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The Mechanisms of Positive Effects of Melatonin in Dyslipidemia: A Systematic Review of Animal and Human Studies

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Abstract: Dyslipidemia and following atherosclerosis as a chronic affection remain one major cause of death all over the world. Given multiple reports on positive effects of melatonin on dyslipidemia, there is a need for reviewing all these studies in order to reach a convincing conclusion. Towards this goal, we have reviewed all previous investigations on use of melatonin in dyslipidemia found from PubMed, Cochrane, Google Scholar, Scopus and web of Science up to January 2012. Of the publications identified in the initial database, 11 clinical trials and 43 nonclinical trials (18 *in vitro* and 25 animal studies) were included and reviewed. Most of the results reveal the potency of melatonin as an antioxidant in preventing lipid peroxidation through different mechanisms and therefore, improving the lipid profile. Melatonin has anti-inflammatory and antioxidative effects, neutralizes free radicals, increases antioxidative enzymes and glutathione levels, prevents electron leakage from the mitochondrial respiratory chain, acts synergistically with vitamin C, E and glutathione, reduces levels of pro-inflammatory cytokines and therefore prevents Low-density Lipoprotein (LDL) oxidation and decreases lipid peroxidation. The results indicate a need for further studies on safety/efficacy measures if melatonin was used in long-term.

Key words: Melatonin, lipid peroxidation, dyslipidemia, low-density lipoprotein, pro-inflammatory cytokines

INTRODUCTION

The increasing prevalence of diabetes, obesity and dyslipidemia in the world is associated with serious health problems such as cardiovascular disease and cancer, which are considered major causes of the death in the world (Hasani-Ranjbar *et al*., 2011). Dyslipidemia presents itself as increased plasma low-density Lipoprotein (LD) resulting in inflammation in the vascular system and vessel of the heart. Liver and intestine have the main role in production and metabolism of lipoproteins. Free fatty acids are converted to acyl-coenzyme A (acyl-CoA) by the acyl-CoA synthetase (ACS) in the liver. Esterification of acyl-CoA produces Triglycerides (TG) and phospholipids. The lipoproteins that transport lipids (TG and cholesterol) in blood are classified by their density. Chylomicrons transport TG from the intestine to the liver. LDL carries cholesterol from liver to the body cells and High-density Lipoprotein (HDL) carries it back to the liver. LDL has the potential to be oxidized by free radicals and damage cells. Its cholesterol content is released into the vessel wall and oxidized. Then, it starts an inflammatory process. Immune system responds to the damage by sending macrophages to absorb oxidized LDL but when it is not enough, it results in deposition of a greater amount of cholesterol.

The lipid-laden macrophages make the fatty streak as the first step in the development of atherosclerosis (Nishida *et al*., 2003; Tailleux *et al*., 2002).

In this process, if there is no longer enough HDL to carry back the extra cholesterol to the liver, inflammation gets worse. Furthermore, increase of LDL oxidability alters its metabolism resulting in more atherogenesis rate (Tailleux *et al*., 2002). The most current prescribed drugs in atherosclerosis treatment are different statins. Besides, their proved efficacy in clinical trials, they have shown side effects both in short term and long term use. Statins are believed to have the antioxidant effect and thus, they can both prevent and reduce inflammation and risk factors in atherosclerosis. Although statins are generally well tolerated, some patients experience adverse effects, including elevated hepatic enzyme levels, gastrointestinal symptoms and statin-associated myalgias (Hadjibabaie *et al*., 2006, 2007; Hasani-Ranjbar *et al*., 2010). Other available drugs are niacin, fibrates and ezetimibe, which are used alone or in combination with statins. However, in some patients, there is a need for combine and use the complex regimen to reach the normal lipid profile and get the main target that is lowering the risk of cardiovascular diseases.

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There is increasing evidence that in certain pathologic states, the increased production and ineffective scavenging of Reactive Oxygen Species (ROS) play a critical role. High reactivity of ROS determines chemical changes in virtually all cellular components, leading to lipid peroxidation (Hasani-Ranjbar *et al*., 2009; Rahimi *et al*., 2005).

Antioxidants could be the first line of treatment against atherosclerosis (Sener *et al*., 2009). Based on mechanisms behind pathogenesis and progress of atherosclerosis and the statin's antioxidant power, there is a hope for any other antioxidant as an alternative or combinative therapy. The pineal endogenous hormone, melatonin (5-methoxy-n-acetyl-tryptamine), may be a valuable help in protecting LDL from oxidation. Melatonin may prevent degenerative diseases by protecting macromolecules (DNA, lipids and proteins) from free-radical damage (Mozaffari and Abdollahi, 2011). Therefore, melatonin has been tested for its potential to regulate lipid profile and prevent LDL oxidation. It is known that melatonin protects macromolecules from oxidation damage not just by its free-radical scavenging but also by its direct effect on antioxidant enzymes (Tan *et al*., 2002). The belief is that endogenous melatonin decreases and oxidative stress increase by aging (Momtaz and Abdollahi, 2012). Therefore, considering the increase in prevalence of cardiovascular and degenerative problems by age, it may be logic to use exogenous melatonin as a therapeutic agent.

