

Therapeutic Response of Serum Lipids to Atorvastatin in Type II Diabetic Patients

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Abstract

Lipid disorders and cardiovascular disease (CVD) risk are known to be increased in patients with diabetes mellitus. The effects of statins on serum lipid levels are well known; however, previous studies did not compare the effects of statins on serum lipid levels in diabetic patients with non-diabetic patients. To investigate the effects of Atorvastatin on serum lipid profiles in hyperlipidemic patients with type 2 diabetes mellitus in comparison with hyperlipidemic patients without diabetes. This study was conducted on 33 type 2 diabetic patients & 34 non-diabetic patients; their age range was 40-80 years, all of them were hyperlipidemic, who had been administered 10, 20, & 40 mg daily of Atorvastatin and completed a 6-month follow-up. Serum lipids were measured before and after treatment at 1, 3, and 6 months. It was found that the reduction in S. Total Cholesterol and S. LDL-C were less in diabetic patients than that in non-diabetic patients when they are using the same doses of Atorvastatin, while the changes in S. HDL-C and S. Triglyceride were nearly similar in both. Furthermore, it is noticed that nearly the same responses of S. Cholesterol and S. LDL-C reduction were achieved in diabetic patients when they are using doubled doses that are used for non-diabetic patients. So, higher doses of Atorvastatin (double doses) are needed to improve serum lipid levels in diabetic patients as compared to non-diabetic patients.

Key words: Diabetic , Lipids , Atorvastatin.

الاستجابة العلاجية لمستوى الدهون في مصل الدم عند مرضى السكري / النوع الثاني

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الخلاصة

بما أن اضطرابات الدهون وخطر الأمراض القلبية الوعائية أكثر عند المرضى المصابين بداء السكري، وأن تأثيرات عقار الستاتين على مستويات الدهون في مصل الدم معروفة إلا أن الدراسات السابقة لم تقارن تأثيرات عقار الستاتين على مستويات الدهون في مصل الدم عند المرضى المصابين بداء السكري مع غير المصابين، وبهدف تحري تأثيرات عقار الأتورفاستاتين (Atorvastatin) على مستويات الدهون في مصل الدم عند المرضى المصابين بداء السكري بالمقارنة مع المرضى غير المصابين بالسكري الذين يعانون من زيادة الدهون بالدم ، أجريت هذه الدراسة على 33 مريض مصاب بداء السكري من النوع الثاني بالمقارنة مع 34 مريض غير مصاب بالسكري جميعهم لديهم زيادة مستوى الدهون بالدم ، تتراوح اعمارهم بين 40-80 سنة، قسما الى مجاميع ليستخدما عقار اتورفاستاتين 10، 20، و 40 ملغ يوميا وليكملوا فترة متابعة مدة 6 شهور. تم قياس مستويات الدهون في مصل الدم قبل وبعد المعالجة في الشهر الاول والثالث والسادس. اظهرت النتائج أن التغييرات في الكوليستيرول الكلي والكوليستيرول واطى الكثافة في مصل الدم كانت أقل في المرضى المصابين بالسكري من تلك التي في المرضى غير المصابين بالسكري الذين استخدموا نفس الجرعة من عقار الأتورفاستاتين (Atorvastatin)، بينما كانت التغييرات في الكوليستيرول عالي الكثافة والدهون الثلاثية متماثل تقريبا في المجموعتين. علاوة على ذلك يُلاحظ بأن الاستجابة كانت نفسها تقريبا للكوليستيرول الكلي والكوليستيرول واطى الكثافة في المرضى المصابين بالسكري عندما يستخدمون جرعة مضاعفة كالتى استخدمت للمرضى غير المصابين بالسكري. نستنتج من ذلك أن المرضى المصابين بالسكري يحتاجون الى جرعة أعلى (جرعة مضاعفة) من عقار الأتورفاستاتين (Atorvastatin)، لتحسين الاستجابة العلاجية لمستويات الدهون في الدم بالمقارنة مع المرضى غير المصابين بالسكري.

