

SIMVASTATIN TREATMENT AMELIORATES DIABETIC TYPE 2 CONDITIONS THROUGH LOWERING THE CONCENTRATION OF PLASMA ICAM LEVELS

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Abstract

Diabetes type 2 is associated with other diseases including cardiovascular diseases. Obesity is a link between diabetes and cardiovascular diseases and associated with insulin resistance. Statins are used to reduce lipids and to lower the risk of cardiovascular diseases. The objective of the present study was to explore the effect of statin treatment on plasma levels of ICAM among diabetics. The study design was a prospective cohort clinical study. The study included 62 diabetic patients who were recruited from the Diabetes/Endocrine Clinics of the Prince Rashed Hospital. Data were collected from participants through a prepared questionnaire and laboratory findings of lipid profiles, glucose and ICAM levels. Study findings showed no significant variations between study and control groups at baseline level. At the end of the experiment, in study group, there were significant changes in some biochemical parameters such as ICAM level ($p=0.005$), cholesterol (0.019), and TG (0.025). The mean difference of study and control groups showed that significant variations were observed for the following variables ICAM ($p<0.005$), cholesterol ($p=0.008$), TG ($p<0.005$), and HDDL ($p<0.005$). Taken together, the present study showed that simvastatin therapy benefits diabetic patients even without

hyperlipidemia through decreasing levels of ICAM-1, which have an inflammatory action and increase insulin resistance. It can be concluded that simvastatin is insulin sensitizer and works as anti-inflammatory agent.

Keywords: Diabetes type 2, ICAM, insulin resistance, statins, cardiovascular disease, simvastatin

Introduction

Insulin resistance is a factor that leads to type 2 diabetes and unfavourable cardiovascular consequences (Vettor et al., 2005; Semenkovich, 2006). Adipose tissues (white type) secrete a lot of adipokines and cytokines (protein signals) (Antuna-Puente et al., 2008; Qasim et al., 2008) which play a role in insulin sensitivity, insulin resistance, blood pressure, energy balance, angiogenesis and others (Endres, 2005; Kostapanos, Milionis, and Elisaf, 2008; Pantsulaia et al., 2009).

Patients with type 2 diabetes have a greater potential for the development of coronary heart diseases and atherosclerosis, in addition to the development of microvascular complications such as retinopathy, nephropathy and neuropathy due to endothelial dysfunction. Recent data showed that statins have a lot of benefits for decreasing these risks (Tekin et al., 2006).

Statins are used as lipid lowering agents, and they mediate their effects through the inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) enzyme through the hepatic cholesterol biosynthesis pathway (Sotomayor et al., 2005; Naples et al., 2008; Shyu et al., 2009). Statins have been found to significantly lower lipids in patients with dyslipidaemia, and thereby reduce the risk of cardiovascular disease and atherosclerosis, in addition to improve insulin sensitivity and decrease the morbidity and mortality rates in patients with or without cardiovascular disease (Güçlü et al., 2004; Huptas et al., 2006; Lalli et al., 2008).

It is plausible that statins decrease inflammation through lowering levels of IL-6 and CRP which are inflammatory markers and consecutively reduce insulin resistance. However, these drugs also may influence the levels of other adipocytokines (adiponectin, resistin) (Antuna-Puente et al., 2008).

Inflammation is a physiological status that occurs as a response to tissue injury. Inflammation is categorized into two classes: acute and chronic. Acute inflammation has the following characteristics: swelling, redness, heat, pain and loss in function. These signs occur due to physiological alterations of vasodilatation, increased vascular permeability and induction of nerve terminals. Chronic inflammation includes tissue damage and wound healing. These inflammatory classifications are differing

in the primary active immune cells that are involved in the inflammatory response (Pickup, 2004).

Expression of endothelial cell adhesion molecules is a marker for endothelial cell activation, and elevated expression is an indication of endothelial dysfunction. Increased soluble endothelial adhesion molecules in the plasma are markers of endothelial dysfunction and inflammation. At normal conditions, endothelial cells enhance expression of adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 to control leukocyte with endothelial cell interaction during the inflammatory response. Studies showed increased circulating levels of E-selectin, VCAM-1 and ICAM-1 in type 2 diabetics (Albertini et al., 1998; Matsumoto et al., 2002; Hamdy, Suwailem, and El-Mesallamy, 2009), which are considered predictors for type 2 diabetics (Thorand et al., 2006). Some studies found that the soluble form of ICAM-1 was not elevated in type 2 diabetics (Güler et al., 2002; Matsumoto et al., 2002), but suggested that elevated levels were indicative for developing of microvascular complications, such as nephropathy (Güler et al., 2002). The suggested explanation for that is the soluble forms of ICAM-1 are found in the circulation in the later stages of diabetes, at the time that the risk of microvascular complications is much greater. Levels of E-selectin and VCAM-1 were accompanied with the degree of hyperglycemia and insulin sensitivity (Matsumoto et al., 2002). Also, oxidative stress has a role in the increased adhesion molecule expressions, and so chronic vitamin E intake for 3 months in type 2 diabetic individuals can decrease plasma ICAM-1 and VCAM-1 levels (Hamdy, Suwailem, and El-Mesallamy, 2009).