Besides antioxidant power, melatonin's lipophilic and hydrophilic property allows it to enter all types of cells and detoxify free radicals (Baydas *et al*., 2002).

DATA SOURCES AND STUDY SELECTION

All investigations using melatonin in dyslipidemia were reviewed by use of relevant bibliographic databases such as PubMed, Cochrane, Google Scholar, Scopus and Web of Science up to January 2012. Of the publications identified in the initial database, 11 clinical trials and 43 non-clinical trials (18 *in vitro* and 25 animal studies) were included and reviewed.

REVIEW OF FINDINGS

***In vitro* studies:** The results of *in vitro* studies showed the protective properties of melatonin against lipid peroxidation in LDL by different mechanisms (Marchetti *et al*., 2011; Bonnefont-Rousselot *et al*., 2003; Sewerynek *et al*., 1995; Daniels *et al*., 1995; Wang *et al*., 2001). The demonstrated results and suggested mechanisms are summarized in Table 1. One of the markers of lipid peroxidation is formation of conjugated dienes (Abdollahi *et al*., 2004). Melatonin can decrease the formation of conjugated dienes (Marchetti *et al*., 2011; Bonnefont-Rousselot *et al*., 2003). It delays the onset of the propagation phase for conjugated dienes and lipid peroxides. It protects polyunsaturated fatty acids of LDL lipids against peroxidation. It prolongs the lag time, delays the peak time and decreases the rate of diene formation (Bonnefont-Rousselot *et al*., 2002, 2003; Walters-Laporte *et al*., 1998; Seegar *et al*., 1997; Pieri *et al*., 1996). In addition, it delays the consumption of LDL endogenous β-carotene and reduces its rate of disappearance but it has no protective effect on α-tocopherol due to its lower scavenging capacity (Marchetti *et al*., 2011; Bonnefont-Rousselot *et al*., 2003, 2002). Melatonin acts like a chain breaking antioxidant (Abuja *et al*., 1997). It scavenges hydroxyl peroxide and other toxic free radicals derived from oxidized LDL (Ox-LDL) (Marchetti *et al*., 2011; Bonnefont-Rousselot *et al*., 2003, 2002). By its antioxidant effect, it reduces lipid peroxides, protein carbonyl and phosphatidylserine levels and increases glutathione level (Sener *et al*., 2009).

A component of oxidized lipoprotein is Lysophosphatidylcholine (LPC) that reduces endothelial nitric oxide (NO) and causes the vasospastic effects. Melatonin significantly inhibits the activity of LPC demonstrated by suppressing its vasospastic effect. This effect is via scavenging hydroxyl radicals arising from LPC (Okatani *et al*., 2000a, b). Melatonin activates monocytes through protein kinase C and induces their cytotoxic properties, along with the IL-1 secretion (Morrey *et al*., 1994). In addition, melatonin reduces the numbers of LDL receptors and inhibits the synthesis of cholesterol in the cells (mononuclear leukocytes). Some studies indicated the association of melatonin receptors with circulating TG and HDL levels (Bhattacharyya *et al*., 2006; Muller-Wieland *et al*., 1994). Melatonin can inhibit the increased expression and activity of Myosin Light Chain Kinase (MLCK) via extracellular signal regulated kinase (ERK/MAPK) signal transduction. Ox-LDL increases expression and activity of MLCK by phosphorylation of ERK (Zhu *et al*., 2008). Melatonin increases the immunoreactivity of LDL (Kelly and Loo, 1997). *In vitro* studies have extensively reported the need for higher doses of melatonin to inhibit LDL oxidation, than its physiological concentrations (Tailleux *et al*., 2002). Some of these studies showed the concentration dependent manner in melatonin inhibitory effect on lipid peroxidation (Sewerynek *et al*., 1995; Daniels *et al*., 1995; Kozel'tsev *et al*., 2007).

Table 1: *In vitro* studies considering the effects of melatonin in hyperlipidemia

