The hypoglycemic and hypolipidemicefficacy of Atorvastatin andFlaxseed oil in type 2 diabetic patients.

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Abstract

Background: Glycemic control and prevention of secondary complications are the most important aims of using pharmacological treatment in diabetes mellitus. Dyslipidemia is a modifiable CVD risk factor that remains largely uncontrolled in patients with type 2 diabetes. The administration of Flaxseed oil may improve tissue responses to insulin and increase the efficacy of drugs which act through this pathway like Sulfonylurea.

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

Patients and Methods: This study was carried out in The Specialized Center for Endocrinology and Diabetes, Baghdad on (43) diabetic patients (26 female and 17 male). All participants are

selected after giving their informed consent, their age range 35-60 years , and have disease duration of 5-10 years. 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 (Flaxseed oil1000mg/day; n=16), in addition to the already given oral hypoglycemic agent (glibenclamide 15 mg/day) and dietary control for 12 Weeks. To each group, the following biochemical parameters were done at baseline ;after 6 weeks and after 12 weeks periods:Fasting serum glucose; glycated hemoglobin and lipid profile tests according to the standard methods.

Results:

Administration ofAtorvastatin was significantly increase FBS and HbA1c serum levels, with a high significant decrease in S. Ch. And significant decrease in S. TG with a high significant decrease in S. LDL. While administration ofFlaxseed oil significantly reduced serum FBS, $HbA1_C$, s. Ch, TG, LDL levels, however, the effects on these parameters were variable between the studied groups.

Conclusion:

The administration of Atorvastatin may induce hyperglycemia despite of it'shypolipidemic effect, while Flaxseed oilwhen used as adjuvant therapy could improve both glycemic control and lipid profile in patients with type 2DM .

Key words: Atorvastatin ;Flaxseed oil; lipid profile; type 2 DM.

فاعلية الاتورفستاتين وزيت بذر الكتان في خفض مستويات السكر والدهون بالدم في النوع الثاني من مرض داء السكري

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الخلاصة

الخلفية العلمية: احكام السيطرة على مستوى السكر بالدم ومنع الاختلاطات الثانوية هي اهم الاهداف المتوخاه في علاج داء السكري .ان اختلال مستوى الدهون بالدم كان سبباً رئيساً لامراض القلب والدورانحيث يصعب السيطرة عليها عند المصابين بداء السكري.الغرض منالدراسة هو اختبار فاعلية الاتورفستاتين وزيت بذر الكتان والتي تمتلك تأثيرات مضادة للتأكسد وفعالية خافضة للدهون على المتغيرات الحاصلة في النوع الثاني من مرضى داء السكري وحالة عدم السيطرة على السكر بالدم.

المرضى والطرائق :انجزت هذه الدراسة في مركز داء السكري في بغداد للفترة من تشرين الاول ٢٠١١الى نيسان ٢٠١٣ وبمشاركة (٤٣) مريضاً ٢٦ منهم من الاناث و١٧من الذكور حيث وزعوا الى ثلاثة مجاميع . أعطيت المجموعة الاولى علاج غفل - النشأ(٥٠ ملغم) والمجموعة الثانية الاتورفستاتنين (٢٠ملغم) يومياً والمجموعة الثالثة زيت بذور الكتان(١٠٠٠ملغم) يومياً اضافة الى عقار جليبين كلامايد الذي اعطي لكل المجموعات مع الحمية الغذائية ولمدة ١٢ اسبوعاً . اجريت لكل المجموعات الفحوصات الكيماحياتية عند خط الاساس وبعد ٦ اسابيع ثم بعد ١٢ اسبوعاً من المعالجة. تم قياسمستوى السكر الصيامي بالدم والهيموكلوبين السكري وصورة الدهون بالدم

النتائج :سبب اعطاء الاتورفستاتين زيادة معتدة في مستويات سكر الدم الصيامي والهيموكلوبين السكريوانخافضاًمعتداً عالياً للكوليسترول بالمصل ونقصاً معتداً في مصل الكليسيريدات الثلاثية اضافة للنقص المعتد العالي للبروتين الدهني واطئ الكثافة ل دل بالمصل ، في حين ان اعطاء زيت بذور الكتان قلل بصورة معتدة مستويات السكر الصيامي والهيموكلوبين السكري والكوليسترول والكليسيردات الثلاثية و ل د ل ايضاً

الاستنتاج: يمكن ان يسبب الاتورفستاتنين ارتفاعا للسكر بالدم بالرغم من ثاثيرة الخافض للدهون ولكن زيت بذور الكتان يمكن ان يحسن مستويات السكر بالدم وصورة الدهون ايضا في النوع الثاني من داء السكري

الكلمة المفتاح الاتورفستاتنين ، زيت بذور الكتان ، صورة الدهون ، النوع الثاني – لداء السكري

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)].

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 [(6)].

