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Effects of Atorvastatin and Melatonin on Glycemic Control and Lipid Profile in Type 2 Diabetic Patients

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Abstract

Background Dyslipidemia is a modifiable cardiovascular disease risk factor that remains largely uncontrolled in patients with type 2 diabetes mellitus. Administration of melatonin may improve tissue responses to insulin and increase the efficacy of drugs which act through this pathway like Sulfonylurea.

Objective To investigate the effectiveness of Atorvastatin and melatonin that possess antioxidant and/or hypolipidemic effects on the changes that occur in patients with type 2 diabetes mellitus due to uncontrolled glycemic status.

Methods Forty one diabetic patients (26 female and 15 male) with an age 35-60 years and disease duration of 5-10 years were studied. Patients allocated to 3 groups, first group was treated with Placebo (starch 50mg; n=13), second group was treated with (Atorvastatin 20mg/day; n=14), while third group was treated with (Melatonin 10mg/day; n=14), in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 weeks. Biochemical parameter (baseline, 6 and 12 weeks later) including and lipid profile tests were done.

Results Atorvastatin and melatonin administration significantly increases fasting serum glucose and glycated hemoglobin levels, with significant decrease in cholesterol, triglycerides, and low density lipoprotein. However, the effects on these parameters were variable between the studied groups.

Conclusion The administration of Atorvastatin may induce hyperglycemia despite of its hypolipidemic effect, while melatonin could improve both glycemic control and lipid profile in patients with type 2 diabetes mellitus.

Key words Atorvastatin; melatonin; glycemic control; type 2 diabetes mellitus.

List of Abbreviation: T2 DM = type 2 diabetes mellitus, TC = total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, FSG = fasting serum glucose, HbA_1c = glycated hemoglobin, CVD = cardiovascular disease, OS = oxidative stress, ROS = reactive oxygen species, Glut 4 = glucose transporter 4.

Introduction

Type 2 diabetes mellitus (T2 DM) is characterized by defective insulin secretion in pancreatic β-cells in response to glucose and by deficiencies in the action of insulin on its target tissues. Hyperglycemia increases the risk of microvascular complications [(1)], while dyslipidemia is a major risk factor for macrovascular complications in patients with type 2 diabetes [(2)]. Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease (CVD) [(3)]. As such, management of LDL-C is the primary goal of therapy for diabetic dyslipidemia [(4)]. As the prevalence of type 2 diabetes increases in the United States, prevention of CVD is becoming an increasingly urgent public health concern, requiring aggressive management of the entire lipid profile [(5)].

Evidence that oxidative stress (OS) is present in diabetes originates from the frequent

observation that both reactive oxygen species (ROS) and antioxidants are increased. The later is logically rather seen in early stage of diabetes and should be interpreted as a tentative compensation of cells against increasing OS [6].

The use of melatonin for medicinal purposes has become something of an 'alternative medicine' fad, although there are few properly controlled trials of its efficacy [7]. Melatonin administration decreased the amount of thiobarbituric acid-reactive substances, increased glutathione levels and superoxide dismutase activity [8].

Atorvastatin is structural analogue of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). It is most effective in reducing LDL. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. It has become standard practice to initiate reductase inhibitor therapy immediately after myocardial infarction, irrespective of lipid levels [9].

The objective of the study was to investigate the effectiveness of atorvastatin and melatonin that possesses antioxidant and/or hypolipidemic effects on the changes that occur in patients with type 2 DM due to uncontrolled glycemic status.

Methods

This study was carried out on forty one (41) patients (26 females and 15 males) with T2 DM who attend the Specialized Center for Endocrinology and Diabetes - AL-Risafa Directorate of Health - Baghdad were enrolled from October 2011 to April 2013.

Inclusion criteria: Patients with T2 DM and hyperlipidemia of both sexes on sulfonylurea (glibenclamide), with age range 35-60 years (46.76 ± 7.89), and have disease duration of 5-10 years.

Exclusion criteria: They should not have other associated chronic diseases like liver and kidney disorders and cardiovascular complications. Patients who are pregnant and breast feeding are excluded. They should not be on insulin therapy or other antidiabetic drugs, or on antioxidant drugs like aspirin, and any associated drugs should be considered. They should not taking other hypolipidemic agent; anti-inflammatory or non steroidal anti-inflammatory drugs.