Investigated effect	Method	Dose (melatonin/control)	Results	Possible mechanisms	Reference
Protection against oxidation of PLPC liposomes and LDL	Oxidation induced by $^{\bullet}OH$ produced by water gamma radiolysis	20, 50, 100 μM in PLPC liposomes and 100 μM in LDL/-	↓Lipid peroxidation in LDL ↓CDs and hydroperoxides formation ↓Radio-induced apo-B carbonylation; Protection of α-tocopherol and β-carotene in LDL	Scavenging of lipid-derived peroxyl radicals; reacting with $^{\bullet}OH$ generated in aqueous phase leads to slow down the reaction of hydroxyl with PLPC	Marchetti *et al.* (2011)
Protective effect against oxidative modifications and phosphatidylserine externalization in platelets	ADP activated platelets were incubated with Ox-LDL or Fe_3+/ascorbic acid for 1 h: at 37°C	10 mM/-	Protected platelets from iron overload-induced and Ox-LDL induced oxidative modifications; ↓MDA and phosphatidylserine ↓GSH ↓PC	Scavenger effect on toxic free radicals	Sener *et al.* (2009)
Preventive effect on Ox-LDL induced increase of MLCK activation and expression	LDL induced increase of MLCK	NA The phosphorylation of ERK)	↓Expression and activity of MLCK induced by ox-LDL (associated with	Though ERK/MAPK signal transduction	Zhu *et al.* (2008)
variants-association of sequence in the melatonin -related receptor gene (*GPR50*) with circulating TG and HDL levels		NA	The receptor has a role in the regulation of lipid metabolism	Sequence variants in the receptor gene was associated with fasting TG and circulating HDL levels	Bhattacharyya *et al.* (2006)
Effect on peroxidation of human LDL	LDL peroxidation initiated by $O^{(2-)*}$ and ethanol-derived $RO^{(2)*}$ from water gamma radiolysis in the presence of ethanol	$50\times10^{(-6)}$, $100\times10^{(-6)}$ or $250\times10^{(-6)}$ mol L^{-1} in ethanol/-	↓Formation of CDs ↓TBARS in a concentration-dependent manner; no protective effect on endogenous antioxidants (α-tocopherol) against peroxyl-induced oxidation (but delayed the consumption of LDL endogenous β-carotene and ↓its rate of disappearance	Melatonin delayed the onset of the propagation phase for CDs and TBARS	Bonnefont-Rousselot *et al.* (2003)
Protective effect of two melatonin related compounds towards LDL oxidation	LDL oxidation initiated by defined free radicals $O^{(2-)*}$ and ethanol-derived $RO^{(2)*}$ produced by gamma radiolysis or by copper ions	DTBHB and GWC20 (100 μM/melatonin 100 μM	They all protected β-carotene from the attack of free radicals and inhibit Cu-induced LDL oxidation	↓Formation of products derived from lipid peroxidation (CDs and TBARS) by ↓lag phase duration of CDs formation	Bonnefont-Rousselot *et al.* (2002)
Antioxidative effect on the oxidized LDL-induced impairment of NO production	LDL was oxidized by incubation with 5 μM $CuSO_4$	20, 100, 500 μM/mannitol	↓Decreased NO reduction	Though ability to scavenge $^{\bullet}OH$	Wakatsuki *et al.* (2001)
Antioxidant property in countering the vasospastic effect of Ox-LDL	-	10 μM/-	↓Vasospastic effect of Ox-LDL	By scavenging $^{\bullet}OH$ arising from Ox-LDL	Okatani *et al.* (2000a)
Antioxidant property	-	1, 10 μM/20 μM mannitol and indomethacin	↓Vasospastic effect of LPC in a concentration dependent manner	By scavenging. OH arising from LPC	Okatani *et al.* (2000b)
Antioxidant activities against LDL oxidation and cytoprotective action against Ox-LDL-induced endothelial cell toxicity	Cu-induced LDL oxidation	79 μM/vitamin E	Inhibited LDL oxidation; not inhibited Ox-LDL toxicity toward endothelial cells (↓LDH release)	↓Intracellular TBARS formation elicited by Ox-LDL	Walters-Laporte *et al.* (1998)
Antiatherogenic effect	Cu-mediated oxidation of healthy pre-menopausal women LDL	1, 5, 10 μM/-	↑Lag time of formation of Ox-LDL (with 10 μM melatonin)	-	Seegar *et al.* (1997)

Table 1: Countinue

Investigated effect	Method	Dose (melatonin/control)	Results	Possible mechanisms	Reference
Antioxidant effect on LDL oxidation	Lipid peroxidation induced by thermolabile initiator or Cu ions	1000 mol/mol LDL/α-tocopherol	Protective effect was found during lag time and propagation phase	By its antioxidant power	Abuja *et al.* (1997)
Capacity to prevent oxidative modification of LDL	LDL oxidation induced by cupric chloride or AAPH	0.125-4 mM/-	Inhibited oxidative modification of LDL *in vitro* in a concentration-dependent manner	↓Electrophoretic mobility ↓immunoreactivity of LDL ↓formation of TBARS caused by either Cu or AAPH	Kelly and Loo (1997)
Protective effect against LDL peroxidation	Cu induced peroxidative modification of LDL	NA	Protected polyunsaturated fatty acids of LDL against peroxidation; ↑lag time duration; delayed peak time; ↓diene formation; by-products of melatonin oxidation might react with lysine residues of apo-B, transforming LDL in its atherogenic form	Scavenging capacity against hydroxyl and peroxyl radicals	Pieri *et al.* (1996)
Protective antioxidant effect	LPS-induced oxidative damage	0.01-3 mM/-	Inhibited lipid peroxidation by a concentration dependent manner	-	Sewerynek *et al.* (1995)
Preventive effect on the deleterious toxic effects of CCl_4	Generation of free radicals by incubating liver homogenates and liver microsomes with CCl_4	2, 1, 0.5 mM/-	↓Production of lipid peroxidation; unable to restore the activity of G6Pase due to its ability to scavenge toxic free radicals		Daniels *et al.* (1995)
Effects on cellular cholesterol metabolism	Incubation of cells (20 h) in lipid free medium resulting in ↓rate of cholesterol synthesis	100 μM/-	Modulated cholesterol metabolism in human cells (inhibits the pathway between lanosterol and cholesterol); ↓LDL receptors and no change in binding affinity	The 5-methoxy group is indispensible for the hormone action on cholesterol synthesis	Muller-Wieland*etal.* (1994)

