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Therole of Serum Melatonin in Acute Myocardial Infarction Patients

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Abstract: *Melatonin hormone is an endocrine product of the pineal gland , it is released following a circadian rhythm that regulates several physiological and neuroendocrine functions .Melatonin have important roles in a variety of cardiovascular pathophysiologic processes. Acute myocardial infarction (AMI) is the major cause of mortality worldwide . In AMI, there is excess production of active oxygen species such as;superoxide anion radical ($O_2^{\bullet -}$) and hydrogen peroxide (H2O2) andHydroxyl radical ($OH^{\bullet}$) . Melatonin and it's precursors are able to reduce oxidative reactions by direct free radical scavenging and indirect antioxidant activity so it has an important role in cardioprotection .*

This study was planned to Evaluate the level of serum melatonin hormone in patients with AMI , Compare melatonin level between normal control group and AMI patients and Study the changes in melatonin level in patients with AMI after 5 days of hospital admission.

The study was carried out in the coronary care unit (CCU) in Ibn Al-Nafes Teaching Hospital, 44 patients with AMI attending CCU and 36 apparently healthy individuals as a control group were involved in the study. blood samples were collected to investigate the level of melatonin hormone in patients at day 0 and day 5 by using ELISA technique, and forlipid profile determination.

The results revealed significant difference regarding serum melatonin between patient and control $p<0.0001$, melatonin level in AMI patients was(5.15±1.56) and in control subjects was (9.37±2.76) , The results of this study revealed no significant difference between melatonin level at day 0 and day 5 in AMI patients from this study its concludetd that melatonin protect patients from acute myocardial infarction

Keywords: *acute myocardial infarction, lipid profile, melatonin , ROS.*

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I. Introduction

Melatonin hormone is an endocrine product of the pineal gland , Melatonin is N-acetyl-5-methoxytryptamine, an indolamine derivative of tryptophan , it has been identified in all major taxa, including bacteria, unicellular eukaryotes, many plants species, and all animals .[1 & 2]

Pineal melatonin production exhibits a circadian rhythm, with a low level during daytime and high levels during night. This circadian rhythm persists in most vertebrates, irrespective of whether the organisms are active during the day or during the night [3] ; During the light phase of the photoperiod, suprachiasmic nucleus (SCN) activity is high, resulting in low norepinephrine levels ; At this point, serotonin does not come into contact with the enzyme responsible for converting it into melatonin. Therefore, plasma levels of melatonin are low during the light phase. However, with the arrival of the dark period, SCN activity becomes quiescent, and noradrenergic activity increases, resulting in activation of β-adrenergic receptors (and to a lesser extent α-adrenergic receptors) on the pinealocyte. The β-adrenergic receptors are coupled to cyclic adenosine monophosphate (cAMP) / protein kinase A signaling pathways that stimulate melatonin synthesis [2].

In mammals , there are at least two melatonin receptors, designated MT1 and MT2, which belong to the superfamily of G protein–coupled receptors[4 & 5].

Circadian rhythms are biological processes that have a 24-hour periodicity even in the absence of external uses. Melatonin is involved in regulating several circadian cycles, including core body temperature and the sleep/wake cycle [6& 7] .

During this 24-hour cycle, rising melatonin levels are associated with decreasing core body temperature, cortisol levels, and alertness. As melatonin levels wane, core body temperature, rapid eye movement (REM)sleep propensity, and cortisol levels increase.

Oxidative stress is a consequence of an inefficient utilization of molecular oxygen (O_2) by cells. Reactive oxygen species(ROS) including the superoxide anion radical ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) are generated as by-products of cellular respiration and other metabolic processes . They damage cellular macromolecules including DNA, proteins, and lipids . Additionally, however, there are also highly devastating agents which are nitrogen based e.g. nitric oxide ($NO^{\bullet}$) and especially the peroxynitrite anion ($ONOO^-$) [8 &9] . Melatonin is known to protect against oxidative stress

in cells. Although melatonin efficiently interacts with various ROS and reactive nitrogen species (RNS) as well as with organic radicals, it also upregulates antioxidant enzymes and downregulates pro-oxidant enzymes While the direct free radical scavenging actions of melatonin are receptor independent, the indirect antioxidative functions may well be mediated by receptors, either located in the membranes of cells or within the nucleus [8 ,10& 11] .

