Original Article

Malondialdehyde Level in the Patients Subjected to Open Heart Surgery in Association with Lipid Profile

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Abstract

Background: Reactive oxygen species are usually produced by the living cell and have different functions in its normal activity and considered as one of the factors that involved in heart disease. Malondialdehyde (MDA) considered as one of the most indictors of oxidative stress and damage produced as a result of lipid peroxidation. **Objectives:** The main objective is to evaluate serum oxidative stress by measuring the changes in the level of MDA as a marker of oxidative stress and demonstrate the correlation of MDA with lipid profile in patients subjected to open-heart surgery. **Methods:** A case–control study was carried out in the Department of Chemistry and Biochemistry, College of medicine, Tikrit University, Tikrit, Iraq. The study was carried out for 50 patients subjected to open-heart surgery recruited from the Medical City/Iraqi Center for Heart Disease and Ibn Al-Bitar Cardiac Surgery Center, Department of Cardiac Surgery, Baghdad, Iraq between October 1, 2017 and March 1, 2018. The levels of MDA and lipid profile were measured in the serum of 50 patients, in three different interval preoperative, early postoperative, and late postoperative and compared with 30 age- and gender-matched controls. **Results:** The results revealed a statistically significant difference in the serum MDA level between patient during preoperative, early postoperative, and late postoperative stage against control group and significant differences in their MDA levels among all patients' stages. Furthermore, there was a significant positive correlation between serum MDA level and total cholesterol in the early postoperative stage. **Conclusions:** There was an increase in the level of MDA in the early postoperative stage as an indicator of reperfusion damage that occurs immediately after open-heart surgery which then decreases dramatically with decrease in total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL-C), and very-LDL-C.

Keywords: Lipid peroxidation, lipid profile, malondialdehyde, open-heart surgery, oxidative stress, reactive oxygen species

Introduction

Open-heart surgery is one of the surgical operations in which the thoracic cavity is opened; this surgery included arteries, muscles, valves, or other parts of the heart. Coronary artery bypass grafting is the most common type of heart surgeries that done on adults, in which a healthy artery or vein is grafted to a blocked coronary artery that allows the grafted artery to "bypass" the blocked artery and bring fresh blood to the heart.[1] In 1953, Gibbon was performed an open-heart surgery which is also called traditional heart surgery. Nowadays, many new heart procedures specialist performed this type of surgery by small incisions only and no need for wide openings. Therefore, the term open-heart surgery can be misleading.[2]

Oxidative stress can be defined as an imbalance between the metabolic reactions producing free radical and antioxidant defenses (enzymatic and nonenzymatic) which is responsible for the protection against free radicals.[3,4] This imbalance may be either due to overproduction of free radicals or a reduction in the antioxidant capacity. It originates from a variety of sources including a normal physiological event such as mitochondrial respiration and exposure to ionizing radiation.[5]

An increase in oxygen supply (hyperoxia) may also cause an elevation in free radicals leading to damage which is considered as side effects that are manifested in a series of functional changes of many biological reactions.[5-7] Furthermore, oxidative stress may occur as a result of endogenous stresses or exogenous sources of free radicals. Highly reactive nature of free radicals allows them to combine strongly with various molecules, such as ion pumps, receptors, and enzymes causing oxidation, and alteration in the normal

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function of these molecules. Some of the free radicals react with nucleic acid and produce dysfunction by participating in a gene mutations that in turn cause an alteration in proteins structure and production leading to cancer.[4,5]

The purpose of this study is to determine the changes in the level of malondialdehyde (MDA) as an indicator of oxidative damage and antioxidant status of the body in a patient subjected to open-heart surgeries and relate this parameter to patients' lipid profile in three stages including preoperative, early postoperative, and late postoperative.

Methods

This study was conducted on 50 patients (18 females and 32 males) age ranged from <20 to more than 70 years old who had undergone open-heart surgery. The information about patients in this study was retrieved from the patient's hospital records. The samples were collected from Medical City/Iraqi Center for Heart Disease and Ibn Al-Bitar Cardiac Surgery Center, Department of Cardiac Surgery, from October 1, 2017 to March 1, 2018 on patients with coronary artery disease who underwent open-heart surgery without major surgical risk factors or abnormal biochemical investigations.