Patients treated previously with full maximum dose of sulfonylurea (glibenclamide) (15 mg/day) and kept on dietary control, (but with poor glycemic control as evidenced by abnormal values of fasting plasma glucose; glycated hemoglobin (HbA_1c); and dyslipidemia; those patients are carefully evaluated while they are on their already established treatment program for DM control) for 2 weeks before randomization into three groups:

Group I: includes 13 patients treated with placebo (starch 50 mg) in capsule dosage form in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control, for 12 weeks.

Group II: includes 14 patients treated with atorvastatin 20 mg given as single daily doses in a tablet dosage form, in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 weeks; and

Group III: includes 14 patients treated with melatonin 10mg hard gelatin capsule once daily (10 mg/day) in addition to the already given oral hypoglycemic agent (glibenclamide) and dietary control for 12 weeks.

After 12 hours fasting, blood samples were collected from all subjects by venepunture (10 ml), before starting drug treatment (as base line samples) and then after 6 weeks and 12 weeks of treatment to follow the changes in the studied parameters. Blood samples were divided into two tubes, one heparinized tube (1 ml of whole blood used for HbA_1c determination) and the other part was transferred into a plane tube to collect serum after centrifugation at 3000 rpm for 10 min at 4 ^{o}C.

Fasting serum glucose level (FSG) was determined using a readymade kit for this purpose, according to the method of Barham and Trendoer [10]; Glycated Hemoglobin (HbA_1c) was evaluated using the VARIANT HbA_1c program utilizes the principles of ion exchange high performance liquid chromatography [11].

Serum total cholesterol (TC) was estimated according to the method of Richmond [12]; serum triglyceride (TG) levels were determined according to the method of Fossati and Prencipe [13]; serum high density lipoprotein cholesterol (HDL-C) levels were estimated according to the method of Burstein [14] and serum low density lipoprotein cholesterol (LDL-C) was calculated by using this formula:

LDL-C = Total cholesterol – (TG/2.2) – (HDL-C)[15].

All Results were expressed in mmol/L except of HbA_1c in percent. Paired *t*-test and ANOVA were used to examine the degree of significance, and a value of $P < 0.05$ was considered significant.

Results

The data presented in table 1 clearly showed that in comparison with value at baseline in the same group after 12 weeks of treatment, no significant difference in FSG of placebo and atorvastatin with a high significant decrease in FSG of melatonin group was recorded. In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there is a significant increase in FSG of atorvastatin group. After 12 weeks of treatment, no significant difference in FSG of atorvastatin with a high significant decrease in melatonin group were recorded (Table 1).

In comparison with value at baseline in the same group after 6 weeks of treatment there is significant decrease in S. HbA1c of Placebo group, a high significant decrease in HbA_1c of melatonin group and significant increase in atorvastatin group.

After 12 weeks of treatment, no significant difference in S. HbA1c of placebo and atorvastatin groups, and a high significant decrease in HbA_1c of melatonin group recorded. In comparison with a placebo-treated group at corresponding duration, after 12 weeks of treatment, no significant difference in HbA_1c of atorvastatin group while a significant decrease in HbA_1c of melatonin group were seen (Table 1).

Table 1. Comparison of fasting serum glucose and glycated hemoglobin at different duration of treatment in each group

Group	Fasting serum sugar (mmol/l)			Glycated hemoglobin (%)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Group I N = 13	11.68±3.64	10.62±2.94*	11.62±2.79	8.35±1.93	8.6±1.94	8.15±1.61
Group II N = 14	11.92±3.22	14.26±4.8*a	13.27±2.88	8.19±1.24	8.83±1.39*	8.57±1.52
Group III N = 14	10.39±2.42	9.15±2.78*	7.64±1.83**b	8.36±1.13	7.76±1.03**	6.91±1.15**a

Comparison is with baseline value within the same group (* = $P < 0.05$), ** = $P < 0.001$), a = significant difference ($P < 0.05$) between drug group and placebo group at corresponding duration, b = $P < 0.001$ between drug group and placebo group at corresponding duration.