Flaxseed supplementation significantly decreased serum glucose or glycosylated haemoglobin concentrations or increased insulin sensitivity in humans [(7).] Dietary flaxseed, flaxseed oil, or flaxseed lignan decreased inflammation, oxidative lung damages, lipid peroxidation, or hyperinsulinemia in animals [(8)]. It was hypothesized that flaxseed supplementation will decrease oxidative stress, thus reducing inflammation biomarkers and insulin resistance [(9).]

Therefore, we evaluated the effect of a flaxseed-derived lignan supplement (containing 1000 mg/day flaxseed oil, equivalent to 27-60 g of whole flaxseed on indexes of glycemic control, insulin resistance and lipid profiles in a randomized, double-blind, placebo-controlled, cross-over study[(10).] The dosage was chosen based upon the dose range of flaxseed which has been used safely and effectively in previous reported flaxseed clinical trials on dyslipidemia [(11;12).]

Aim of the study:

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

Patients,Materials and Methods:

This study was carried out on fortythree (43) patients(26females and 17males) with type 2 diabetes mellitus (DM) who attend the Specialized Center for Endocrinology and Diabetes-AL-RisafaDirectoratc of Health-Baghdad were enrolled from October 2012 to April 2014.

Inclusion criteria:

Patients with type 2 diabetes mellitus 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;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:

- **1- Group (A):** 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.
- **2- Group (B):** includes 14 patients treated with **Atorvastatin** 20mg 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.
- **3- Group (C):** includes 16 patients treated with Flaxseed oil 500mg soft gelatin capsule twice daily(1000mg/day) after meal, 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.

Serum Glucose Level (FPG)was evaluated using a ready made kit for this purpose, according to the method of [13]; Glycated Hemoglobin (HbA_{IC})was evaluated usingThe VARIANT hemoglobin A_{IC} program utilizes the principles of ion exchange high performance liquid chromatography (HPLC)[14] .Serum total cholesterol(T.C) was estimated according to the method of Richmond [15] ;Serum Triglyceride (TG)levels were determined according to the method of Fossati and Prencipe[16] ;serum HighDensity Lipoprotein Cholesterol (HDL-C) levels were estimated according to the method of Burstein [17] andserum Low Density Lipoprotein Cholesterol (LDL-C) was calculated by using this formula:

LDL-C = Total cholesterol – (TG/2.2) – (HDL-C)[18].

All Results were expressed in mmol/L except of HbA_{IC} 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 FBS of Placebo,Flaxseed,and Atorvastatin. In comparison with a placebo-treated group at corresponding duration, after 6 weeks of treatment there is a significant increase in FBS of Atorvastatin group and no significant difference in FBS of Flaxseed treated group. After 12 weeks of treatment, no significant difference in FBS of Atorvastatin and Flaxseed treated groups were recorded (Table 1).

In comparison with value at baseline in the same group after 6 weeks of treatment there is a significant decrease in S. HbA1c of Placebo group, a highlysignificant decrease in S. HbA1c of Flaxseed group,and a significant increase in Atorvastatin group were recorded. After 12 weeks of treatment, no significant difference in S. HbA1c of Placebo and Atorvastatin treated groups, and a significant decrease in S. HbA1c of Flaxseed treated grouprecorded.

In comparison with a placebo-treated group at corresponding duration, after 12 weeks of treatment, no significant difference in S. HbA1c of Atorvastatin and Flaxseed-treated groups were found(Table 1).

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 S.Ch.,S.TG and S.HDL with a significant increase in S. LDL levels of placebo group. While a high significant decrease in S. Ch. and s.TG was found in Atorvastatin and Flaxseed treatedgroups. No significant difference in S. HDL of Atorvastatin-treated group and a high significant increase in S. HDL of Flaxseed-treated group were recorded.While a high significant decrease in S. LDL of Atorvastatin-treated group, anda significant decrease in S. LDL of Flaxseed-treated group were found (Table -2).

In comparison with a placebo-treated group at corresponding duration, after 12 weeks of treatment there was a highly significant decrease in S. Ch. of Atorvastatin and Flaxseed treated groups were found (Table 2). No significant difference in S. TG of Atorvastatin and Flaxseed treated groups and a significant increase in S. HDL of Atorvastatin anda high significant increase in Flaxseed treated groups. There was no significant difference in S. LDL ofFlaxseed treated groupand a significant decrease in S. LDL of Atorvastatin treated group were found (Table 2).

Discussion:

Atorvastatin has been reported in some cases to disrupt glycemic control in patients with type 2 diabetes [(19)]. 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 [(20)]. These statements agreed with the results obtained in the present study which shown an increment in the FBG and HbA1c levels after 12 week of treatment with atorvastatin (Table 1).

