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Assessment of Iron Status and the End- Product of Lipid Peoxidation in Ischemic Heart Disease in Male Patients

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Objective: In the present study, an attempt is carried out to estimate the degree of iron overload in IHD patients in addition to the measurement of lipid peroxidation end product, malondialdehyde (MDA). The level of these compounds will indicate the risk of tissue damage caused by oxidative stress and iron overload.

Methodes: Sixty eight patients with ischemic heart diseases including stable angina (AS), unstable angina (UA) and myocardial infarction (MI) (aged 40-60 years) were involved in the present study during their admission to Al- Sader Teaching Hospital / Al- Najaf Al- Ashraf. Age matched twenty two healthy men were included as control group. All blood samples were taken early morning from fasting subjects.

Serum levels of iron and total Iron Binding Capacity (TIBC) were measured spectrophotometrically while unsaturated iron-binding capacity (UIBC), estimated total iron body stores (ETIBS), transferrrin saturation percentage (TS%) and transferrin concentration were calculated mathematically. Serum ferritin and MDA were measured using ELISA technique.

Results: Results of the present study in general revealed that there is a mild state of iron overload in IHD patients in comparing with healthy control. The results of iron status showed significant increase ($P<0.05$) in all iron indices of IHD patients in comparing with healthy control group except TIBC and UIBC, which decrease significantly ($P<0.05$) in those patients in comparing with control group. Moreover, a significant ($P<0.05$) increase in serum ferritin and ETIBS was found in IHD patients compared with control group. Serum MDA is increased significantly in IHD patients as compared with control group.

Conclusions: From the present study, it can be concluded that, iron status parameters showed be uses as a useful routine measures in IHD patients and iron stores in patients reveal a possible role of iron overload in the development of coronary atherosclerosis. MDA elevation in IHD patients indicating a possible role of oxidative stress processes in the pathophysiology of the heart diseases. Smoking has adverse effects on MDA and iron status leading, among many other known causes, to increase IHD risk.

Key words: Iron, TIBC, UIBC, ferritin, malondialdehyde.

Introduction: Ischemic heart diseases (IHD) are the most common cause of morbidity and mortality in most countries (Sebregts *et al.*, 2000). Due to the significant impact of coronary heart disease, it is important for prevention purposes to identify the determinants of risk for developing this disease. Ischemic heart disease (IHD) and coronary artery disease are the generic designation for the three forms of cardiac diseases, i.e., angina pectoris [unstable angina (UA), stable angina (SA)], sudden cardiac death and myocardial infarction (MI). In most cases the imbalance results from insufficient blood flow secondary to the development of atherosclerosis resulting in narrowing of the coronary arteries, thus, IHD is also frequently called coronary artery disease (CAD) (Buja, 1988) .

Iron is a mineral, vital to the body due to its role in a number of metabolic reactions. Functional iron within the cells must be bound to proteins, which is necessary for the promotion of oxygen transport, cell growth and differentiation, electron transport, and energy metabolism, as well as antioxidant and pro-oxidant reactions (Corti *et al.,* 1997; Gropper *et al.,* 2009). Iron is needed in relatively high amounts in the body for the proper functioning of many metabolic processes. However, when too much iron is taken into the body or when overload occurs due to another disorder, such as hemochromatosis, toxicities can result.

This overload occurs when iron-protein complexes become unbound within the cell. Iron is freed due to the saturated binding capacity of transferrin, as well as ferritin and hemosiderin (Gropper *et al.,* 2009). Free iron, or ferrous iron (Fe^{2+}) is harmful to the body because of its role in oxidative damage. When the iron transport and storage proteins (transferrin and ferritin) become saturated, free iron (Fe^{2+}) reacts with hydrogen peroxide forming ferric iron (Fe^{3+}) and free radicals, also known as the Fenton reaction. Free radicals, especially the hydroxyl radical are extremely reactive and initiate tissue damage and lipid peroxidation (Gropper *et al.,* 2009; Olesnevich, 2009).

Consequently, when excess iron is consumed and transferrin becomes saturated, free iron can be released (Gropper et al., 2009). The production of free radicals by free iron have been found in some studies to cause oxidative damage to the coronary arteries, and possibly oxidize low-density lipoprotein cholesterol, resulting in even more coronary damage (Corti et al.,1997). Significant injury can then progress to atherosclerotic disease. Moreover, an increase in free radical production causes oxidative stress, which may possibly cause thrombosis and interfere with typical vasomotor regulation. Thus it is biologically plausible that iron may play a role in the development of a heart disease.

Oxidative stress is characterized by an increased concentration of oxygen derived products that provoke critical, even irreversible, cell injury. Oxygen reduction leads to the synthesis of reactive intermediate compounds such as the superoxide anion, hydroxyl radical, hydrogen peroxide and peroxidative derivatives of polyunsaturated fatty acids (PUFA) such as conjugated dienes, lipid hydroperoxides and malonyldialdehyde (MDA) (Caimi et al., 2003).