الكلمات المفتاحية: داء السكري ، الدهون ، الأتورفاستاتين

Introduction

The increased risk of cardiovascular events in diabetic patients is well established (1-4). Recent studies demonstrate that diabetic patients without a prior coronary artery disease (CAD) had approximately similar risk of acute coronary syndrome as non-diabetic patients with prior CAD (4,5). Many have demonstrated that CAD patients with diabetes have higher mortality following a myocardial infarction than their non-diabetic counterparts (2-5). Although at high risk for future cardiovascular

events, patients with CAD and diabetes are as likely as those without diabetes to benefit from Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) as a lipid lowering treatment. Many large trials are consistent in their findings with that in which CAD patients with diabetes experienced reductions in relative risk with statin treatment of similar magnitude to the risk reductions for CAD patients without diabetes (6,7).

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The results from other studies further demonstrate the benefits of statin treatment to reduce the risk of cardiovascular events compared with placebo in type 2 diabetic subjects both with and without cardiovascular disease^(8,9). Given their elevated risk and similar lipid management goals, one would expect CAD patients with diabetes to be treated at least as aggressively as those without diabetes. Nevertheless, CAD patients, in general, continue to receive less than optimal lipid management, and those with diabetes may be relatively under-treated compared with those without diabetes⁽¹⁰⁻¹²⁾. Statins are highly effective in lowering serum lipid concentrations and preventing ischemic heart disease (IHD); however, we do not know by how much statins at different doses affect serum lipid concentrations in diabetic patients in comparison with non-diabetic hyperlipidemic patients. The Aim of the Study is to quantify the effects of different doses of Atorvastatin on serum lipid concentrations in hyperlipidemic patients with type 2 diabetes mellitus in comparison with hyperlipidemic patients without diabetes.

Patients and Methods

This study was conducted in Karbala city since February 2009 till February 2010 on thirty-three (33) type 2 diabetic patients (13 males & 20 females; mean age 56.5 ± 8.4) and thirty-four (34) non-diabetic patients (14 males & 20 females; mean age 56.8 ± 10.6), whom fasting serum lipids concentrations (S.Cholesterol, S.HDL-C, S.LDL-C, & S.TG) were measured as a baseline and all of them were having hyperlipidemia. Lipid profiles were measured by using "Spinreact" enzymatic colorimetric test.⁽¹³⁾ Diabetic patients were divided into three subgroups who had been administered 10, 20, & 40 mg daily Atorvastatin respectively, while non-diabetic patients were divided into two subgroups who had been administered 10 & 20 mg daily Atorvastatin respectively. Each one was completed a 6-month follow-up period in which Serum lipids were measured after 1, 3, and 6 months of treatment. All Diabetic patients were on treatment with oral hypoglycemic agents; 5 patients out of 33 (15%) were on sulfonylurea,

10 patients (30.5%) were on metformin, while 18 patients (54.5%) were on sulfonylurea plus metformin. The percentage values are presented as Means \pm Standard Deviations. The Statistical analysis used for continuous variables was paired Student's T-test. *P*-value of < 0.05 was considered as significant.

Results

The Percentages of Changes in Serum Lipid Concentrations in Diabetic and Non-Diabetic patients after treatment with different doses of Atorvastatin are shown in Tables 1– 4 and Figures 1– 4. It is clear from Table 1 and Fig. 1 that there are significant differences between the changes of Serum Cholesterol Concentrations in Diabetic and Non-Diabetic patients when they are treated with the same doses of Atorvastatin ($P < 0.05$). Meanwhile, It is noticed that the changes in S. Cholesterol concentrations in Diabetics treated with 20mg Atorvastatin were near the changes observed in Non-diabetics when they are treated with 10mg Atorvastatin, and it is also noticed that the changes in S. Cholesterol concentrations in Diabetics treated with 40mg Atorvastatin were near the changes observed in Non-diabetics when they are treated with 20mg Atorvastatin. The same observations above were also applied to a large extent on the changes of S. LDL-C concentrations shown in Table 2 & Fig. 2. In that, there are significant differences between the changes of S. LDL-C Concentrations in Diabetic and Non-Diabetic patients when they are treated with the same doses of Atorvastatin ($P < 0.05$). Meanwhile, Diabetic patients responding to a similar degree of S. LDL-C concentration changes with that of non-diabetics when they are treated with double doses used for non-diabetics. Regarding the Changes in S. HDL-C concentrations which are shown in Table 3 & Fig 3, it is observed that they are slightly better in Non-diabetics than in Diabetic patients using the same doses of treatment but without significant difference ($P = NS$). However; the Changes in S. Triglyceride concentrations were about to be similar in Diabetic and Non-diabetic patients using the same doses of treatment as shown in Table 4 & Fig. 4 ($P = NS$).