Concerning the effect of drugs treatment on lipid profile in comparison with value at baseline in the same group after 12 weeks of treatment, there was no significant difference in TC, TG and HDL-C with a significant increase in LDL levels of placebo group. While a high significant decrease in TC and TG was found in atorvastatin and melatonin groups. No significant difference in HDL-C of atorvastatin group and a high significant increase in HDL-C of melatonin group

were recorded. While a high significant decrease in LDL-C of atorvastatin and melatonin groups were found.

In comparison with a placebo-treated group at corresponding duration, after 12 weeks of treatment there was a significant decrease in TC was found in melatonin group with a highly significant decrease in TC of atorvastatin group were found (Table 2). No significant difference in TG of atorvastatin and melatonin groups and a significant increase in HDL-C of atorvastatin and melatonin groups. There was no significant difference in LDL-C of melatonin group and a significant decrease in LDL-C of atorvastatin group was found (Table 2).

Table 2. Comparison of lipid profile at different duration of treatment in each group

Lipid profile		Group I N = 13	Group II N = 14	Group III N = 14
Cholestrol (mmol/l)	Baseline	5.77±1.25	6.79±1.77	6.19±0.82
	6 Weeks	5.68±0.89	5.84±1.39**	5.79±0.77**
	12 Weeks	6.08±0.95	4.65±1.01**b	4.94±0.81**a
Triglyceride (mmol/l)	Baseline	1.92±0.83	2.55±1.53	2.84±1.07a
	6 Weeks	2.07±1.2	1.76±1.04*	2.34±0.86**
	12 Weeks	2.12±0.86	1.5±0.83*	1.98±0.81**
High-density lipoprotein (mmol/l)	Baseline	0.99±0.3	1.39±0.25a	0.97±0.11
	6 Weeks	1.16±0.21*	1.38±0.24a	1.08±0.1**
	12 Weeks	1.04±0.22	1.39±0.29a	1.24±0.09**a
Low-density lipoprotein (mmol/l)	Baseline	2.72±1.02	2.96±1.39	3.97±0.57b
	6 Weeks	2.51±1.01*	2.38±0.56	3.8±0.58b
	12 Weeks	2.94±0.96*	2.12±0.82**a	3.29±0.43**

Comparison is with baseline value within the same group (* = $P < 0.05$, ** = $P < 0.001$), a = $P < 0.05$ between drug group and placebo group at corresponding duration, b = $P < 0.001$ between drug group and placebo group at corresponding duration.

Discussion

Atorvastatin has been reported in some cases to disrupt glycemic control in patients with T2 DM [16]. The mechanism by which atorvastatin disrupts glycemic control remains unknown; however, atorvastatin was shown to inhibit adipocyte maturation and glucose transporter 4 (Glut 4) expression by blocking isoprenoid biosynthesis, thus impairing glucose tolerance [17]. These statements agreed with the results obtained in the present study which shown an increment in the FSG and HbA_1c levels after 12 week of treatment with atorvastatin (Table 1). There is evidence for a diabetes-preventing effect of melatonin, whereas pinealectomy increases the risk of diabetes [18]. Likewise, further data demonstrated that melatonin directly influences both glucose metabolism and insulin secretion from the *β*-cell of the pancreas [19].

In this respect, the data presented in this study are consistent with those indicated previously (Table 1), in which the administration of 10 mg per day of melatonin after 12 weeks significantly ($P < 0.001$) decreases FSG and HbA_1c levels. The presumed action of melatonin as a regulator of β-cells responsiveness to glucose may be exerted by both direct and indirect mechanisms. It has been reported that melatonin receptors are present in the pancreas [20].

Atorvastatin competitively inhibit this enzyme resulting in decreasing *de novo* cholesterol synthesis, and increasing expression of LDL receptors on hepatocytes. This increases LDL-C uptake by the hepatocytes, resulting in decreasing the amount of LDL-cholesterol in the

blood [21]. Like other statins, atorvastatin also reduces blood levels of TGs and slightly increases levels of HDL-C [22]. The present results in table 2 were compatible with the studies mentioned above about the effects of atorvastatin on serum levels of cholesterol; triglycerides and LDL.

As shown in table (2), treatment with 10 mg melatonin significantly reduces total cholesterol, triglyceride, and LDL-C plasma levels. These data are compatible with those reported by (Sudhakumari *et al*, 2001) [23] who showed that plasma melatonin levels were inversely related to the levels of lipids. In conclusion, administration of melatonin in therapeutic doses significantly improves the impaired lipid profile in dyslipidemia states associated with diabetes mellitus [24].