The criteria of exclusion were patients with malignant disease, infectious disease, inflammatory skin disease, hematological disease, renal disease, and liver disease. Groups of our study consist of all cases of the elective and emergent of cardiopulmonary bypass patients.

The results of the patient groups were compared with thirty nearly comparable age and sex-matched healthy individuals with age ranged between 15 and 62 years old used as a control group. The exclusion criteria include: A history of infection, inflammation, cancer, diabetes mellitus, circulatory diseases including coronary artery disease, peripheral vascular disease, stroke, hypertension, and malignancy which affect oxidation state and congestive heart failure. Additionally, the control group were non-obese and did not receive any treatments.

The local Ethical Committee of the College of Medicine, University of Tikrit, Iraq, approved this study. In addition, informed written consents were obtained for participation in the study was signed by the patients or the legal guardians of the investigated patients according to the Helsinki principles.

Sample collection

Five milliliters of blood samples were collected from overnight fasting patients in three different stages including before the surgical intervention (preoperative period), at the end of the surgical intervention within approximately 24 h after the surgical intervention (early postoperative period), and approximately 1 month after the surgical intervention (late postoperative period) and controls in plain tubes and allowed to clot at room temperature for 10–15 min. The tube then was centrifuged (3000 rpm) for 15 min. The clear serum was pipetted into clear dry Eppendorfs and stored at −20°C until used for different investigations.

Biochemical assays

Malondialdehyde levels were quantitatively measured by enzyme-linked immunosorbent assay (ELISA) kit supplied by AMSBIO, UK, using a competitive-ELISA method according to the manufacturer instructions[8] whereas the level of lipid profile including total cholesterol, triglyceride, and high-density lipoprotein-cholesterol (HDL-C) were measured by colorimetric method using kits provided by Biomaghreb (Tunisia) according to the manufacturer manual instruction.[9-11] Furthermore, low-density lipoprotein-cholesterol (LDL-C) level was assessed using the following equation.[12]

(LDL-chol) = ([total chol] − [HDL-chol] – [TG])/5

Results

Malondialdehyde

The results of this study revealed a statistically significant difference ($P < 0.001$) in the serum MDA level between patient during preoperative, early postoperative, and late postoperative stage against control group as shown in Table 1. In addition, patients during all stages of sampling showed significant differences in their levels. A Pearson product–moment correlation results showed that there was a nonsignificant correlation between serum MDA level and total cholesterol in preoperative state, $R = 0.155$, $R^2 = 0.024$, $n = 50$, $P = 0.283$. A scatterplot summarizes the results [Figure 1].

Regarding correlation between those two variables in early postoperative state, there was a significant positive correlation between serum MDA level and total cholesterol in the early postoperative stage, $R = 0.286$, $R^2 = 0.0819$, $n = 50$, $P = 0.044$ as summarized in Figure 2. However, the assessment of correlation between serum MDA level and total cholesterol in late postoperative state has shown no relationship between the two variables, $R = 0.035$, $R^2 = 0.0012$, $n = 50$, $P = 0.811$ as summarized in Figure 3

Total cholesterol

Comparison of total cholesterol level was done between study groups using Student's *t*-test. Each patient's subgroups; preoperative, early postoperative, and late postoperative were compared to the control group using independent samples *t*-test. There was a statistically significant difference in cholesterol level between preoperative stage levels and that of control. However, difference was nonsignificant between early and late postoperative stages of patients subjected to open-heart surgery when compared to control as demonstrated in Table 1. Results obtained in Table 1 also revealed that there were significant differences among all patients' subgroups as the level of preoperative stage showed the significantly higher level that reduced significantly in the early postoperative stage reaching to the lowest level at the late postoperative stage.