Dietary milled flaxseed and flaxseed oil consumption for 12 weeks did not positively or negatively affect HbA1c or fasting glucose concentrations in this study of adults with well controlled Type 2 DM [(21)].A study done by (Yeong and Ardith, 2011) found that flaxseed supplementation decreased insulin resistance, although the plasma insulin concentration did not change significantly, an homeostasis model assessment of insulin resistance (HOMA-IR index) was significantly decreased, suggesting a decrease in insulin resistance or decreased glucose concentration following flaxseed supplementation. A highly significant positive relationship between HOMA-IR and insulin indicates that the decreased HOMA-IR is more closely related to insulin concentration than glucose concentration. This may explain the results of the present study showing that administration of flaxseed oil(1 gm per day for 12 weeks) has no significant changes on FBS levels, but significantly ($p<0.05$) decreases serum HbA1C levels(table -1).[(22)]

Atorvastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate limiting step in hepatic cholesterol biosynthesis. Unlike most other statin, however, it is a completely synthetic compound. Generally, statins (among them atorvastatin) are the most effective than other lipid lowering agents in reducing low-density lipoprotein cholesterol (LDL-C)[23]. Atorvastatin competitively inhibit this enzyme resulting in decreasing de novo cholesterol synthesis, and increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, resulting in decreasing the amount of LDL-cholesterol in the blood [24].Like other statins, atorvastatin also reduces blood

levels of triglycerides and slightly increases levels of high-density lipoprotein cholesterol (HDL-C) [25].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.
Several randomized controlled studies showed the beneficial effects of a flaxseed-supplemented diet on lipid profiles in both normal- and hypercholesterolemic subjects [26;27].Other studies reported that secoisolariciresinoldiglucoside (SDG), the major plant lignan in flaxseed [28] , significantly reduced total cholesterol and LDL cholesterol (LDL-C) concentrations in rabbits [29] .Flaxseed oil has shown to have beneficial effects on hepatic cholesterol metabolism in high fat diet rats [30] .Flaxseed oil and fish oil have been reported to have a TG lowering effect in Streptozocin-diabetic rats [31; 32].Another study explained thatflaxseed oil has been shown to increase HDL-C levels in STZ-diabetic rats [32] .Recent studydemonstrated that dietary flaxseed increasesHDL-C levels in diabetic rats [٣٣].

Acknowledgment: We would like to thank the college of Medicine, Al-Nahrain university and the specialized center for Diabetes and Endocrinology , Baghdad, Iraq for supporting this project.

Table (1): Comparison of FBS and S. HBA1c at different duration of treatment in each group

Group	**FBS** (mmol/l)			**S. HbA1c** (%)		
	Baseline	**6 weeks**	**12 weeks**	**Baseline**	**6 weeks**	**12 weeks**
Placebo (n=١٣)	11.68+3.64	10.62+2.94*	11.62+2.79	8.35+1.93	8.6+1.94	8.15+1.61
Atorvastatin (n=١٤)	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
Flaxseed (n=16)	11.69±5.13	10.97±3.38	10.49±3.21	8.37±1.71	7.41±1.82**	7.74±1.3*

Comparison is with baseline value * = Significant difference from basline(P<0.05),

** = highly Significant difference from baseline (P<0.001).

a= significant difference(p<0.05) between drug group and placebo group at corresponding duration.

b= highly significant difference(p<0.001) between drug group and placebo group at corresponding duration.

Table (2): Comparison of lipid profile at different duration of treatment in each group

Group	**S. Ch.**(mmol/l)			**S. TG**(mmol/l)			**S. HDL**(mmol/l)			**S. LDL**(mmol/l)		
	Baseline	**6 Weeks**	**12 weeks**	**Baseline**	**6 Weeks**	**12 weeks**	**Baseline**	**6 Weeks**	**12 Weeks**	**Baseline**	**6 Weeks**	**12 weeks**
Placebo (n=١٣)	5.77+1.25	5.68+0.89	6.08+0.95	1.92+0.83	2.07+1.2	2.12+0.86	0.99+0.3	1.16+0.21*	1.04+0.22	2.72+1.02	2.51+1.01*	2.94+0.96*
Atorvast-atin (n=١٤)	6.79+1.77	5.84+1.39**	4.65+1.01**b	2.55+1.53	1.76+1.04*	1.5+0.83*	1.39+0.25a	1.38+0.24a	1.39+0.29a	2.96+1.39	2.38+0.56	2.12+0.82**a
Flax-seed (n=16)	6.65±1.06	5.59±0.72**	4.88±0.56**b	3.69±2.02a	2.81±1.16*	2.23±1.03**	1.34±0.4a	1.51±0.32**a	1.74±0.33**b	3.21±0.98	2.86±0.46*	2.64±0.45*

Comparison is with baseline value * = Significant difference from basline(P<0.05),
** = highly Significant difference from baseline (P<0.001).
a= significant difference(p<0.05) between drug group and placebo group at corresponding duration.
b= highly significant difference(p<0.001) between drug group and placebo group at corresponding duration.

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