2,2'-azo-bis- (2-amidinopropane) dihydrochloride, AAPH: Adenosine diphosphate, ADP: Apo lipoprotein B (apo-B), CCl_4: Carbon tetrachloride, CD: Conjugated diene, ERK: Extracellular signal-regulated kinase, G6Pase: Glucose-6 phosphatase, GSH: Reduced glutathione, HDL: high-density-lipoprotein, h: Hour (h), $^{\bullet}OH$: hydroxyl radical, LDH: Lactate dehydrogenase (LDH); low-density lipoproteins, LPC: Lysophosphatidylcholine, LPS: Lipopolysaccharide, MDA: Malondialdehyde, MARK: Mitogen-activated protein kinase, MLCK: Myosin light chain kinase, NA: Not available, NO: Nitric oxide, Ox-LDL: Oxidized low-density lipoprotein, PC: protein carbonyl, PLPC: 1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphocholine, $RO^{(2)*}$: Peroxyl radicals. $O^{(2)*}$ Superoxide anion, TBARS: Thiobarbituric acid reactive substances, TG: Triglyceride, ↑: increased, ↓: decreased

ANIMAL STUDIES

By a review of Table 2, we can see specific effects of melatonin in different models of rats and mice. There are large numbers of studies showing that melatonin; with its antioxidant potential protects atherogenesis and fatty liver disease in obese animal models. There are other models such as myocardial infarction, drug-induced cardiotoxicity, oxidative injuries and finally diabetes. The most obvious and bold beneficial results were the potential to decrease and restore the elevated total cholesterol, TG, LPO, LDL, tumor necrosis factor (TNF-α) and lipid peroxide. Melatonin also reduced body weight in obese rat models besides its regulatory effects on lipid profile. It, furthermore, decreased heart muscle cholesterol and augmented cholesterol clearance. Moreover, it stimulated glutathione to help protecting LDL from oxidation. Melatonin influences cholesterol metabolism by modulating the macrophage activity and regulating the secretion of cytokines, such as IL-2 (Hoyos *et al*., 2000).

CLINICAL TRIALS

The studies included 11 clinical trials examined any relation between melatonin and lipid profile. In seven of them; melatonin was used as an intervention, including four placebo-controlled trials. The doses of melatonin were started at 0.3-10 mg in three to twelve weeks of treatment. Melatonin was administered orally in all seven trials (Table 3).

The reported results showed that melatonin decreased the level of LDL and lipid peroxides in metabolic syndrome patients (Kozirog *et al*., 2011) and reduced LDL susceptibility to oxidation (Wakatsuki *et al*., 2000). Besides its lowering effect on LDL, it also increased the HDL level and reduced plasma cholesterol (Tamura *et al*., 2008). Co-treatment of melatonin and zinc reduced oxidative damage induced by hyperglycemia in type 2 diabetic patients, which were on medical therapy with metformin. Melatonin improved lipid profile in comparison to placebo with a dose of 10 mg (Kadhim *et al*., 2006) whereas; it had no significant effect on lipid metabolism in diabetic patients with a dose of 2 mg (Garfinkel *et al*., 2011).

In a study performed to evaluate its role on serum levels of lipids, there was no significant effect on hypercholesterolemia with 3 mg melatonin (Rindone and Achacoso, 1997). Additionally, any significant influence on cholesterol and TG were observed in non-alcoholic fatty liver disease when compared to placebo (Gonciarz *et al*., 2010) but in comparison between healthy subjects and acute Myocardial Infarction (MI) patients, melatonin concentration was lower in acute MI patients associated with high level of oxidized LDL (Dominguez-Rodriguez *et al*., 2005). Another trial suggested a relationship between melatonin secretion and acute coronary diseases. They measured urinary melatonin metabolite (6-sulfatoxymelatonin), Cu/Zn Superoxide Dismutase (SOD) activity along with LDL and Malondialdehyde (MDA) in 21 patients with unstable angina. The results showed a lower level of both melatonin metabolite and Cu/Zn SOD in unstable angina in comparison to healthy volunteers. This supports the hypothesis that melatonin level is a clinical marker in coronary atherosclerosis (Vijayasarathy *et al*., 2010).

Furthermore, there was a report represented the reduced concentration of nocturnal melatonin in multiple sclerosis patients with hypercholesterolemia that indicates melatonin as a reducing factor on serum cholesterol by affecting its metabolism (Sandyk and Awerbuch, 1994). There is another study, analyzed nine women's salivary melatonin, plasma TG and non-essential fatty acids showing the correlation between melatonin as a circadian rhythm marker and TG (Morgan *et al*., 1998).