Table 1 : Percentage of serum cholesterol reduction after treatment with Atorvastatin *

Period of treatment	Type II Diabetic patients			Non-Diabetic pts.	
	10 mg	20 mg	40 mg	10 mg	20 mg
1 month	-5.8% ± 2.0	-14.2% ± 6.6	-23.4% ± 3.9	-11.9% ± 6.1	-25.9% ± 4.8
3 months	-13.9% ± 4.7	-22.9% ± 8.4	-37.9% ± 6.3	-20.0% ± 7.6	-39.0% ± 7.4
6 months	-24.1% ± 8.2	-33.1% ± 10.3	-45.9% ± 8.1	-30.9% ± 9.9	-45.5% ± 9.1

Table 2: Percentage of serum LDL-Cholesterol reduction after treatment with Atorvastatin*

Period of treatment	Type II Diabetic pts.			Non-Diabetic pts.	
	10 mg	20 mg	40 mg	10 mg	20 mg
1 month	-6.7% ± 3.8	-21.3% ± 4.5	-32.9% ± 4.9	-17.7% ± 4.6	-34.5% ± 8.2
3 months	-13.7% ± 5.8	-28.4% ± 8.9	-50.2% ± 9.7	-26.3% ± 6.2	-50.6% ± 12.1
6 months	-22.9% ± 6.2	-39.6% ± 9.5	-61.8% ± 12.9	-38.9% ± 11.5	-60.7% ± 13.5

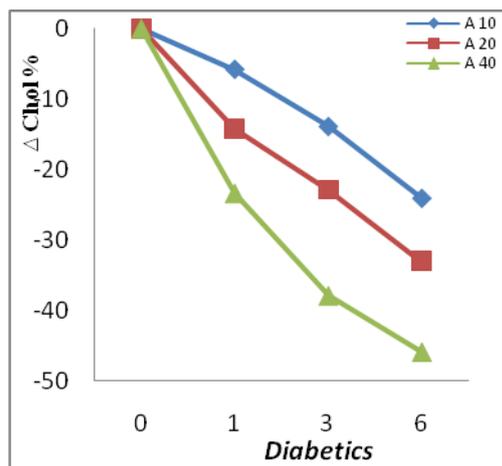
Table 3 :Percentage of serum HDL-Cholesterol elevation after treatment with Atorvastatin *

Period of treatment	Type II Diabetic pts.			Non-Diabetic pts.	
	10 mg	20 mg	40 mg	10 mg	20 mg
1 month	+3.3% ± 2.4	+5.2% ± 2.8	+5.7% ± 2.9	+7.2% ± 3.0	+7.7% ± 3.7
3 months	+6.7% ± 4.5	+8.5% ± 4.6	+9.5% ± 5.2	+10.6% ± 3.9	+10.9% ± 4.3
6 months	+9.4% ± 4.5	+10.5% ± 4.8	+11.6% ± 6.0	+11.3% ± 5.7	+11.7% ± 5.8

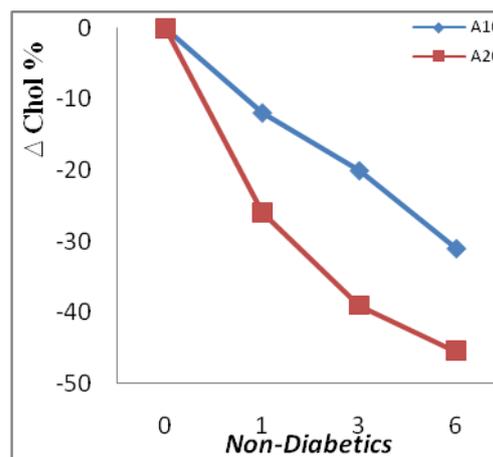
Table 4 :Percentage of serum triglyceride reduction after treatment with Atorvastatin *

