)	26.27 ± 8.87	42.60 ± 18.16	<0.001
CK-MB (ng/ml)	3.02 ± 0.18	3.22 ± 0.82	0.13^{NS}

Although the serum level of total cholesterol was insignificantly elevated in comparison with control (176.31 ± 46.68 VS. 162.90 ± 23.71 mg/dl, P= 0.8), but the serum levels of triglyceride (255.26 ± 111.90 VS. 147.52±42.76 mg/dl, P<0.001), LDL (97.14±33.78 VS. 76.64 ± 20.58 mg/dl, P<0.01) and VLDL (76.64 ± 20.58 VS. 36.40 ± 12.09 mg/dl, P<0.001) were significantly elevated and serum level of HDL was significantly declined (38.37 ± 9.06 VS. 42.79 ± 10.03mg/dl, P<0.01) in the patients of stable angina compared with control (table 3).

Table (3): Lipid profile in the stable angina and control groups

Lipid profile	Control group (n = 44)	Stable angina group (n = 88)	P. value
TC (mg/dl)	162.90 ± 23.71	176.31 ± 46.68	0.08^{NS}
TG (mg/dl)	147.52±42.76	255.26 ± 111.90	<0.001
HDL (mg/dl)	42.79 ± 10.03	38.37 ± 9.06	0.01
LDL (mg/dl)	76.64 ± 20.58	97.14± 33.78	0.01
VLDL (mg/dl)	36.40 ± 12.09	76.64 ± 20.58	<0.001

Both IL-1β (19.08 ± 8.80 VS 13.98 ± 4.14 pg/ml**,** P<0.01) and IL-6 **(**4.43 ± 1.29 VS. 3.22 ± 0.85 pg/ml**,** P<0.001**)** were elevated significantly in patients of angina in comparison with control (table 4).

Table (4): Cytokines inflammatory markers levels in the stable angina and control groups

Cytokines	Control group (n = 44)	Stable angina group (n = 88)	P. value
IL-1β (pg/ml)	13.98 ± 4.14	19.08 ± 8.80	<0.01
IL-6 (pg/ml)	3.22 ± 0.85	4.43 ± 1.29	<0.001

As mentioned in table 5, SOD (121.20 ± 17.43 VS. 105.26 ± 8.69 U/ml) and GPx (88.23 ± 12.79 VS. 81.19 ± 9.62 U/ml) were significantly (<0.001 and <0.01, respectively) declined in stable angina in comparison with control.

Table (5): Oxidative stress markers levels in the stable angina and control groups

Parameters	Control group (n = 44)	Stable angina group (n = 88)	P. value
SOD (U/ml)	105.26 ± 8.69	121.20 ± 17.43	<0.001
GPx (U/ml)	81.19 ± 9.62	88.23 ± 12.79	<0.01

The result showed significant differences in age distribution between control and patients (P<0.001). BMI and sex distribution showed insignificant statistical variations between the control and patients groups (P=0.27, P=0.44, respectively). These results agree with Dinarvand et al. [22], who found significant differences in age between the stable angina and control groups, whereas there are insignificant difference in BMI. This could be attributed to gradual development of the ischemic heart diseases and reaching the peak complain in advance ages with no variation between males and females [23-24].

As shown in table (2) analysis of lipid profile in patients showed significant elevation in the levels of TG, LDL and VLDL, and significant decline in the serum level of HDL in stable angina in comparison with control group. The current findings were in consistent with Amer et al., Dragan et al., and Karajibani et al., [23,25-26], who found significant elevation of TG (P<0.001) and LDL (P<0.001) and significant decline of HDL levels (P<0.001) in the patients with MI and stable angina pictoris. Bastani et al. [27], also found an increase in the levels of total cholesterol, triglycerides and LDL-C with decreasing the levels of HDL in patients with coronary artery disease in comparison with control which also agree with the current results on stable angina. Alteration of the metabolism

of lipid is associated with oxidative stress and inflammation, is an essential driver of the pathological changes associated with formation of atherosclerotic plaque [28]. Triglyceride play an important primary role in the ischemic events [29]. On the other hand lowering of triglyceride levels can reduce the incidence of angina attacks and enhance heart function [30]. Therefore, it is necessary to manage triglyceride levels through lifestyle changes and drug therapy [31].