DISCUSSION

Lipids have the main role in cardiovascular diseases via development of atherosclerosis plus modifying the structure and stability of the cellular membranes. It has been documented that serum LDL and HDL levels have opposing influence on the risk of cardiovascular diseases (Patel *et al*., 2010). Ox-LDL increases free radical production, lipid peroxidation and platelet activation resulting in an increase in the sensitivity to aggregating (Sener *et al*., 2009). During LDL oxidation process, lipid peroxides such as MDA are produced following the formation of conjugated dienes. In this process, endogenous antioxidants such as α-tocopherol and β-carotene are used (Vijayasarathy *et al*., 2010). The complete lipid peroxidation in LDL has been explained by Abuja *et al*. (1997). This process can be assumed as three phases; first, the lag phase in which conjugated dienes are produced slowly because of LDL resistance to oxidation. In lag phase, lipophilic antioxidants are able to inhibit radical chain propagation. After the lag time, while antioxidants are used, chain propagation speeds the conjugated formation. However, amphiphilic antioxidants can lower the rate of this phase. Finally, the last phase is destroying the conjugated dienes during subsequences reactions (Abuja *et al*., 1997). There are reviews explaining the melatonin's extensive role in metabolic regulation and cardiovascular system (Korkmaz *et al*., 2009; Nishida, 2005; Sewerynek, 2002) but we emphasized on the

Table 2: Animal studies considering the effects of melatonin in hyperlipidemia

Investigated effect	Model	Method	Melatonin dose/duration/control	Results	Possible mechanisms	Reference
Antioxidant effect	Rat	NAFLD induced by high-fat diet for 8 weeks	10 mg kg^{-1}/d/p.o./8 weeks/pioglitazone	↓Cholesterol ↓TG ↓TNF-β ↓MDA ↓GSH	-	Zaitone *et al.* (2011)
Effects on obesity and obesity-associated systolic hypertension and dyslipidemia	Rat	Diabetic fatty rats, an experimental model of the metabolic syndrome	10 mg kg^{-1}/d/p.o./6weeks/ vehicle	↓Mean weight gain without food intake differences; Sig improvement in dyslipidemia; ↓hypertriglyceridemia ↓LDL ↑HDL No effect on total cholesterol levels	-	Agil *et al.* (2011)
Effect on body weight progression, mean levels and 24 h pattern of circulating adiponectin, leptin, insulin, glucose, TG and cholesterol were examined	Rat	High-fat diet: 35% fat	25 μM/day/p.o./11 weeks/ vehicle	↓Body weight ↓hyperglycemia ↓hyperinsulinemia ↓plasma adiponectin ↓leptin ↓TG and cholesterol	-	Rios-Lugo *et al.* (2010)
Cardioprotective effect	Rat	Isoproterenol induced myocardial infarction	10 mg kg^{-1}/day/i.p./7 days/-	↓TG ↓LDL ↓Phospholipids ↓Total cholesterol	Though maintaining endogenous antioxidant enzyme activities	Patel *et al.* (2010)
Improving metabolic profiles	Rat	Obese models were established using high-fat/high-sucrose-fed for 5 months	4mg kg^{-1}/day/ i.p./8 weeks/vehicle	↓Plasma glucose ↓total cholesterol ↓TG	-	She *et al.* (2009)
Effect on chosen metabolic and hormonal variables	Rat	-	4 μM/day/p.o./12 weeks/-	↓Serum triacylglycerol and heart muscle cholesterol in females ↑Serum and heart muscle cholesterol in males ↓liver PL in females ↑heart muscle PL in males ↑MDA in heart muscle in males and in liver in both sexes	-	Bojkova *et al.* (2008)
Radioprotective effect	Rat	Oxidative stress and tissue injury induced by gamma radiation (2 and 4Gy from cesium-137 source)	10 mg kg^{-1}/4 days before irradiation/i.p./vehicle	↓Total lipids ↓Cholesterol ↓TG ↑HDL ↓LDL and GGT	By preventing oxidative stress though stimulating GSH, modulating serum GGT activity and exerting hypolipidemic impact	El-Missiery *et al.* (2007)
Effects on food intake, body weight and leptin in combination with estradiole	Rat	Ovariectomized rats as a model of menopausal status	20 μM/day/p.o./7 weeks/vehicle	↓Food intake and body weight ↓cholesterol no Sig. effect on leptin	-	Sanchez-Mateos *et al.* (2007)
Effect on antioxidant status, lipid peroxidation and lipid	Rat	Normal rats	0.5, 1.mg kg^{-1}/day/i.p./45 days/vehicle	↓Oxidative stress ↓lipid peroxidation ↓cholesterol	↑Activity of the brain and liver antioxidant enzymes; ↓Superoxide dismutase	Subramanian *et al.* (2007)