Oxidation of circulating low density lipoprotein (LDL) has been linked to the initiation and pathogenesis of atherosclerosis and ultimately to the pathogenesis of cardiovascular disease (Nuttall et al., 1999). Oxidative stress alters the plasma lipoprotein profile (particularly LDL), the coagulative parameter (with an increased thrombotic risk), the endothelium (with a decrease in prostacyclin synthesis and an increase of thromboxane production) and the cell membranes (which undergo peroxidation) (Caimi et al., 2003).

Oxidative stress is involved in the pathogenesis of atherosclerosis (Antoniades et al., 2003). High blood pressure and increased heart rate can increase consumption of oxygen by the heart, causing increased production of free radicals. If the body's antioxidant system does not respond to quench these increased levels of free radicals, oxidative damage to the heart muscle can result. This is one of the mechanisms whereby obesity can promote lipid peroxidation of the myocardium, the middle layer of the heart composed of heart muscle. Oxidative stress can also impair the ability of the endothelium, the inner layer of cells that line the blood vessels, to expand and dilate in response to blood flow. Based on this scenario, an accumulation of reactive oxygen species has been linked to 'cardiac contractile dysfunction', potentially leading to arrhythmia and heart attack (Vincent et al., 1999) . Lipid peroxidation plays

a key role in rendering low density lipoprotein atherogenic (Heinecke, 1999). Oxidation, particularly oxidative modification of low density lipoproteins within the artery wall and its subsequent unregulated uptake by macrophages, has been postulated to be important in disease development (Stadler et al., 2004).

In fact, several studies have found significant associations between iron storage and atherosclerosis (Kiechl *et al.,* 1994). In addition, some studies are suggestive of a link between iron overload and myocardial infarction (Salonen *et al.*,1992; Tuomainen *et al.,* 1998). Nonetheless, many studies have found evidence that does not support the link between iron storage and coronary heart disease (Sempos *et al.,* 2000; Sun *et al.,* 2008), or atherosclerosis (Moore *et al.*,1995; Yunker *et al.*,2006). Finally, most past reviews have concluded that there is not enough evidence to determine the extent of involvement of stored iron on coronary heart disease and/or atherosclerosis (Danesh and Appleby, 1999; Sempos and Looker, 2001).

The present study has been designed to evaluate and compare the levels of and the biochemical markers of body iron stores (serum ferritin and transferrin saturation) and serum malondialdehyde (an oxidative stress marker), in control healthy subjects, and in patients suffering from ischemic heart diseases.

Materials and Methods

Patients: Sixty eight patients were divided into three study groups **:** myocardial infarction patients group included 25 subjects aged 40-69 years , unstable angina patients group included 20 subjects aged 40-69 years and stable angina patients group included 23 subjects aged 40- 69 years. The samples were collected from Al- Sader Teaching Hospital/Al- Najaf Al-Ashraf during the period from February till July, 2011.

Each patients group of the study was divided into subgroups according to the smoking.

Control group consists of 22 healthy non smoker males with normal blood pressure and their age range is between (40-69) years old. Exclusion criteria included a history of infection, inflammation, cancer, diabetes mellitus, and congestive heart failure.

Blood (8 ml) samples were taken after an overnight fast of 12–14 hours, from the antecubital vein of the patients as well as control individuals.
Blood was allowed to clot and serum was separated by centrifugation at 2500 rpm for 15 minutes. Serum was stored at -20 ºC until analyzed for study parameters.

Serum iron concentration was measured by iron (direct method) kit (Biolabo SA, France). Which was based on the following principle (Ferene, 1984):

After dissociation of iron- transferrin bound in acid medium, ascorbic acid reduces Fe3+ iron in to Fe2+. Fe2+ iron then form a coloured complex with 3-(2-Pyridyl) -5, -6-difuryl-1, -2, -4-triazine-disulfonate (Ferene). The absorbance thus measured at 600 nm (580-620) is directly proportional to the amount of iron in the specimen. Thiourea is added in the reagent to prevent the copper interference.

Total iron binding capacity was measured by T.I.B.C. kit (Biolabo SA, France), which was based on the following principle (Tietz, 1999):
T.I.B.C. is determined by addition of sufficient Fe3+ to saturate iron binding sites on apotransferrin. The excess Fe3+ is removed by adsorption with basic magnesium

carbonate powder. After centrifugation, bound iron remaining in supernatant is measured with direct method REF 92108 (Ferene).

Unsaturated iron-binding capacity (UIBC), the amount of protein (apotransferrin) still available to bind iron, can be estimated from the formula:

UIBC=TIBC – Serum iron.

Transferrrin saturation percentage (TS%) was calculated from the following equation (Christine *et al*., 2001):

*TS%=(Serum Iron/TIBC)*100%*

Transferrin concentration can be calculated using the following formula (Morgan ,2002).

*Transferrin Conc. (g/L) =S.Iron (µmol/L)/ (TS%*3.98)*

Ferritin ELISA kit for quantitative determination of ferritin in human serum was supplied by Accu-Bind, USA. The ferritin quantitative test is based on a solid phase enzyme-linked immunosorbent assay (ELISA). The assay system utilizes one rabbit anti-ferritin antibody for solid phase (microtitre wells) immobilization and a mouse monoclonal anti-ferritin antibody in the antibody-enzyme horseradish peroxidase (HRP) conjugate solution.