Multiple studies have revealed that high levels of LDL-C were correlated with an increased risks of cardiovascular disease [32]. The dangers of cardiovascular disease and stroke are amplified when LDL cholesterol levels are high. High levels of LDL cause cholesterol to be transported to the artery walls, where it can then accumulate and contribute to the development of plaque [33]. Cholesterol is cleared from the bloodstream and flushed out of the body attributed to HDL's transport of the fatty substance to the liver. By preventing plaque formation, HDL protects the arterial walls and lowers the likelihood of ischemic heart diseases. Therefore, the risks of ischemic heart diseases, peripheral artery disease and stroke, and were decrease with increasing levels of HDL cholesterol [34].

Our study showed that the serum levels of cytokines inflammatory markers (IL-1β and IL-6) among stable angina patients group were significantly elevated compared to the control. The study agree with [23-24], who found that the levels of IL-6 and IL-1β were significantly elevated in acute MI and stable angina. Bouzidi and Gamra [35], found that IL-6 serum level in CAD patients was significantly elevated. As a significant member of the interleukin-1 family, IL-1β is a typical proinflammatory cytokine. It is mainly produced by activated innate immune cells, such as macrophages and monocytes, and plays a significant part in the first stages of inflammation. IL-1β is released during ischemia, triggering neutrophil infiltration into the myocardium. After reperfusion, under the synergistic action of IL-1β with other cytokines and complements, the neutrophils are subsequently activated and interact with endothelial cells, generating ROS and aggravating myocardial injury. Remodeling and healing of the heart tissue after ischemia is associated with intense inflammatory response. The cryopyrin inflammasome is stimulated by injury and promoted activation of IL-1β by caspase-1. IL-1β induced leukocytes chemotactic recruitment in the injured myocardium, and promoted additional production of chemokines and cytokines [23-24].

The elevation of the level of IL-6 in stable angina indicated an active inflammatory process within the coronary arteries. This inflammation can contribute to the progression of atherosclerosis, and the subsequent reduction of myocardial blood flow. The chronic inflammatory state reflected by increased IL-6 levels may also predispose patients to acute coronary events, as the cytokine is involved in plaque destabilization and thrombosis [35].

The significance of increased IL-6 levels in stable angina has practical implications for patient management and treatment. Anti-inflammatory treatments targeting IL-6 pathways are being explored as potential therapies for reducing cardiovascular risk. For example, tocilizumab, an IL-6 receptor antagonist, has shown promise in reducing inflammatory markers and stabilizing atherosclerotic plaques [36]. Accordingly, it was suggested that targeting IL-6 could be a viable strategy to manage chronic inflammation in stable angina and may be potentially improve clinical outcomes.

The result showed a significant increase the levels of SOD and Gpx among patients group compared to the control. These findings were in consistent with the result of Dinarvand et al.,[22] and Peng et al., [37], who demonstrated significant elevation of SOD activity in CAD patients compared to the control group, but disagree with them in that no significant change was noted in GPx. Bagatini et al. [38] and Weinbrenner et al., [39], also recorded an elevation of SOD in coronary heart disease. The significant increase in the SOD activity could be occurred because of its protective role in against tissue damage induced by ROS [38]. However, our results disagreed with the findings of Senthil et al., [40] and Pandey et al., [41], they found that SOD activity was decreased in platelets and erythrocytes in patients with MI. This could occur due to correlation between SOD and oxidative stress when sample was taken early. Increased SOD enhances oxidative injury by enhancing the formation rate of

oxidants to a toxic level [42]. Glutathione peroxidase protected cells against oxidative damage by converting hydrogen peroxides into water and conversion of other harmless molecules. Studies have shown that GPx levels rise in cases of stable angina, which can be interpreted as a protective response by the body against the increased oxidative stress [43]. Increased GPx activity could reflect the body's attempt to maintain oxidative homeostasis and reduce damage to cardiac tissue. Studies indicate that high levels of this enzyme were correlated with a lower level of oxidative stress and inflammation in stable angina, which helps improve the general condition of patients and reduce the risk of future complications [44].

4. Conclusion and future scope

Knowing the pathogenic event associated with any disease is an important step in preventing and treating this disease. From our results we can conclude that some proinflammatory cytokines (IL-6 and IL-1β) and some antioxidant enzymes were changed in stable angina, which clearly indicated that ischemic heart disease is an oxidative stress status and chronic inflammatory events. The suppression of these inflammatory biomarkers may represent a future therapeutic importance in the treatment of stable angina. Furthermore, early diagnosis remains the main principles in the treatment of stable angina, and these biomarkers represent an additive diagnostic parameter in this disease.

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Conflict of Interest

There is no conflict of interest.

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