Table 2: Countinue

Investigated effect	Model	Method	Melatonin dose/duration/control	Results	Possible mechanisms	Reference
profile in the brain and liver				↓Pls ↓TG and free fatty acids in the examined tissues	↑CAT ↑GSH	
Cardioprotective effect	Rat	Doxorubicin induced acute cardiac toxicity	5 mg kg^{-1}/day/i.p./10 days/-	↓Serum TG ↓Cholesterol	Though the antioxidant and free radical scavenging	Ahmed *et al.* (2005)
Hypolipidemic and antioxidative effects in plasma, liver and aorta	Mice	High cholesterol diet	10 mM/day/p.o./16 weeks/-	↓Plasma and liver Cholesterol ↓CDs ↓liver TG	↑Catabolism of cholesterol to bile acids ↓Cholesterol synthesis ↓LDL receptor activity	Sener *et al.* (2004)
Effects on body weight and metabolic parameters	Rat	High-fat diet induced obesity	30 mg kg^{-1}/day/p.o./3 weeks /vehicle	Regulatory effect on body weight; ↓Body weight gain; no effect on plasma insulin level; ↓plasma glucose ↓leptin ↓TG	-	Prunet-Marcassus *et al.* (2003)
Effect on plasma levels of TG, fatty-acid, metabolism of plasma and hepatic lipids in type 2 diabetic rats	Rat	Animal model of type 2 diabetes mellitus	1.1 mg/day/implanted under the abdominal skin/30 weeks/-	↓TG ↓Fatty acids in plasma ↓Hepatic lipids	Though restored insulin resistance	Nishida *et al.* (2002)
Effect on atherosclerosis in proximal aorta	Mice	Atherogenic diet with reduced vitamin E	0.02% w/w/d/16 weeks/vehicle	No Sig effect on the plasma lipid, Glucose or insulin, Serum anti-oxidant capacity, ↑Sig atherosclerosis development in the proximal aorta as compared to controls independent of any lipidic or glucidic alteration	↑Sensitivity of atherogenic lipoproteins to oxidative stress during the fasting period and an altered cellular metabolism	Tailleux *et al.* (2002)
Protective effects of melatonin on STZ-induced diabetes mellitus	Rat	STZ-induced diabetes	100 µM/d/SC/-/vehicle	↓Total cholesterol ↓TG ↓LDL ↑HDL ↓Lipid peroxidation ↓MDA	Blocks many complications of diabetes by reducing oxidative stress and hence protects organisms from oxidative damage and dyslipidemia.	Baydas *et al.* (2002)
Antioxidant effect	Mouse	STZ-induced hyperglycaemia		5 mg/kg/d P.O for 15 days prior to STZ treatment/- ↑HDL and GSH	↓Serum TG ↓Cholesterol and LDL ↓MDA	Abdel-Wahab and Abd- Allah (2000)
Therapeutic effect on acute liver injury	Rat	Liver injury induced by I.P injection of CCl_4 (1.6 g kg^{-1})	10, 50, or 100 mg kg^{-1} i.p. single dose/vehicle	Prevented the progression of acute liver injury in a dose dependent manner; ↓GSH ↓L.p.o. no effect on decreased serum TG and increased liver TG	Antioxidant action	Ohta *et al.* (2000)

Table 2: Countinue

Investigated effect	Model	Method	Melatonin dose/duration/control	Results	Possible mechanisms	Reference
Effect on serum lipids	Rat	Hypercholesterolemic diet	10 mg/lit p.o. for 3 months /water	↓LDL ↓Cholesterol ↓Lipid peroxidation prevent ↓of HDL no effect on VLDL and TG	Participates in the regulation of cholesterol metabolism and in the prevention of oxidative damage to membranes	Hoyos *et al.* (2000)
Protective effects against oxidative stress in diabetic rats	Rat	Diabetes and oxidative stress experimentally induced by the injection of STZ	100, 200 μ/kg/d I.P 3 days before diabetes induction for	↓Lipoperoxidation ↓oxidative stress 8 weeks/-	- ↓MDA ↓TG ↑HDL ↓GSH	Montilla *et al.* (1998b)
Effect on the nephopathy and the oxidative stress induced by adriamycin	Rat	Nephopathy and the oxidative stress induced by a single and high dose of Adriamycin injection (20 mg kg^{-1} I.P)	50 μg kg^{-1}/d I.P 3 and 7 days before and after adriamycin injection/-	Protective effect against nephopathy and the oxidative stress	By restoring GSH, CAT and proteinuria to the levels of controls; Free radical scavenging	Montilla *et al.* (1998a)
Effect on metabolic change	Rat	Metabolic changes induced by continuous irradiation (15 days) and/or administration of 7,12-dimethylbenz/ a/anthacene	20 μL mL^{-1} in drinking water during continuous irradiation for 15 days/vehicle	Prevention of the biochemical pattern of fatty liver, prevention of ↓TG in the thymus	Unknown	Ahlers *et al.* (1997)
Effects on serum total and free cholesterol levels, cholesterol esterification index, phospholipid levels	Rat	Male rats were grafted an anterior pituitary under the kidney capsule	25, 50, 100 μg/rat S.C for 4 days (30 days after graft)/-	Normalized the augmented serum phospholipid levels found in pituitary-grafted rats ↓Serum phospholipids in control rats ↓free plasma cholesterol	-	Esquifino *et al.* (1997)
Effect on cholesterol metabolism	Rat	Dietary induced hypercholesterolemia	12.5 mg kg^{-1} I.P/-	↓Total serum cholesterol ↓VLDL ↓LDL enhanced catabolism of cholesterol to bile acids no effect on sterol biosynthesis ↓(HDL/total LDL cholesterol ratio)	Augmentation of endogenous cholesterol clearance mechanisms, By lowering of the cholesterol fraction associated with LDL	Chan and Tang (1995)
Anti-hypercholesterolemic effect	Rat	High-cholesterol (1% cholesterol, 0.5% cholic acid) diet	4 mg/day/i.p. for 10 28 days/-	No effect on lipase activity ↓VLDL and LDL ↑HDL	-	Mori *et al.* (1989)
Effects on genetic	Rat	Genetic hypercholesterolemia (involved biochemical nephotic changes and histopathological changes in the kidney)		↓Plasma cholesterol levels and improvement of fatty changes of the liver Nahypercholesterolemia	Unknown	Aoyama *et al.* (1988)