Period of treatment	Type II Diabetic pts.			Non-Diabetic pts.	
	10 mg	20 mg	40 mg	10 mg	20 mg
1 month	-12.9% ± 2.7	-15.9% ± 3.7	-17.3% ± 3.9	-11.7% ± 4.6	-13.0% ± 5.6
3 months	-18.4% ± 7.3	-24.8% ± 8.5	-28.6% ± 10.3	-20.0% ± 8.6	-22.0% ± 7.8
6 months	-24.8% ± 8.8	-32.8% ± 10.2	-38.6% ± 12.8	-27.6% ± 10.7	-31.8% ± 11.7

*Values presented as Means ± Standard Deviations

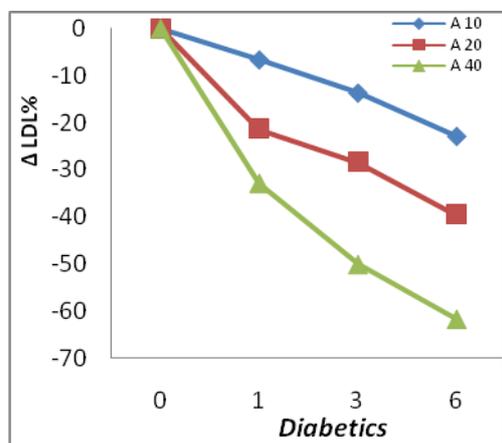


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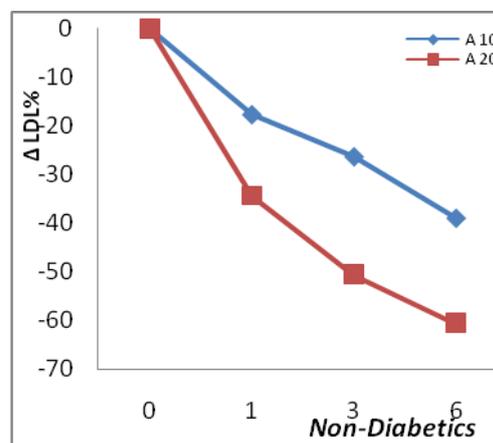


- B -

Figure 1 :Line chart showing percentage of serum cholesterol changes after treatment with atorvastatin in diabetics(A) & non-diabetics(B)

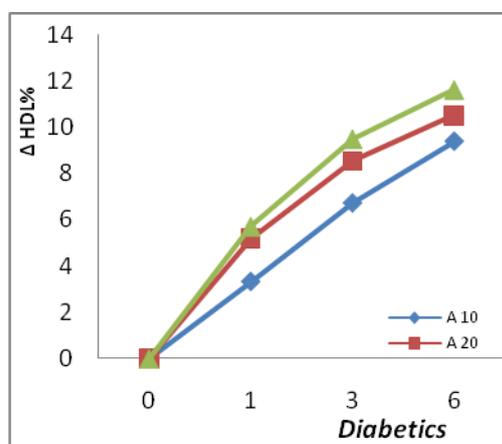


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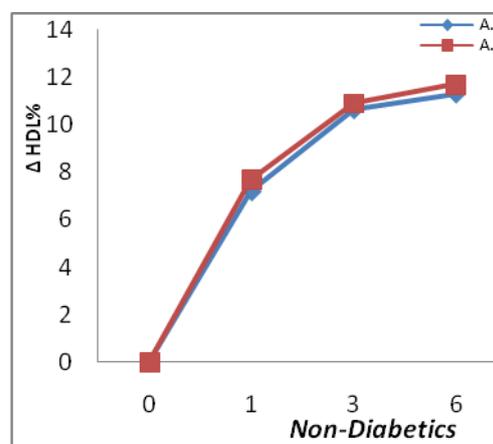


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Figure 2 :Line chart showing percentage of serum ldl-cholesterol changes after treatment with atorvastatin in diabetics(A) & non-diabetics(B)



- A -



- B -

Figure 3 : Line chart showing percentage of serum hdl-cholesterol changes after treatment with atorvastatin in diabetics(A) & non-diabetics(B)