Estimated Total Iron Body Stores (ETIBS) were calculated using the following formula (Tietz, 1995): *ETIBS (in µmol) = (serum ferritin in µg/L) * 143*

Malondialdehyde (MDA) was measured by using the CellBiolabsTM MDA Adduct ELISA Kit (USA) which is an enzyme immunoassay developed for rapid detection and quantitation of MDA-protein adducts. The quantity of MDA adduct in protein samples is determined by comparing its absorbance with that of a known MDA-BSA standard curve. The Kit has detection sensitivity limit of 2pmol/mg MDA adduct. Each Kit provides sufficient reagent to perform up 96 assays, including standard curve and unknown protein samples.

Statistical Analysis: The results were expressed as (mean±standard deviation). ANOVA test has been used for the comparison between the patients and control groups while Pooled t- test has been used for the comparison among subdivided groups in the measured parameters.

The difference between groups is considered as statistically different when ($p<0.05$). All statistical analysis were performed using SPSS Statistics version19.0.1 Multilingual program (2010), IBM-USA. While the figures constructed using EXELL program of Microsoft Office 2007.

Results:

The serum concentration of iron status parameters in different ischemic heart diseases and control groups are presented in the table (1).

The results showed that there is a significant increase ($P<0.05$) in serum iron concentration in all patients groups, SA (36.75 µmol/l), UA (30.09 µmol/l) and MI (34.28 µmol/l) in comparing with control group (23.58±5.65 µmol/l). Furthermore, serum iron concentration in SA groups revealed the most significant increase ($P<0.05$) in comparing with UA and MI groups.

There was also significant ($P<0.05$) increases in serum TS% in all patients groups. While TIBC and UIBC were significantly lower ($P<0.05$) in patients groups as compared with control group. Transferrin concentration was significantly increase ($P<0.05$) in MI and SA patients.

Also, there was significant increases ($P<0.05$) in serum ferritin in all patients groups: SA patients (443.56 pmol/l), UA patients (387.99 pmol/l) and MI patients (386.27 pmol/l) compared to control group (181.97 pmol/l). SA group showed the higher level of ferritin among the groups.

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Additionally, the significant increase (P<0.05) in ETIBS in patients group in comparing with control groups is further confirmed the fact that the IHD have a higher iron stores in their body than controls.

Table (1): Iron indices in IHD patients and control groups

Groups / Parameter	Control (n=22)	SA (n=22)	UA (n=20)	MI (n=25)
S.Iron (µmol/l)	23.58±5.65	36.7536±7.59*●	30.09 ±8.21*	34.2814±7.83*
TIBC (µmol/l)	76.74±9.11	63.02± 9.32*	57.80±8.29*	59.058±5.79*
TS%	32.10±10.25	54.11±10.14*	58.83±11.92*	57.88±11.23*
Transferrin (g/l)	0.14±.02	0.15± 0.02*	0.13±0.02	0.19±.02*
UIBC (µmol/l)	53.18±12.73	26.77±11.89*	27.72± 9.75*	24.81±6.86*
Ferritin (pmol/l)	181.97±39.24	443.56±103.13*	387.99±150.18*	386.27±123.72*
ETIBS (mmol/l)	26.02±5.61	63.43± 14.75*	55.48±21.48*	55.24±17.69*

( ) : significantly different in comparing with control group.*
(●): significant different in comparing with other groups.

Malondialdehyde (MDA) concentration in studied groups as shown in figure (1). The results indicate the presence of a significant (P< 0.05) increase in MDA concentration in serum of SA patients (58.88 pmol/mg), UA patients (86.78 pmol/mg) and MI patients (101.19 pmol/mg) in comparison with that of control group (37.98 pmol/mg).

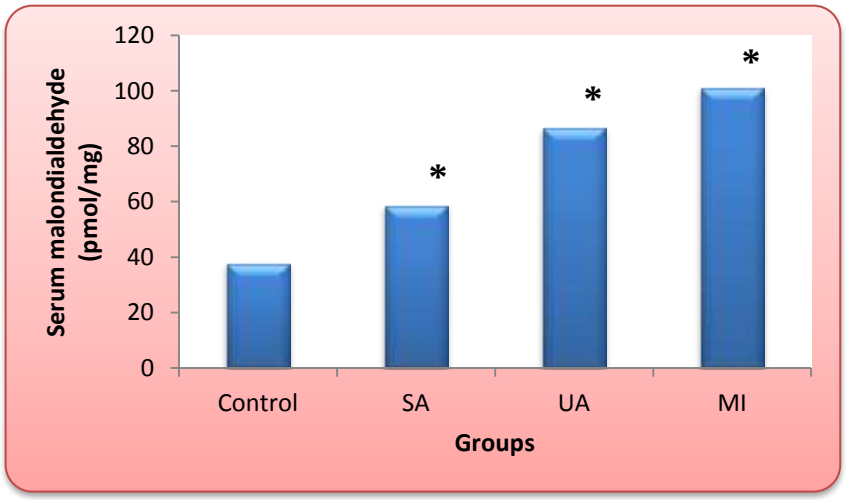

Figure (1): Serum malondialdehyde in IHD patients and control group.