CCl_4: Carbon tetrachloride, CAT: Catalase, CDs: Conjugated dienes, d: Day, GGT: Gamma-glutamyltransferase, GSH: Reduced glutathione, HDL: High density lipoprotein, h: hour, i.p.: Intra peritoneal LPO: Liver lipid peroxide, LDL: Low density lipoprotein, MDA: Malondialdehyde, mth: Month, NA: Not available, NAFLD: Non-alcoholic fatty liver disease, p.o.: Orally, PL: Phospholipid, Sig: Significant Sc: Subcutaneously, STZ: Streptozocin, TG: Triglyceride, TNF-β: Tumor necrosis factor-β, VLDL: Very low-density lipoprotein, Weeks: Weeks, ↓: Increased, ↑: Decreased

Table 3: Clinical studies considering the effects of melatonin in hyperlipidemia.

Evaluated effect	Study type	Subjects	No. of patients/sex /age range	Melatonin dose/duration/route of administration/control	Results	Reference
Treatment of lipid metabolism	Randomized, double-blind, cross over study	Type 2 diabetic patients with insomnia	36/11 M, 25 F/46–77 year	2 mg/day/3weeks/ p.o./Placebo	No effect on lipid metabolism	Garfinkel *et al.* (2011)
Efficacy in metabolic syndrome	Clinical trial	patients with metabolic syndrome, who did not respond to 3-month lifestyle modification	30/-/-	5 mg/day/2 months/p.o./-	↓BP, LDL, TBARS; improved antioxidative defense; ↑CAT activity	Kozirog *et al.* (2011)
Effects on plasma liver enzymes and lipids	Pilot study	Patients with NAFLD	42/-/-	10 mg/day/3months/ p.o./Placebo	No Sig difference in cholesterol and TG level; improves plasma liver enzymes with no Sig side effect	Gonciarz *et al.* (2010)
The relationship between night-time serum melatonin levels and serum levels of total cholesterol, TG, HDL and LDL and effects on lipid metabolism	Clinical trial	Peri-and postmenopausal women	36 (first study), 10 (second study)/ F/30–73 year	1 mg/day/1month/p.o./-	Sig ↑serum levels of HDL; night-time serum melatonin levels had a negative correlation with serum total cholesterol and LDL and a loose positive correlation with HDL	Tamura *et al.* (2008)
The effects on the lipid profile in type 2 DM patients poorly controlled with metformin	Placebo-controlled, double-blind clinical trial	Type 2 diabetic patients	46/25 M, 21 F/40–64 year	10 mg/day/90 days/p.o. /Placebo	Daily administration of melatonin and zinc (50 mg) improved the impaired lipid profile; ↓oxidative induced by hyperglycemia	Kadhim *et al.* (2006)
The relationship between nocturnal serum melatonin levels and Ox-LDL	Controlled clinical trial	Acute myocardial infarction patients	60 patients, 60 healthy/35 M, 25 F/-	NA/healthy subjects	Nocturnal serum levels of melatonin were lower in patients with higher Ox-LDL than the control group	Dominguez-Rodriguez *et al.* (2005)
Effect on the susceptibility of LDL to oxidation	Clinical trial	Normolipidemic post-menopausal women	15/F/48–72 year	6 mg/day/2weeks/p.o./No. control	↑Plasma TG; no Sig effect on plasma levels of total cholesterol, HDL and LDL; ↓LDL susceptibility to oxidative modification	Wakatsuki *et al.* (2000)
Effect on serum lipids	Pilot study (randomized single-blind, cross-over placebo control)	Patients with LDL level greater than 160 mg/dL despite a 3-month trial of a low-fat diet	21/-/-	0.3, 3 mg/day/6 weeks/ p.o./Placebo	No uniform effect on serum lipids in patients with hypercholesterolemia; ↓total cholesterol and LDL with the 3-mg dosage in 3 patients	Rindone and Achacoso (1997)