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Author contribution

Dr. Haitham M. Kadhim collected the cases and interpretation of results and discussion; Professor Dr. Faruk H. Aljawad interpreted the results; and Professor Dr. Hashim M. Hashim suggested the statistical analysis and clinical assessment throughout the study.

Conflict of interest

There is no conflict of interest**.**

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References

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000; 321: 405-12.
2. Farmer JA. Diabetic dyslipidemia and atherosclerosis: evidence fromclinical trials. Curr Diab Rep. 2008; 8: 71-7.
3. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulindependent diabetes mellitus: United Kingdom Prospective DiabetesStudy (UKPDS 23). BMJ. 1998; 316: 823-8.
4. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008; 31: 811-22.
5. Goff DC Jr, Gerstein HC, Ginsberg HN, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007; 99:4i-20i.
6. Zobali F, Avci A, Canbolat O, et al. Effects of vitamin A and insulin on the antioxidant state of diabetic rat heart: a comparison study with combination treatment. Cell Biochem Funct. 2002; 20: 75-80.
7. Rang HP, Dale MM, Ritter JM, et al. Rang and dales pharmacology, 6th ed.: Churchill Livingstone, 2011; p 503.
8. Pandi-Perumal SR, Srinivasan V, Maestroni GJM, et al. Melatonin, Nature's most versatile biological signal? FEBSJ, 2006; 273:2813–2838.
9. Bertrum KG. Basic and clinical pharmacology, 9th ed. McGraw-Hill, 2010; p.p. 627
10. Barham D, Trendoer P. An improved color reagent from the determination of blood glucose by the oxidative system. Analyst. 1972; 97: 142-5.
11. Mayer TK, Freedman ZR. Protein Glycosylation in diabetes mellitus: A review of laboratory measurements and of their clinical utility. Clin Chem Acta. 1983; 127: 147-84.
12. Richmand W. Proceedings in the development of an enzymatic technique for the assay of cholesterol in biological fluids. Clin Sci Mol Med. 1974; 46: 6-7.
13. Fassati P, Principe L. Measurement of serum triglyceride colorimetrically with an enzyme that produce H_2O_2. Clin Chem. 1982; 28(10): 2077-80.
14. Burstein M, Scholink HR, Morfin R. Measurement of HDL-C in the plasma with a sensitive colorimetric method. J Lipid Res. 1970; 19: 583.
15. Burtis CA, Ashwood ER. Tietz, Textbook of clinical chemistry, 3rd ed.: WB Sawanders Comp. 1999. p. 837-46, 766-73, 921-2.
16. Yamakawa T, Takano T, Tanaka S, et al. Influence of putavastatin on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2008; 15: 269-75.
17. Nakata M, Nagasaka S, Kusaka I, et al. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): Implications in glycemic control. Diabetologia. 2006; 49: 1881-92.
18. Conti A, Maestroni GJ. Melatonin rhythms in mice: role in autoimmune and lymphoproliferative diseases. Ann NY Acad Sci. 1998; 840: 395-410.

19. Peschke E, Mühlbauer E, Musshoff U, et al. Receptor (MT (1)) mediated influence of melatonin on cAMP concentration and insulin secretion of rat insulinoma cells INS-1. J Pineal Res. 2002; 33: 63-71.
20. Williams LM, Hannah LT, Adam CL, et al. Melatonin receptors in red deer fetuses. J Reprod Fertil. 1997; 110: 145-51.
21. Nissen S, Sipahi I, Libby P, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006; 295(13): 1556-65.
22. Fox LP, Merk HF, Bickers DR. Dermatological pharmacology: In: Brunton LL, Lazo JS, Parker KL (eds). Goodman & Gilman's: the pharmacological basis of therapeutics. 11th ed. McGraw-Hill; 2008. p. 1679-706.
23. Sudhakumari CC, Halder C, Senthikumaran B. Seasonal changes in adrenal and gonadal activity in the quail, Perdiculaasiatica: Involvement of the pineal gland. Comp Biochem Physiol Biochem Mol Biol. 2001; 128(4): 793-804.
24. Ismail SH. Dose dependent hypolipidemic effects of melatonin in dyslipidemia associated with diabetes, University of Baghdad, PhD thesis. 2004.

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