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(*) denote a significant (p< 0.05) difference compared to control group.

The results of the measured parameters in smokers and non smokers MI patients are presented in table (2). The table showed the means of serum iron status in smoker and non smoker MI patients, the results show a significant (P< 0.05) difference in serum iron (37.64 umol/l), TIBC (55.92 umol/l), TS% (61.93) and transferrin concentration (0.15±0.01 g/l) in smoker group as compared to serum iron (28.25 umol/l), TIBC (60.80 umol/l), TS% (50.57) and transferrin concentration (0.14±0.02 g/l) in non smoker group.

Table (2) also showed that the mean of ferritin and ETIBS in smoker and non smoker IHD patients, the results of MI patients show a significant (P< 0.05) increase in serum ferritin (442.39 Pmol/l) and ETIBS (63.26 mmol/l) in smoker group as compared to serum ferritin (285.25 Pmol/l) and ETIBS (40.79 mmol/l) in non smoker group. No significant difference was found in UIBC between smoker and non smoker group.

Malondialdehyde(MDA) concentration in smoker and non smoker MI patients is shown in the table (2), the results show a significant (P< 0.05) increase in MDA (107.91 pmol/mg) in smoker group in comparison with MDA (89.09 pmol/mg) in non smoker group.

Table (2): Iron status comparison between smokers (n=16) and nonsmokers (n=9) MI patients.

Parameters	Groups	Mean±S.D.	*p*-value
MDA (pmol/mg)	Smokers	107.91 ± 28.33	0.043*
	NonSmokers	89.09 ± 18.18	
Iron (µmol/l)	Smokers	37.64 ± 5.47	0.005*
	NonSmokers	28.2 5 ± 8.02	
TIBC (µmol/l)	Smokers	55.92 ± 6.22	0.048*
	NonSmokers	60.80 ± 4.87	
UIBC (µmol/l)	Smokers	23.21 ± 5.36	0.158
	NonSmokers	27.67 ± 8.53	
TS %	Smokers	61.93 ± 8.23	0.023*
	NonSmokers	50.57 ± 12.58	
Tran.con (g/l)	Smokers	0.15 ± 0.01	0.037*
	NonSmokers	0.14 ± 0.02	
Ferritin (pmol/l)	Smokers	442.39 ± 98.39	0.001*
	NonSmokers	285.2 5± 99.98	
ETIBS (mmol/l)	Smokers	63.26 ± 14.07	0.001*
	NonSmokers	40.79 ± 14.29	

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The results of UA patients are shown in Table (3) which indicate that: a significant (P< 0.05) difference in serum iron (37.697 umol/l), TIBC (54.129 umol/l) , TS% (59.910) and transferrin concentratoin (0.15 g/l) in smoker group as compared to serum iron (25.010 umol/l), TIBC (63.304 umol/l), TS% (47.809) and transferrin concentration (0.13 g/l) in non smoker group.

The results of serum ferritin and ETIBS in UA patients are shown in the same table, which indicate that: a significant (P< 0.05) increase in serum ferritin (532.611 Pmol/l) and ETIBS (76.163 mmol/l) in smoker group as compared to serum ferritin (291.572 Pmol/l) and ETIBS (41.695 mmol/l) in non smoker groups. No significant difference was found in UIBC between smoker and non smoker group.

On the other hand, in patients with UA, there was a non significant increase in MDA between smoker and non smoker groups.

Table (3): Iron status comparison between smokers (n=8) and nonsmokers (n=12) UA patients.

Parameter	Groups	Mean±S.D.	*p*-value
MDA (pmol/mg)	Smokers	102.50 ± 22.90	0.156
	NonSmokers	76.28 ± 54.13	
Iron (µmol/l)	Smokers	37.69 ± 4.74	0.001*
	NonSmokers	25.01 ± 5.62	
TIBC (µmol/l)	Smokers	54.12 ± 8.42	0.005*
	NonSmokers	63.30 ± 4.16	
UIBC (µmol/l)	Smokers	25.60 ± 7.54	0.410
	NonSmokers	29.11 ± 11.07	
TS%	Smokers	59.91 ± 9.376	0.030*
	NonSmokers	47.80 ± 13.54	
Tran.con (g/l)	Smokers	0.15 ± 0.011	0.007*
	NonSmokers	0.13 ± 0.01	
Ferritin (pmol/l)	Smokers	532.61 ± 20.70	0.001*
	NonSmokers	291.57 ± 115.46	
ETIBS (nmol/l)	Smokers	76.16 ± 2.96	0.001*
	NonSmokers	41.69 ± 16.51	

Table (4) showed the results of iron status in SA patients, which indicate that: a significant (P< 0.05) difference in serum iron (42.453 umol/l), and TS% (66.082) in smoker group as compared to iron (30.578 umol/l), and TS% (50.963) and in non smoker group.

The same table also shows the results of iron body store in SA patients, which indicates that a non significant increase in serum ferritin (474.241 Pmol/l) and ETIBS (67.816 mmol/l) in smoker group as compared to serum ferritin (410.321 Pmol/l) and ETIBS (58.676 mmol/l) in non smoker group.