Triglycerides

Results obtained in the current study revealed that the level of triglycerides (TG) in all patients' subgroups were significantly higher than that of control. Furthermore, TG levels

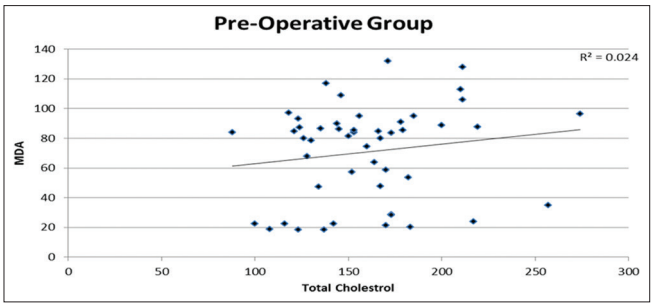

Figure 1: Scatterplot of the correlation between serum malondialdehyde level (ng/ml) and total cholesterol (mg/dl) at preoperative state

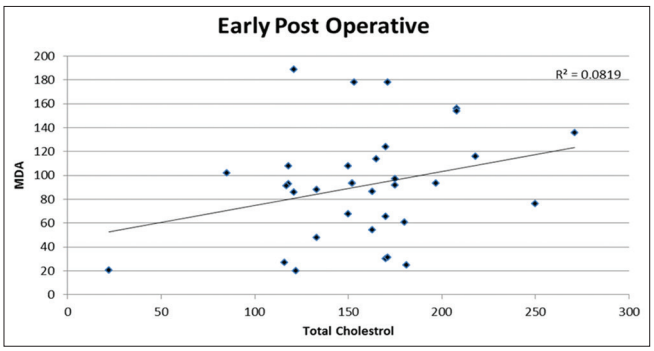

Figure 2: Scatterplot of the correlation between serum malondialdehyde level (ng/ml) and total cholesterol (mg/dl) at early postoperative state

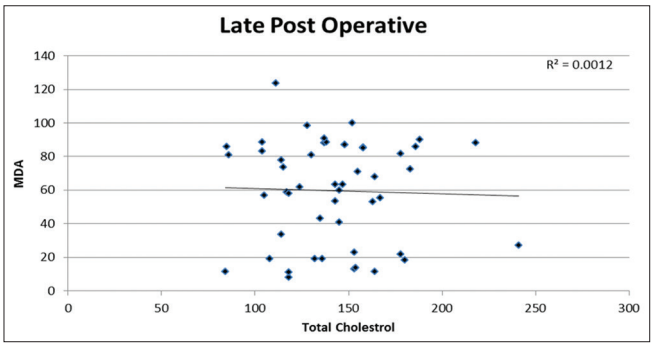

Figure 3: Scatterplot of the correlation between serum malondialdehyde level (ng/ml) and total cholesterol (mg/dl) at late postoperative state

showed significant differences among patients' subgroups as demonstrated in Table 1. The level of TG was at the maximum during the preoperative stage and become reduced significantly in the early postoperative stage until reached to the lowest level at the late postoperative stage.

Low-density lipoprotein-cholesterol

The pattern of LDL-C levels in patients and controls were similar to that of total cholesterol in that a significant difference in LDL-C level were observed between preoperative stage and that of control and nonsignificant differences were reported between early and late postoperative stages of patients subjected to open-heart surgery when compared to control as demonstrated in Table 1. Results obtained in Table 1 also revealed that there were significant differences among all patients' subgroups as the level of preoperative stage showed the significantly higher level that reduced significantly in the early postoperative stage reaching to the lowest level at the late postoperative stage.

High-density lipoprotein-cholesterol

Results obtained in the current study revealed that the level of HDL-C in all patients' subgroups was significantly lower than that of control. Furthermore, HDL-C levels showed a nonsignificant rise in early postoperative stage when compared to the levels of HDL-C in patients during the preoperative stage whereas the level increases significantly in late postoperative stage when compared with other two stages as revealed in Table 1.

Discussion

Malondialdehyde

Malondialdehyde is a product of peroxidation of lipid, and it reflects the extent of tissue damage mediated by free radicals. Measurement of MDA level in patients in all three studied stages showed a significant higher level than that of controls that may indicate a higher oxidative stress. This finding is in agreement with Sorathia *et al*. who found a highly significant difference in MDA levels between of coronary artery disease patients and controls.[13] In the current study, the level of MDA showed to increase significantly in the early postoperative stage in a comparison with the preoperative one and significantly reduced in a late postoperative stage in a comparison with both preoperative stage and early postoperative stage which may indicate that the open-heart surgery cause an immediate increase in the level of free radicals as a result to an effect of ischemic reperfusion injury followed by a decrease in the oxidative stress as demonstrated from the results obtained after 1 month of the surgery. These findings can be explained as follows:

- The initial rise of MDA after surgery indicates increasing oxidative stress during and following the surgical procedure, mainly due to reperfusion, surgical damage, and cardiopulmonary bypass. This finding is compatible with the results in the study of Türker *et al*.[14] and the study of Mentese *et al*.[15] who found significant increase in total oxidative status in preoperative state. Cardiopulmonary bypass causes the initiation of several processes that affect blood contents, whether cellular or noncellular leading to the activation of polymorphonuclear leukocytes due to the passage of blood through extracorporeal circulation. These polymorphonuclear leukocytes are believed to be a primary source of ROS that occur during cardiac surgery[16]
- The following decline in MDA after 1 month indicates reduction in oxidative stress mostly due to the resolution of the factors that elevate the oxidative stress during surgery. Dias *et al*. also suggested a gradual decrease in free radicals, which are associated with oxidative stress, after the completion of the cardiac surgery[17]
- The overall decline in MDA from preoperative state to late postoperative state indicates a long-term decline in

Table 1: The levels of malondialdehyde and lipid profile for patients and control groups

Parameter	Group	Mean±SD	P^a	P^b	P^c	P^d	P^e	P^f
MDA (ng/ml)	Control (*n*=30)	17.55±6.54	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Preoperative	70.91±31.86						
	Early postoperative	93.68±47.77						
	Late postoperative	59.61±30.43						
Total cholesterol (mg/dl)	Control (*n*=30)	137.20±29.92	0.006	0.106	0.491	0.012	<0.001	0.008
	Preoperative	160.06±27.58						
	Early Postoperative	151.96±43.61						
	Late postoperative	142.2±32.06						
TG (mg/dl)	Control (*n*=30)	98.87±27.38	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
	Preoperative	196.38±105.49						
	Early postoperative	181.74±94.46						
	Late postoperative	146.66±65.82						
HDL-cholesterol (mg/dl)	Control (*n*=30)	52.33±6.34	<0.001	<0.001	<0.001	0.746	<0.001	<0.001
	Preoperative	34.40±7.61						
	Early postoperative	34.76±11.65						
	Late postoperative	43.61±5.91						
LDL-cholesterol (mg/dl)	Control (*n*=30)	65.26±29.49	0.007	0.069	0.576	0.198	<0.001	0.001
	Preoperative	86.38±34.74						
	Early postoperative	80.85±40.27						
	Late Postoperative	69.25±31.49						

P^a, P^b, and P^c: *P* value between preoperative, early postoperative, and late postoperative, respectively against controls, P^d: *P* value between preoperative and early postoperative, P^e: *P* value between early postoperative and late postoperative, P^f: *P* value between preoperative and late postoperative.
TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MDA: Malondialdehyde, SD: Standard deviation

oxidative stress as an effect of the surgery, suggesting that surgical management of the cases could reduce oxidative stress on the long run. A similar inhibition of MDA in late postoperative state was described by Türker *et al*.[14]

These findings were consistent with findings by Dogan and Turker who described a significant rise in MDA during operation when compared to both preoperative state and postoperative state (24 h after operation).[18] Another study by Lazzarino *et al*. have also showed an elevation in MDA level shortly after surgery, as a result of ischemic reperfusion injury.[19] Furthermore, several previous studies illustrated the presence of an excessive production of free radicals mainly in open-heart surgery leading to an increase in oxidative stress systemically which is commonly related to the higher production of MDA.[18]

However, there was still a significant difference between the patients 1 month after surgery and controls, suggesting that oxidative stress in patients, despite its significant decline was still higher than oxidative stress in healthy people, which is consistent with the findings by Sorathia *et al*.[13]

Assessment of correlation between MDA level and total cholesterol level showed variable results in different states. In preoperative state and late postoperative state, there was nonsignificant correlation between total cholesterol level and MDA level ($R = 0.155$, $R = 0.035$, respectively), and no direct link between total cholesterol and oxidative stress could be established in those situations. This is supported by the findings described by Rao and Kiran who found nonsignificant positive correlation between MDA level and total cholesterol level in coronary artery disease patients ($R = 0.258$).[20]

However, in early postoperative state following surgery, there was a significant weak positive correlation between total cholesterol level and MDA level, which might indicate that higher total cholesterol level could increase the oxidative stress during the surgical procedure. This finding is contrary to what was found by Rao and Kiran, but it is in agreement with Rosenbaum *et al*. who suggested that hypercholesterolemia is associated with an increase in oxidative stress after arterial injury.[21]