Acute myocardial infarction results from the partial interruption of blood supply to a part of the heart muscle, causing the heart cells to be damaged or die [12] .

Myocardial infarction mostly results from atherosclerosis[13] . The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade, sometimes resulting in total occlusion of the artery [**13**]

According to the criteria and consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction as revised in 2007 a cardiac troponin rise accompanied by either typical symptoms, pathological Q waves, ST elevation or depression or coronary intervention are diagnostic of MI [14].

Myocardial ischemia occurs when oxygen delivery to the myocardium is insufficient to satisfy mitochondrial oxidation. During ischemia there is insufficient oxygen availability but oxygen free radicals are still formed from the residual molecular oxygen. Also , the activities of the mitochondrial electron-transport chain are reduced increasing electron leakage from the respiratory chain, which reacts with residual molecular oxygen and forms, among other free radicals , the superoxide anion O2 [15,16].

Oxidized low-density lipoprotein (LDL) is a critical factor in the initiation and progression of atherosclerosis. During the initial step of LDL oxidation, lipid peroxidation is induced by free radicals which attack polyunsaturated fatty acids, molecules that are easily oxidized. This reaction results in the formation of lipid radicals. Lipid radicals generate conjugated dienes, intermediate lipid peroxida-tion products and eventually resulting in the formation of peroxyl radicals; these latter agents are sufficiently reactive to propagate the chain reaction of lipid peroxidation. As a result of lipid peroxidation, several nonradical products are formed, including malondialdehyde and other reactive aldehydes. Melatonin by itsantioxidant and anti-inflammatory properties acts a protective factor in atherosclerosis [17].

II. Materials And Method

This study was carried out at the coronary care unit (CCU) in Ibn Al-Nafes Teaching Hospital . The study involved (44) patients with AMI and 36 apparently healthy individuals as a control group. All subjects gave written, informed consent to be included in the present study, which was approved by our local ethical committee. The age was matched between the patients and controls groups, ranging from (40-60) years.4 ml of fasting venous blood were collected from patients and control at 8:00 AM for estimation of melatonin and lipid profile , 2 ml were used for lipid profile determination , another 2 ml of blood were used for estimation of melatonin hormone by Enzyme Linked ImmunoSorbant Assay (ELISA) . After 5 days another 2 ml of venous blood were collected from patients only for melatonin estimation .

The assay procedure follows the basic principle of competitive ELISA whereby there is a competition between a biotinylated and a non-biotinylated antigen for a fixed number of antibody binding sites. Quantification of unknowns was achieved by comparing the enzymatic activity of unknowns with a response curve prepared by using known standards .(The type of ELISA kit was Ref:54021. IBL International GMBH ,Floghafenstrasse 52a. D-22335 Hamburg , Germany) .

The statistical methods and display were made with the use of Statistical Package for the Social Sciences (SPSS) version 17 and Microsoft office 2007. The results were considered to be significant when ($P<0.05$).

All values were presented as mean ± SD , unpaired student T-test was used to compare between patient and control group , paired T-test was used to compare between patient group (day 0 versus day 5) .Correlations were used between different parameters of the study.

III. Results

The results showed a significant difference regarding serum melatonin between patient and control $p<0.0001$,melatonin level in AMI patients is 5.15±1.56 and in control subjects is 9.37±2.76.as shown in Table 1.

Regarding lipid profile , total serum cholesterol in AMI patients was 196.16± 19.2 versus in control subjects was 185.58 ±21.88 and p 0.0262 ; S.TG in AMI patients was 190.64±53.19 versus in control subjects was 171.39±31.96 and p 0.0493 . S.HDL in AMI patients was 35.91±6.89 versus 45.58±8.93 in control subjects is and $p<0.0001$.

S.LDL in AMI patients was 122.12±19.13 versus in control subjects was 105.72±21.01 and $p<0.0006$.