Malondialdehyde (MDA) concentration in smoker and non smoker SA patients are shown in the table (4), the results show a significant (P< 0.05) increase in MDA (71.717 pmol/mg) in smoker group in comparison with MDA (44.974 pmol/mg) in non smoker group.

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Table (4): Iron status comparison between smokers (n=12) and nonsmokers (n=11) SA patients.

Parameter	Groups	Mean ±S. D.	*p*-value
MDA (pmol/mg)	Smokers	71.71 ± 32.54	0.021*
	NonSmokers	44.97 ± 20.06	
Iron (µmol/l)	Smokers	42.45 ± 4.68	0.001*
	NonSmokers	30.57 ± 4.67	
TIBC (µmol/l)	Smokers	60.99 ± 12.11	0.330
	NonSmokers	64.85 ± 5.62	
UIBC (µmol/l)	Smokers	22.62 ± 10.76	0.070
	NonSmokers	31.25 ± 11.83	
TS%	Smokers	66.08 ± 10.24	0.001*
	NonSmokers	50.96 ± 8.11	
Tran.con (g/l)	Smokers	0.15 ± 0.01	0.220
	NonSmokers	0.14 ± 0.02	
Ferritin (pmol/l)	Smokers	474.24 ± 63.30	0.124
	NonSmokers	410.32 ± 128.50	
ETIBS (mmol/l)	Smokers	67.81 ± 9.05	0.139
	NonSmokers	58.67 ± 18.37	

Discussion: In the present study, the increase in serum iron status parameters in different ischemic heart diseases in comparing with healthy control group revealed the mutual interaction between iron stores in the body and the physiological functions of the heart muscle and blood vesicles in the circulation system. These interactions may include the harmful effect of iron precipitation in the human tissues including myocardium and endothelium of blood vesicles. The hypothesis that body iron stores are associated with risk of coronary heart disease (CHD) has generated extensive debate (Gillum, 1997, de Valk and Marx, 1999). In one study carried out in the Arab population in neighboring country (Saudi Arabia), Alissa *et al* (2007) found that the indices of iron status were related to several coronary risk factors in the Saudi population. Furthermore, dietary iron was significantly related to dietary cholesterol and fiber, age, smoking habits, and serum total cholesterol level (Alissa *et al* 2007). Excess iron may be involved in the development of atherosclerosis (Brewer, 2007, Sullivan and Mascitelli, 2007), but one study found reducing body iron stores in patients with symptomatic peripheral artery disease through phlebotomy did not significantly decrease all-cause mortality or death plus nonfatal myocardial infarction and stroke (Zacharski *et al*., 2007).

The significant increase in serum iron, transferrin concentration and TS% in patients in comparing with control group and decrease in TIBC, and UIBC level are in

accordance with other studies related the iron level with vascular disorders (Lauffer , 1991). The abnormal iron deposition may cause oxidant-induced damage in various organs. Cardiac iron deposition may be involved in the development of cardiac fibrosis induced by angiotensin II. In addition, iron overload may enhance the formation of neointima under conditions of increased circulating angiotensin II but not catecholamines (Ishizaka *et al*., 2002).

The ferritin concentrations in this study were higher in the IHD patients in comparison with the normal individuals, these results indicated mild iron overload in the patients groups due to the fact that serum ferritin acts as a marker for iron overload disorders i.e., abnormally raised ferritin levels may reflect iron overload. Ferritin, a major iron storage protein, is essential to iron homeostasis and is involved in a wide range of physiologic and pathologic processes. In clinical medicine, ferritin is predominantly utilized as a serum marker of total body iron stores. Elevated serum and tissue ferritin are linked to coronary artery disease (Knovich *et al*., 2009).

It is noteworthy that the synthesis of ferritin is post-transcriptionally regulated by the cytoplasmic transcripting factor that activates ferritin synthesis when iron is excess in the cell (Harrison and Arosio, 1996). This adaptive response is important for preventing cells from free iron toxicity. Therefore the increase in ferritin is due mainly to the increase in serum iron.

Two research groups; Haidari *et al* (2001) and Bozzini *et al(* 2002) reported significantly increased levels of serum ferritin in coronary heart disease patients as compared to normal control subjects. Haidari *et al* (2001) also observed a significantly increased level of serum ferritin in men with coronary heart disease than normal healthy men. The results are also showed serum iron and transferrin saturation significantly high, whereas total iron binding capacity was found to be significantly low in coronary heart disease patients as compared to the control subjects.

In one study, it's suggested that chronic diseases can also cause large amounts of ferritin to be released in the circulation (Mir *et al*., 2008). Other studies were found a modest association of ferritin and transferrin saturation with peripheral artery diseases, particularly among those with high cholesterol levels (Menke *et al*., 2009). Several clinical studies strongly support a relationship between body iron stores and susceptibility to coronary events or carotid atherosclerosis. Sullivan (1992) found that high serum ferritin levels were associated with an increased risk of myocardial infarction. Since ferritin levels reflect total iron stores, they postulated that increased iron predisposed to atherosclerosis.