Study objective

The main objective of the present study is to explore the effect of statin treatment on plasma levels of ICAM among diabetics.

Materials and Methods

Study Design

The study design was a prospective cohort clinical study. The approval of the Institutional review boards (IRB) of both Jordan University of Science and Technology, and King Abdullah University Hospital was obtained. In addition, the approval of the royal medical services for conducting the study at Military Prince Rashed Hospital was also obtained.

Study Setting

Sample recruitment was in 2011. Laboratory work; including biochemical analysis, ELISA was conducted. The study was conducted at healthcare facility in the north of Jordan; Military Prince Rashed Hospital.

Sample Population

Subject Description

The study included 62 diabetic patients who were recruited from the Diabetes/Endocrine Clinics of the Prince Rashed Hospital.

Data Collection and Patient Interviews

A custom design questionnaire was utilized for appropriate data collection and further statistical analysis. The study procedure and goals were explained to patients both verbally and through the designed consent form. Patients who approved to participation-with total realization of confidentiality- signed the consent form, and were interviewed by the researcher using the designed questionnaire. Each patient's medical profile of the diabetic clinic was reviewed for further collection and confirmation of patient's demographics, clinical history and current drug regimen.

Sample Collection and Handling

Blood samples were withdrawn from the participants after an overnight fasting by a specialized laboratory technician. Each sample was distributed in an evacuated EDTA tube (5 mL blood) as well as an anticoagulant-free plain tube (10 mL blood). The later were centrifuged at 4000 rpm for 4 minutes. Five hundred micro liters of each serum sample were sent for biochemical analysis.

Statistical Analysis

Data were analysed using SPSS version 17. Frequencies means and standard deviations were used to describe data wherever appropriate. Chi-square test and T- test were used to test the difference between proportions. P –value of < 0.05 was considered statistically significant.

Study findings

General characteristics of study participants

As shown in table 1, there is a comparison between study and control groups at baseline with their statistical significance (p value < 0.05). Several parameters were investigated. Age, BMI, gender, family history of cardiovascular diseases, family history of thyroid disorders, family history of diabetes, heart diseases, and dyslipidemia were not varied significantly between study and control groups at baseline (p value > 0.05).

Table 1: General characteristics of study participants

| Variable | Study group Mean +/- SD or % | Control group Mean +/- SD or % | P value |
|--------------|---------------------------------|-----------------------------------|---------|
| Age | 55.34 +/- 13.54 | 57.06 +/- 10.27 | 0.516 |
| BMI | 29.36 +/- 5.07 | 35.71 +/- 29.62 | 0.261 |
| Gender | | | |
| Male | 19 (57.6%) | 14 (48.3%) | 0.317 |
| Female | 14 (42.4%) | 15 (51.7%) | |
| FHCD | 8 (24.2%) | 3 (10.3) | 0.136 |
| FHTD | 3 (9.1%) | 5 (17.2) | 0.282 |
| FHDM | 24 (72.7%) | 17 (56.6%) | 0.184 |
| HD | 0 (0%) | 3 (9.1%) | 0.144 |
| Dislipidemia | 15 (51%) | 22 (66.7%) | 0.174 |

Concentration of biochemical tests in study and control groups

As shown in table 2, after the end of experiment, in study group, there were significant changes in some biochemical parameters such as ICAM level ($p=0.005$), cholesterol (0.019), and TG (0.025). No significant variations were observed for other biochemical parameters, and no significant variation was observed in control group.