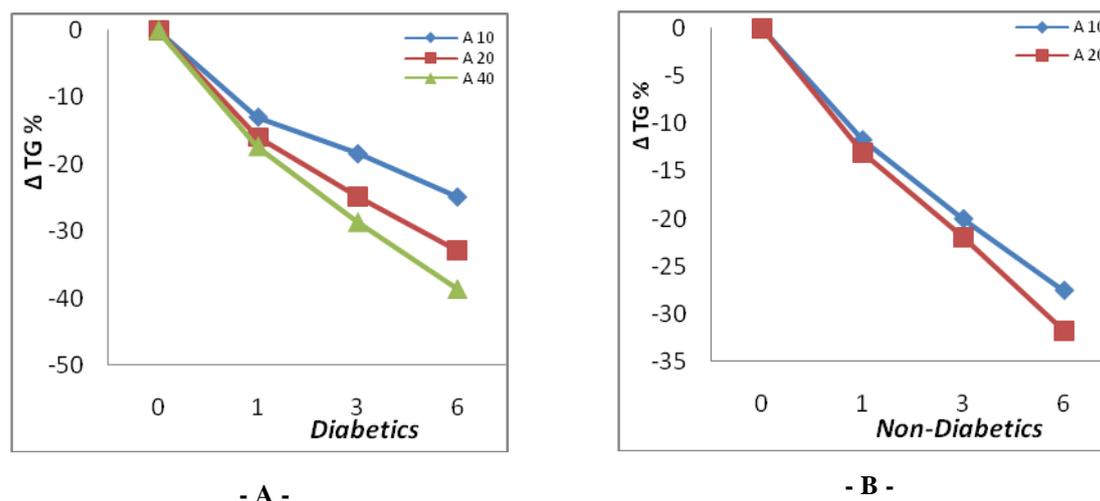


Figure 4 :Line chart showing percentage of serum triglyceride changes after treatment with atorvastatin in diabetics(A) & non-diabetics(B).

Discussion

This study provides evidence that the response of lipid profile to Statin in diabetic patients differ from that in non-diabetics, in which the changes in S.Cholesterol and S. LDL-Cholesterol were less in diabetic patients than that in non-diabetic patients when using the same doses of Atorvastatin. Furthermore, it is noticed that nearly the same changes were achieved in diabetic patients when they are using doubled doses that are used for non-diabetic patients. These findings were agreed by *Robert et al*, when subjects with type 2 diabetes were randomized; mean LDL-C reduction in the atorvastatin group over 4 years was (29%) versus placebo⁽¹⁴⁾. Besides, another trial done by *Law et al* showed that reductions in LDL cholesterol in non-diabetic patients were (40%) with atorvastatin 10mg/day⁽¹⁵⁾. After treatment, Lipid levels for diabetic patients have improved less rapidly than those for non-diabetic patients. *Mark et al* stated that mean non-HDL-C levels, already higher among patients with diabetes, did not decline as rapidly for this group, increasing the gap between them and patients without diabetes⁽¹⁶⁾. Although the mean concentration of LDL cholesterol in diabetic patients is not significantly different from that in individuals without diabetes, qualitative changes in LDL cholesterol may be present. Diabetic patients tend to have a higher proportion of LDL particles that are smaller and denser, are more susceptible to oxidation, and may thereby increase the risk of cardiovascular events⁽¹⁷⁾ and may also explain the difference in response of S.Cholesterol and S. LDL-C to Statin between diabetic and non-diabetic patients. The changes in S. HDL-Cholesterol in

both diabetic and non-diabetic patients were nearly similar in spite of the less rapid improvement in diabetics; nevertheless, they did not reach what were achieved by other reports such as that was found by *Klaus et al* that HDL-cholesterol increased significantly (+19%) after 4 weeks of Atorvastatin therapy (10 mg/day)⁽¹⁸⁾. That difference may be because our patients are less likely to do exercise to support HDL-C elevation. Likewise, the changes in S.Triglyceride were also similar in both diabetic and non-diabetic patients which was less than what was reported by *Klaus et al* that fasting Triglycerides were reduced by (-43%) after 4 weeks of Atorvastatin therapy (10 mg/day)⁽¹⁸⁾. Besides, when reviewing literatures; there is no known drug – drug interaction between Atorvastatin and oral hypoglycemic agents⁽¹⁹⁾ to be responsible for that difference in response between diabetic and non-diabetic patients. In conclusion, higher doses of Atorvastatin (double doses) are needed to improve serum lipid levels in diabetic patients as compared to non-diabetics.

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