Another study reported a correlation between high serum ferritin and the progression over 5 years of carotid atherosclerosis in 826 men and women (Kiechl *et al*., 1997). In another research on 2036 men and women, there was not a significant correlation between serum ferritin levels and myocardial infarction, but there was an inverse relationship between total iron binding capacity and myocardial infarction, particularly in men (Magnusson *et al*., 1994). They postulated that since the TIBC reflects circulating transferrin levels, higher levels of this protein may reduce LDL-C oxidation.

Other studies were found the relationship between iron overload and ROSs with aging process (Beckman and Ames, 1998). Furthermore, there found that smoking lead to increase of iron and perform to free radical (Weinberg, 2009). Changes in iron metabolism might be consequent upon obesity possibly via peroxide generation (Roberts *et al*., 2006). Transferrin saturation values in excess of 60 percent may be indicative of iron overload. Transferrin saturation percentage (TS%) can be elevated by increased iron stores and a variety of other conditions. Elevated transferrin

saturation reflects increased iron stores (Looker and Johnson , 1998). The findings of Ralph *et al* (2010) support a biologic rationale for measurement of serial ferritin levels in patients with atherosclerosis. Because iron-induced oxidative stress contributes to inflammatory responses, determination of optimal iron marker levels to be maintained by calibrated phlebotomy is a clinically relevant concept for future outcome studies in IHD.

The finding of a 10-fold higher expression of both H-ferritin and L-ferritin messenger RNA in human and animal atherosclerotic aortas compared with normal aortas (Pang *et al*., 1996) strongly indicates that these cells are exposed to high amounts of low-molecular-weight iron complexes. In a time course experiment, the induction of ferritin expression occurred in parallel with the progression of the lesions. Furthermore, Prussian blue stain showed the presence of iron deposits in advanced lesions but not in the early lesions of rabbit and human aortas. This finding suggests that the ferritin gene expression is not only induced by iron but that it could also be promoted by other, still unknown, factors as well. The production of apoferritin within the macrophages and endothelial cells could be a protective mechanism against the damaging effects of free iron (Balla *et al.*, 1992) or oxidized LDL-C (Juckett *et al*., 1995).

The ability of iron to cycle reversibly between its ferrous and ferric oxidation states is essential for the biological functions of iron but may contribute to vascular injury through the generation of powerful oxidant species. Rajapurkar *et al* (2012) examined the association between chemical forms of iron that can participate in redox cycling, often referred to as “catalytic” or “labile” iron, and cardiovascular disease (CVD). Rajapurkar *et al* provide preliminary evidence for a strong detrimental association between high serum catalytic iron and CVD even after adjusting for several co-morbid conditions; however, broader prospective studies are needed to confirm these findings, which would support therapeutic trials to assess the beneficial effects of iron chelators on CVD. Other confirmation for the results is that, iron reduction in one study caused a significant age-related improvement in cardiovascular disease outcomes (Ralph *et al.*, 2010).

The results of iron status in smokers and non-smokers IHD patients in this study indicated a significant difference in all iron indices in smoker patients compared with non smoker patients.

After smoking, elevation in the systemic blood pressure occurs as a result of an increase in peripheral resistance. Also an increase in heart rate is a result of direct chronotropic effects and adrenal catecholamine secretion (Narkiewicz *et al*., 1998). Diastolic function is impaired during acute exposure to cigarette smoke (Ghaidari *et al*., 2010) .

There are several likely ways that cigarette smoke does its damage. One is oxidative stress that mutates DNA, promotes atherosclerosis, and leads to chronic lung injury. Oxidative stress is thought to be the general mechanism behind the aging process, contributing to the development of cancer, cardiovascular disease (Terry , 2008).

Smoking is a risk factor for coronary artery, peripheral vascular and cerebrovascular diseases. Smoking causes endothelial dysfunction, atherosclerosis and arrhythmias through the combined effects of nicotine, carbon monoxide and polycyclic aromatic hydrocarbons (Heeringa *et al*., 2008).

The effect of nicotine is complex since evidence suggests that it acts simultaneously as a ganglionic depressant and stimulant. As the cigarette is smoked, and nicotine is consumed, catecholamine levels rise in the blood stream (Pomerleau and Pomerleau, 1984) which stimulate the heart to increase output, but also causes adrenergic vasoconstriction (Winniford *et al*., 1986) and increase blood pressure. Chronic exposure to carbon monoxide also results in polycythemia which contributes to the increase in blood viscosity caused by nicotine (Davis *et al*., 1989), leads to increased blood viscosity and eventually to microvascular clotting (Grines *et al.*, 1995).

There is an significant difference in iron, TIBC, TS%, transferrin concentration , ferritin and ETIBS in smoker MI and UA patients as compared with non smoker patients. Also, there is a significant difference in iron and TS% only in smoker SA patients as compared with non smoker.

Serum iron was increase in chronic cigarette smokers patients when compared with non smoking patients. These results are in agreement with previous studies (Sagone *et al.,* 1973). As tissue hypoxia leads to inadequate oxygenation of blood circulation through lungs results in erthrocytosis and consequent increased production of erythropoietin (El-Zayadi *et al.,* 2002*).*

Increased total red blood cell count increases the number of destroyed red blood cells in the normal turnover process which subsequently increases iron overload (Sagone *et al.*, 1973). This finally leads deposition of excessive iron in the parenchymal cells causing hepatocellular liver damage (Bacon and Britton , 1990).