BP: Blood pressure, CAT: Catalase, d: Day, DM: Diabetes mellitus, F: Female, HDL: High-density-lipoprotein, h: Hour, LDL: Low-density lipoproteins, M: Male, Mth: Month, NAFLD: Non-alcoholic fatty liver disease, Ox-LDL: Oxidized low-density lipoprotein, PO: Orally, Sig: Significant, TBARS: Thiobarbituric acid reactive substances, TG: Triglyceride,TNF-β: Tumor necrosis factor-β, Wk: Week Year: Year, ↑: Increased, ↓: Decreased

regulatory effect of the hormone on lipid profile both in clinical and non-clinical setting. Melatonin is known to take part in many metabolic processes as a regulator. Thus, any disturbance in its rhythm and secretion leads to several consequences known as metabolic diseases (Korkmaz *et al*., 2009). Morgan *et al.* (1998) determined the correlation of the internal clock to metabolic factors based on a hypothesis of the increased risk of cardiovascular disease in the shift workers. They observed delayed TG postprandial clearance after the phase shift showing the role of nocturnal melatonin level in lipid levels (Morgan *et al*., 1998). In another study, Damian *et al.* (1988) evaluated the effect of melatonin on HDL-cholesterol and serum cholesterol in the rat. Administration of melatonin-free pineal extract, in doses of 2 mL/day/animal along 3, 6 and 12 days caused a significant decrease in HDL-cholesterol and resulted in a reduction of testosterone due to decline of its major precursor, cholesterol.

Nishida *et al*. (2003) investigated the effect of pinealectomy on lipid metabolism in type 2 diabetic rats. Pinealectomy caused an increase in free cholesterol and hepatic TG via Acyl-CoA Synthetase (ACS) that its activity was significantly augmented, while Microsomal TG Transfer Protein (MTP) decreased.

Plasma pharmacokinetic of melatonin has been poorly investigated. There are no studies on the plasma melatonin pharmacokinetics in healthy subjects after prolonged administration of melatonin (Gonciarz *et al*., 2010). Prunet-Marcassus *et al*. (2003) demonstrated that melatonin efficiency was time dependent (Prunet-Marcassus *et al*., 2003). The effect of melatonin when administered before the end of the light period was increased due to an increased density of melatonin receptor and longer duration of high melatonin level. Melatonin is an amphipathic antioxidant diffusible into cells freely (Vijayasarathy *et al*., 2010; Korkmaz *et al*., 2011). After oral administration, melatonin rapidly passes into the blood stream (Korkmaz *et al*., 2011). Considering the short half-life of melatonin to get a prolonged effect, some studies used melatonin infusion, implants, or melatonin in water (Prunet-Marcassus *et al*., 2003). Pharmacologically pure form of melatonin is easily synthesized and affordable with a very long shelf life (Korkmaz *et al*., 2011). In administration of melatonin, its variable oral absorption, short biological half-life and high amount of its first-pass metabolism should be considered besides attention to its solubility profile in aqueous medium (Vlachou *et al*., 2006). By hypothesized radical scavenging power of melatonin depending on its location and partitioning into lipid or aqueous medium (Mekhloufi *et al*., 2007) assessed the location of melatonin in lipid assemblies. For LDL, melatonin was mostly seen in the aqueous phase containing phospholipids, unesterified cholesterol and apo-lipoprotein B100, verifying that melatonin is not incorporated into LDL completely when protects it from oxidation by free radicals (Mekhloufi *et al*., 2007). It is indicated that lipophilicity of melatonin is not enough to permit accumulation in the lipid phase and its antioxidant activity is lower than that of α-tocopherol. Therefore, the effective concentrations of melatonin in an *in vitro* aqueous medium to protect LDL against lipid peroxidation should be higher than that of in vivo situation (Abuja *et al*., 1997).

Melatonin has a benign safety profile even in pregnancy or neonates (Gitto *et al*., 2009). It has no toxicity and teratogenicity when administered in physiological and pharmacological amounts to humans and animals (Korkmaz *et al*., 2011). There is a report for decreased serum uric acid, bilirubin and increased serum glucose following melatonin administration (Hoyos *et al*., 2000). In the year 2000, Seabra *et al*. (2000) performed a randomized double blind placebo controlled clinical trial to assess melatonin's probable toxicity. Forty healthy volunteers received either placebo or melatonin in a dose of 10 mg daily orally for four weeks (10 placebo and 30 melatonin). At the end of the study by measuring different factors, they observed no significant difference between melatonin and placebo group and there was no report of any toxicity or side effects (Seabra *et al*., 2000).

Taking collectively, the present review support the positive effects of melatonin in dyslipidemia that is mediated through its anti-oxidative potentials and protection from detrimental effects of pro-inflammatory cytokines like IL-6, IL-12, TNF-α and IFN-γ that all lead to lower oxidation of LDL (Broncel *et al*., 2007). In the recent years, several studies have brought strong evidences that antioxidant compounds obtained from herbal products (Sarwar *et al*., 2011) can protect body from dyslipidemia (Momtaz and Abdollahi, 2010) and ailments related with dyslipidemia like nonalcoholic fatty liver disease (Malekirad *et al*., 2012), acute hepatic failure (Rahimi *et al*., 2012), diabetes (Mehri *et al*., 2011), aging (Hasani-Ranjbar *et al*., 2012), multi-diseases (Mohammadirad *et al*., 2011) and even in healthy subjects (Malekirad *et al*., 2011).

This review reveals that there is a simple and clear mechanism defining melatonin's defensive effect on the oxidation process of LDL but justifying the effective dose, duration of treatment and adverse effects remain to be elucidated in further controlled clinical trials in the hope to use melatonin as a supplementary in dyslipidemia and related disorders.

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