Atherogenic index of plasma (AIP) in AMI patients is 0.72 ± 0.17 versus in control subjects is 0.58 ± 0.14 P< 0.0001 .Table(1)

Table (1): Comparison between AMI patients and control group by unpaired t-test

Parameters	Control N=36 mean±SD	Patients N=44 mean±SD	P value
Age (years)	46.94±4.86	51.2±6.12	0.0008
Melatonin (pg/mL) (day 0)	9.37±2.76	5.15±1.56	<0.0001
S. Cholesterol (mg / dl)	185.58±21.88	196.16±19.2	0.0262
S. TG (mg / dl)	171.39±31.96	190.64±53.19	0.0493
S. HDL (mg / dl)	45.58±8.93	35.91±6.89	<0.0001
S. LDL (mg / dl)	105.72±21.02	122.12±19.31	0.0006
Atherogenic index of plasma (AIP)	0.58±0.14	0.72±0.17	0.0001

All values are presented as Mean± (SD)

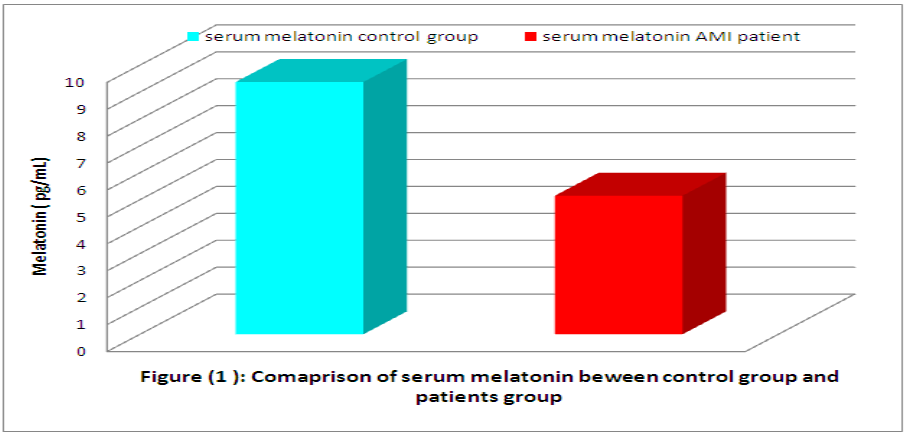

Figure (1): Comaprison of serum melatonin beween control group and patients group

"Fig"[1] shows difference in the level of melatonin hormone between AMI patients and control group serum melatonin is decreased significantly in patients with AMI , p<0.0001.

Table [2] shows no significant difference between melatonin level at day 0 and day 5 in AMI patients regarding age , gender , smoking and hypertension .

Table (2): Comparison between melatonin level at day 0 and day 5 by paired t-test

Parameters	Day 0 mean±SD	Day 5 mean±SD	P value
All MI patients (N=44)	5.15±1.56	5.04±1.23	0.5744
Male MI patients (N=28)	5.36±1.68	5.09±1.19	0.3293
Female MI patients (N=16)	4.77±1.28	4.96±1.32	0.303
Smoker MI patients (N=26)	5.37±1.67	5.14±1.2	0.3811
Non-Smoker MI patients (N=18)	4.84±1.38	4.9±1.28	0.8326
MI patients with HT (N=20)	5.62±1.93	5.32±1.07	0.3332
MI patients without HT (N=24)	4.76±1.06	4.81±1.32	0.8309

All values are presented as Mean ± SD

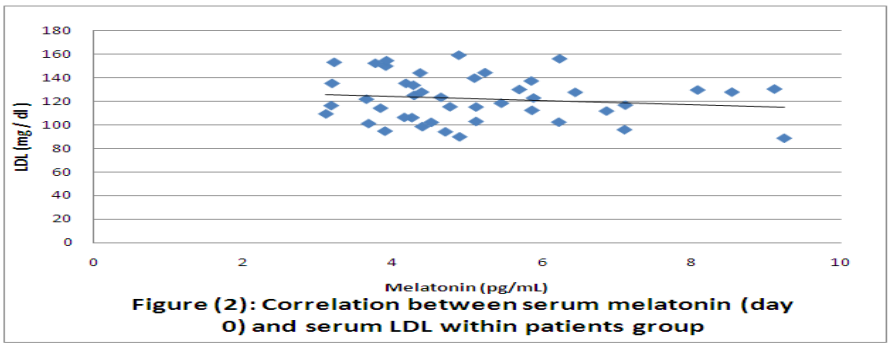

Figure (2): Correlation between serum melatonin (day 0) and serum LDL within patients group