Significantly increase in serum ferritin with smoking patients may be due to increase iron in smokers patients. According to one study, it suggested that a high stored iron concentration, as assessed by serum ferritin, is a strong in the male Iranian population (Haidari *et al.,* 2001). Other studies found the smoking has been shown to be associated with an increased level of serum ferritin (Lee and Jacobs, 2004).

Serum indices of iron homeostasis revealed disparities between nonsmokers and smokers. Relative to nonsmokers, serum iron and ferritin concentrations and transferrin saturation in cigarette smokers were significantly increased (Ghio *et al.,* 2008).

Significantly decrease in serum TIBC and serum UIBC in smoker when compared with non smoker patients ($P<0.05$) came in agreement with Saudi studies which indicated that serum TIBC and serum UIBC were statistically decreased in smoking comparing with non smoking (Al-Malki, 2009).

Our results show that serum levels of malondialdehyde increased significantly in all groups of IHD patients compared with the control group. According to these results we suggested that presence of MDA in serum at certain levels may predict the insurgence of vascular pathologies.

Many agents have appeared to be potential sources of intracellular oxidative stress. The lipid peroxidation-derived aldehydes have been shown to induce intracellular peroxide production and our results is consistent with previous studies showing that increased MDA levels is an indication of induced lipid peroxidation (Boaz *et al.,* 1999; Korantzopoulos *et al.,* 2003), and increased lipid peroxidation is in relation with coronary heart disease (Kharb and Singh, 2000; Del Rio *et al.*, 2005; Izbirak, 2007). It is therefore likely that reactive aldehydes tend to trigger the formation of reactive oxygene species or are oxidants themselves and potentiate oxidative stress in the cells. Excess oxidative stress is toxic exerting cytotoxic effects, causing membrane damage, and activating pathways of cell death (apoptosis and/or necrosis) (Kumar *et al.,* 2002).

Malondialdehyde is also related to innate genotoxicity. This molecule may be derived by lipid peroxidation, but it can also be generated by physiological metabolisms, and a highly mutagenic product. MDA is therefore, more than a simple marker, but a clear alarm of high risk of mutation (Marnett , 1999; Vander Veen *et al.*, 2003).

Another aspect of MDA is its toxicity towards the cardiovascular system. MDA action on lipoproteins has been related to atherogenesis and, probably its reactivity towards collagen is responsible for the stiffening of the cardiovascular tissue (Slatter *et al.*, 2000; Izbirak, 2007). Activation of free radical processes and lipid peroxidation, decreased antioxidant capacity. The combination of effective iron-chelatory agents with natural or synthetic antioxidants can be extremely helpful in clinical practice in the regulation of the antioxidant status of patients with different disesess (Pavlova *et al*., 2007). Oxygen free radicals promote the oxidation of lipids, which has been postulated to be involved in the development of atherosclerosis. This is supported by the observed association between the titer of autoantibodies against oxidatively modified LDL-C and the progression of carotid atherosclerosis in men. Free iron catalyzes free radical production, which generates a range of potent oxidants that can induce oxidation of lipids (McCord, 1991). Thus, free iron might increase the risk of coronary heart disease (CHD) by promoting the oxidation of lipids and possibly of catecholamines. Free radical formation and lipid peroxidation can be prevented by the iron-chelating agent desferrioxamine. Iron chelators have also prevented or limited experimental myocardial ischemia or improved recovery after reperfusion injury in isolated rat hearts and other animal models (Williams *et al.*, 1991).

Pucheu *et al* (1995) suggested that measurement of malondialdehyde is a good marker of radical stress during reperfusion of the ischaemic myocardium, and also showed significantly increased malondialdehyde concentrations in group of CHD patients who were subjected to intravenous thrombolysis than those who had not been subjected to thrombolysis.

Ahmad and colleague's (2009) showed significantly increased levels of lipid peroxides in patients suffering from coronary heart disease as compared to the control subjects. Dincic *et al* (1998) showed evidence -of increased free radical activity in patients with myocardial ischaemia than the control subjects. Our results also show significantly increased concentrations of malondialdehyde, as an index of lipid peroxidation, in IHD patients.

Endothelial injury in association with hypoxia may result in the activation of not only the cyclooxygenase-dependent pathway of prostaglandin synthesis in endothelial cells (Holvoet *et al.*,1999; Morrow *et al.*,1992) but also in increased production of F2a-isoprostanes, noncyclooxygenase-derived prostaglandin- like compounds (Morrow *et al.*, 1992), that are strong inducers of platelet activation. Plaque instability is associated with increased platelet adhesion and activation. Activated platelets may then produce large amounts of aldehydes, further enhancing the modification of LDL. The association of unstable angina and AMI with plasma levels of MDA-modified LDL supports the hypothesis that the generation of MDA-modified LDL is associated with ischemic injury or plaque instability rather than with the extent of coronary atherosclerosis (Holvoet *et al.*, 1999).