Table 2: Concentration of biochemical tests in study and control groups

| variable | Study group | | | Control group | | |
|-------------|--------------------------|-------------------------|------------|--------------------------|--------------------------|---------|
| | Mean Before± SD | Mean After ± SD | p-value | Mean Before± SD | Mean After ± SD | p-value |
| ICAM | 31056.03± 11666.72394 | 12398.98± 8539.78707 | < 0.005 | 21008.62± 16706.93922 | 17648.69± 10989.33070 | 0.411 |
| Glucose | 232.75 ±76.87 | 221.87 ± 82.36 | 0.571 | 245.86 ± 94.187 | 201.03 ± 81.89 | 0.051 |
| Cholesterol | 220.7576±55.646 | 201.9091±53.65070 | 0.019 | 214.2414±47.2407 | 215.7241±43.522 | 0.890 |
| TG | 265.8182±210.41 | 223.0303±178.6752 | 0.025 | 225.4483±115.130 | 215.5862±110.29 | 0.741 |
| HDL | 44.7545±9.48641 | 47.5121±11.71038 | 0.302 | 45.2483±14.51141 | 44.6966±15.2369 | 0.853 |
| LDL | 121.6364±42.011 | 112.5152±37.82370 | 0.349 | 120.0690±38.888 | 128.0345±36.882 | 0.432 |
| WBC | 7.34 ±1.58 | 8.23 ±1.52 | 0.464 | 7.34 ±1.58 | 7.5 ±1.78 | 0.611 |
| Ck | 79.96 ±49.86 | 92.60 ±63 | 0.431 | 93.95 ±11.21 | 88.59 ±12.67 | 0.785 |

Comparison of the mean difference variation of biochemical markers between the study and control groups

We investigated the mean difference of study and control groups to show the magnitude of simvastatin therapeutic effects on study group in comparison with the control group. As shown in table 3, significant variations were observed for the following variables ICAM ($p<0.005$), cholesterol ($p=0.008$), TG ($p<0.005$), and HDDL ($p<0.005$).

Table 3: Comparison of the mean difference variation of biochemical markers between the study and control groups

| variable | Study group Mean difference | Control group Mean difference | P-value |
|--------------------|--|--|-------------------|
| ICAM | -18657.06 | -3359.931 | < 0.005 |
| Cholesterol | -18.8485 | 1.4827 | 0.008 |
| TG | -42.7879 | -9.8621 | < 0.005 |
| HDL | 2.7576 | -0.5517 | < 0.005 |
| LDL | -9.1212 | 7.9655 | 0.642 |
| WBC | 0.89 | 0.16 | 0.642 |
| Ck | 12.64 | -5.36 | 0.415 |

Discussion

Our results showed that the level of ICAM decreased significantly after treatment with simvastatin among study group in comparison with control group (p value <0.01) which indicates the magnitude of simvastatin therapy decreased the level of ICAM adipocytokine and this finding is consistent with other studies that showed increased circulating levels of ICAM in type 2 diabetics (Albertini et al., 1998; Matsumoto et al., 2002; Hamdy, Suwailem, and El-Mesallamy) and so decreased the microvascular complications in type 2 diabetic patients were elevated expression of ICAM is an indication of endothelial dysfunction and developing of microvascular complications, such as nephropathy (Güler et al., 2002).

The results showed that the mean difference of study group in comparison with the mean difference of control group for glucose was statistically significant (p value <0.05) and this significance by decreasing the level of glucose among control group more than the decreasing among study group may be explained by the small number of participants and the short period of the study which not give a strong indication for strict glucose monitoring in this short period.

The results showed that the mean difference of study group was decreased by 18.84 mg/dl in comparison with the mean difference of control group which increased by 1.48 mg/dl for Cholesterol (p value 0.008) and this indicate the strong lipid lowering effect of simvastatin in decreasing cholesterol level. For TG the mean difference decreased by 42.78 mg/dl among study group and decreased by 9.86 mg/dl in control group (p value <0.01) which indicate also the beneficial effect of simvastatin in decreasing TG level .For HDL the mean difference increased by 2.75 mg/dl among study group in comparison with decreased mean difference by 0.55 mg/dl among control group (p value <0.01) which revealed the beneficial effects of simvastatin in increasing the good cholesterol (HDL) in diabetic patients that decrease the atherosclerotic risks in these patients. LDL were significantly varied (p value < 0.032) between study and control groups were the mean

difference among study group decreased by 9.12 mg/dl and increased by 7.96 mg/dl in control group which indicate the magnitude of simvastatin in decreasing the LDL level which has an important risk factor for atherosclerosis and macrovascular complications in type 2 diabetic patients. In view of these results, simvastatin has a strong action as a lipid lowering agent.

The results showed that the mean difference of study group in comparison with the mean difference of control group for WBC, Neutrophil count, and CK were not statistically significant (p value > 0.05 for the all). These findings can be viewed from different points among which no significant changes were identified before conducting the study regarding these variables. Another point represents a kinetic mode in which changes to be induced depend on a function of time or a large number of participants. Both of these factors are lacked in the present study. Taken together, the treatment of simvastatin induced several positive changes as enhancing insulin sensitivity, reducing inflammatory parameters and lipid lowering effect.

Conclusion

The present study showed that simvastatin therapy benefits diabetic patients even without hyperlipidemia through decreasing levels of ICAM-1, which have an inflammatory action and increase insulin resistance. It can be concluded that simvastatin is insulin sensitizer and works as anti-inflammatory agent.

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