r = - 0.132, p= 0.392

"Fig"[2]shows a negative correlation between LDL level and serum melatonin that when serum LDL decreases there is small but not significant increase in serummelatonin.

IV. Discussion

Coronary artery ischemia-reperfusion (I/R) injury that is known to occur on restoration of coronary flow after a period of myocardial ischemia ; Reperfusion of ischemic myocardium leads to severe damage, which is indicated by free radicals as Reactive oxygen species (ROS) and Reactive Nitrogen species (RNS) [18]. These reactive oxygen species cause peroxidation of membrane lipids, denaturation of proteins, and modification of DNA, all of which can ultimately lead to cell death [19]. Melatonin hormone and it's metabolites are known to be a powerful antioxidants and scavenger of free radicals so it can stop DNA damage and hence can stop cell death [19]. In this study demonstrated that the level of serum melatonin hormone level was significantly decreased ($P<0.05$) in patients with AMI (5.15±1.56 pg/mL) when compared to healthy subjects (9.37±2.76 pg/mL) ; Our data verify a previous hypothesis, that melatonin level is decreased in patients with coronary artery disease [20 , 16].

Dominguez-Rodriguez , Abreu-Gonzalez and Reiter in 2012 demonstrated that melatonin has cardioprotective effect as it acts direct free radical scavenger and indirect antioxidant , it reacts with various ROS and RNS , it also upregulates antioxidant enzymes and down regulate prooxidant enzymes .This decrease in melatonin hormone level may be due to consumption of Melatonin because it's action in protection against ischemic - reperfusion myocardial damage, although there are difference in the mechanism by which this compound exerts the cardioprotective effect ; Petrosillo et al. in 2009 suggested that the protective actions of melatonin and its metabolites, against myocardial damage are due to their indirect actions on anti- and prooxidant enzymes by inhibiting the opening of mitochondrial permeability transition pore so it leads to release of cytochrome – c that lead to cell death and melatonin can protect nuclear and mitochondrial DNA from damage , melatonin can preserve the content and integrity of cardiolipin molecules , which play a critical role in mitochondria bioenergetics. Melatonin can prevent cell damage and cell injury by its capability of increasing mRNA level for antioxidant enzymes like magnesium – superoxide dismutase , copper – zinc superoxide dismutase and glutathione peroxidase , these enzymes in turn protect cells including cardiac cells from death and damage caused by free radicals , it also acts as potent anti-inflammatory[21] .LDL is a critical factor in the initiation and progression of atherosclerosis and it contributes to endothelial dysfunction and plaque destabilization through multiple mechanisms [22] .Human studies have confirmed that oxidized LDL and oxidized lipid by products are present within atherosclerotic plaques [23]. LDL particles accumulate in the plasma infiltrate the intimal space of the arteries where they are oxidized by oxygen free radicals. During the initial step of LDL oxidation, lipid peroxidation is induced by free radicals which attack polyunsaturated fatty acids, molecules that are easily oxidized. This reaction results in the formation of lipid radicals [24] . melatonin does not undergo an enzymatic pathway of reduction after oxidation , but binds irreversibly to free radicals, and these compounds are removed by the kidneys. Not only melatonin but also precursors of its synthesis and products of its metabolism (eg, tryptophan, serotonin, 6-sulphatoxymelatonin) are able to reduce oxidative reactions [25].

V. Conclusion

From this study its concluded that there was aSignificant decrease in serum melatonin concentration in patients with acute myocardial infarction .Also melatonin can affect lipid profile as there was negative correlation between serum melatonin and AIP . Melatonin was decreased in day 5 after AMI although statistically it was not significant.

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