This study shows increase in MDA levels in smoker patients as compared with non smoker patients.

Cigarette smoking adversely affects the lipid profile, leading to lower levels of HDL-c and higher levels of LDL-c and triglycerides. Production of oxygen free

radicals is increased with smoking, which may play a role in atherosclerosis, leading to CHD. In general, smokers have about twice the risk of developing CHD as do nonsmoker's (Parinley, 1997). Wang and associates (1996) studied healthy men (smokers and nonsmokers) and showed increased level of oxygen free radicals in smokers as compared to nonsmokers, and studied smoker and nonsmoker patients with CHD, and found significantly elevated level of oxygen free radicals in smokers with CHD than nonsmoker CHD patients.

Cigarette smoke contains approximately 1017 oxidant molecules per puff (Dilyara *et al*., 2007). Free radicals from cigarette smoke cause peroxidation of the polyunsaturated fatty acids of cell membranes that amplify oxidative stress during smoking. The F2-isoprostanes, prostaglandin-like compounds, are products of free radical-catalyzed lipid peroxidation . Several studies (Morrow *et al*., 1995; Reilly *et al*., 1996; Helmersson *et al*., 2005) have reported an increased level of isoprostane 8-iso-prostaglandin F2 (PGF2)_ formation in smokers.

Increased levels of malondialdehyde, which are degradation product of lipid peroxides, have been found associated with current smoking status in population-based studies (Rumley *et al*., 2004; Smith *et al*., 1993). Similarly, higher levels of thiobarbituric acid reactive substances (TBARS) have been found in smokers compared to nonsmokers (Orhan *et al*., 2005).

In conclusion, our study demonstrates a significant relationship between elevated level of malondialdehyde and IHD. Elevated levels of malondialdehyde indicate increase in the level of production of oxygen free radicals, suggesting their possible role in atherogenesis, leading to coronary heart disease.

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دراسة حالة الحديد ونواتج فوق أكسدة الدهون في أمراض نقص التروية القلبية عند الرجال

الخلاصة

الهدف: في هذه الدراسة أجريت محاولة لتحديد درجة زيادة الحديد في أجسام مرضى نقص التروية القلبية بالإضافة إلى قياس تركيز النواتج النهائية لأكسدة الدهون (مالون ثنائي الديهايد MDA) . حيث أن مستوى هذه المواد يؤشر إلى احتمالية التعرض لتلف الأنسجة الذي ينتج عن ارتفاع تركيز الحديد أو من الشدة التاكسدية.

طرق العمل: تمت في هذه الدراسة متابعة تراكيز المواد المذكورة أعلاه عند مرضى القلب كوسيلة لمتابعة وحتى التنبؤ والتشخيص لامراض القلب. اشترك في هذه الدراسة 68 مريضا بامراض القلب المختلفة وتراوحت اعمارهم بين 40-60 سنة وكالاتي: الجلطة القلبية و الذبحة الصدرية المستقرة و الذبحة الصدرية غير المستقرة من الداخلين في مستشفى الصدر التعليمي. كما اشترك 22 شخصا سليما كمجموعة سيطرة حيث تم سحب عينات الدم في الصباح وقبل الفطور (في حالة الصيام).

تم قياس تركيز الحديد وسعة الارتباط بالحديد الكلية (TIBC) باستخدام الطرق الطيفية اللونية بينما تم حساب كل من الدوال الآتية رياضيا: سعة الارتباط بالحديد غير المشبع (UIBC)، مخزون الحديد الكلي المخمن (ETIBS)، نسبة تشبع الترانسفرين (TS%)، وتركيز الترانسفرين. تم قياس تراكيز الفرتين و MDA في المصل بتقنية الايلايزا.

النتائج: أظهرت النتائج بصورة عامة حالة متوسطة من حالات فرط الحديد عند مرضى القلب مقارنة بالأصحاء، كانت هناك زيادة ملحوظة في كل متغيرات الحديد عند المرضى مقارنة بمجموعة السيطرة عدا

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TIBC وUIBC واللذان اظهرا انخفاضا معنويا عند المرضى مقارنة بالاصحاء، كما كان هناك ارتفاع في تركيز الفرتين وخزين الحديد الكلي عند مرضى القلب مقارنة بمجموعة السيطرة مما يؤكد حالة فرط الحديد الموجودة عند مرضى القلب. بالنسبة للمعايير الأخرى فقد لوحظ ارتفاع في تركيز MDA عند المرضى مقارنة بمجموعة السيطرة.

الاستنتاجات: يستنتج من هذه الدراسة ان قياس متغيرات الحديد يعتبر وسيلة مهمة لمتابعة حالة فرط الحديد في دم وأنسجة المرضى والتي بزيادتها تزداد احتمالية تطور تصلب الشرايين وامراض القلب. ان ارتفاع المالوندايالديهايد في مرضى القلب يؤكد حالة الشدة التاكسدية كمؤثر في عملية الاصابة بهذه الامراض. ظهرت نتائج التدخين انها ذو تأثير سلبي على المالوندايلديهايد وحالة الحديد عند مرضى القلب.