Total cholesterol

There was a significant difference in total cholesterol level between preoperative state and controls, which is similar to the correlation described in the studies of Nobili *et al*.[22] and Gotto *et al*.,[23] however, the level of cholesterol in early and late postoperative states was not significantly higher. This is generally a good indicator for the prognosis of the patients undergoing surgery. Regarding the cases group, there is a significant steady decline in total cholesterol level from preoperative state through early postoperative state, reaching lowest value in late postoperative state. Such a decline was described by Figueroa *et al*. in their prospective study.[24] They have suggested that hemodilution was the main factor in that decline, but other factors including dietary changes and increased catabolism after surgery may also contribute to this decline.[24]

Triglycerides

TGs were found to be much higher in all patients' subgroups when compared to controls, reaching up to double the level

of controls. This association between TG and coronary artery disease was described by several studies including that by Freedman *et al*.,[25] and Gotto *et al*.[23] Highest TG level was observed in a preoperative stage followed by a significant reduction in both postoperative stages subjected to this study. This significant decline was similar to the Pakistani study by Iqbal *et al*.[26] Shaukat *et al*. have demonstrated a similar decline in TG after coronary artery surgery and suggested that withdrawal of β-blockers may have played an important role in that decline.[27]

Low-density lipoprotein-cholesterol

The results demonstrated from this study illustrated that the level of LDL-C in patients during the preoperative stage was significantly higher than controls while a nonsignificant elevation was determined in other subgroups in a comparison with controls which prove the previous theories about the role of LDL-C in the pathogenesis of cardiac diseases in agreement with Koba *et al*. who demonstrated similar results in patients with coronary heart disease.[28] LDL level showed a nonsignificant decline in early postoperative state followed by a significant reduction in its level in late postoperative state giving an overall significant reduction in LDL level between preoperative state and late postoperative state.

The assumed explanation of these results is that the patients' management is contributed to the reduction in the LDL-C level including a diet control and food enriched with vitamins and antioxidants derived from fruits and vegetables that enhance the recovery period leading to levels of LDL-C comparable to that of control. These results are in contrary with the findings of Iqbal *et al*. who also described a decrease in LDL level after surgery, but it was a significant decrease, which was followed by significant increase later on.[26] The disagreement of the current study with that of Iqbal *et al*. might be because their study has fewer females and younger patients than our study.

High-density lipoprotein-cholesterol

The level of HDL was significantly lower in patients subjected to this study in all stages of sampling when compared to controls. Similarly, a study by Gao *et al*. found a significantly lower concentration of HDL in coronary heart disease patients when compared to controls that may be explained by the previous study that proves the correlation between a low HDL-C level on the pathogenesis of cardiac disease and its involvement of this low levels in a bad prognosis for such patients.[29] Results of this study revealed that a significant elevation of HDL-C level was observed only after 1 month of the operation, despite that it is still significantly lower than that of controls. The extent of coronary artery occlusion is associated with lower HDL levels, which may explain the improvement in HDL level after cardiac surgery.[25] HDL level is generally associated with good prognosis, and this lower-than-control level is a point of concern.

Very-low-density lipoprotein-cholesterol

As known before, very-LDL-C (VLDL-C) level followed the level of TG given that VLDL is responsible mainly for the transport of endogenous TG from the lever to different tissues and the amount of cholesterol carried by this lipoprotein is nearly equal to one-fifth the amount of TG given that the pattern of VLDL-C is similar to that of TG in this study. Level of LDL-C was significantly higher than control group in the all studied patient subgroups in agreement with the findings of Koba *et al*.[28] and Hopkins *et al*.[30] The level of LDL-C started to decline slowly in the early postoperative state, followed by significant decline in the late postoperative stage, but still significantly lower than that of controls inconsistent with a study of Güvener *et al*. who stated a similar significant decrease in VLDL level during and after cardiopulmonary bypass surgery.[31]

Conclusion

There was an increase in the level of MDA in the early postoperative stage as an indicator of reperfusion damage that occurs immediately after open-heart surgery which then decreases dramatically with decrease in total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL-C), and very-LDL-C.

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Conflicts of interest

There are no conflicts of interest.

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