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Original Article

The Effects of Atorvastatin Consumption on Biochemical Variables in Patients with Type 2 Diabetes Mellitus and Pre-diabetes

Ali Nosrati Andevari [1,2] M.Sc., Soheila Moein [1,2*] Ph.D., Durdi Qujeq [3,4*] Ph.D., Zoleika Moazezi [5] MD., Karimollah Hajian-Tilaki [6] Ph.D.

[1] Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2] Department of Biochemistry, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[4] Department of Biochemistry, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[5] Department of Internal Medicine, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[6] Department of Statistics and Epidemiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

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ABSTRACT

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Keywords
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Background and Aims: Atorvastatin may alter glycemic traits and lipid profiles. This study aimed to evaluate the effects of atorvastatin on biochemical variables in patients with type 2 diabetes and pre-diabetes (borderline diabetes).

Materials and Methods: This study included 80 individuals divided into five groups. Patients with type 2 diabetes mellitus and pre-diabetes used atorvastatin 20 mg/day for three months. After three months, variables such as serum fasting blood glucose (FBS), cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and glycosylated hemoglobin (HbA1c) levels were measured to assess the status of diabetes and pre-diabetes condition. Linear regression was applied to determine the association between atorvastatin uses and alters of biochemical variables levels.

Results: The serum FBS and HbA1c levels in patients with diabetes and pre-diabetes who use atorvastatin were significantly lower than in patients with diabetes and pre-diabetes who did not use atorvastatin (p=0.001). Serum cholesterol and LDL-C levels decreased in diabetic and pre-diabetic patients who used atorvastatin in comparison with diabetic and pre-diabetic patients who did not use atorvastatin (p=0.001). In patients with pre-diabetes, the use of atorvastatin slightly increased serum HDL-C levels. However, in patients with diabetes, the use of atorvastatin slightly decreased serum HDL-C level (p= 0.001). Diabetic and pre-diabetic patients who use atorvastatin significantly decreased serum triglyceride levels (p=0.016), while in diabetic and pre-diabetic patients, using atorvastatin slightly increased the serum insulin level (p= 0.003).

Conclusions: Atorvastatin using alters fat and sugar indices in diabetic and pre-diabetic patients.

[*]**Corresponding Author:** Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. **Email:** dqujeq@gmail.com

Introduction

In the pre-diabetes status, blood glucose concentrations are raised beyond the normal range. Nevertheless, these concentrations are lower than the threshold for developing diabetes. Indeed, pre-diabetes is a condition that increases the risk of developing diabetes mellitus [1, 2]. One of the most harmful consequences for pre-diabetics is the onset of type 2 diabetes mellitus [3]. Type 2 diabetes mellitus includes most cases of diabetes mellitus. In patients with type 2 diabetes mellitus, insulin resistance and increased compensatory insulin secretion from pancreatic Langerhans islands appear. Also, these patients promote the process of reducing the secretion function of Langerhans islands [4- 6].

It is well known that hypercholesterolemia often occurs in diabetic patients. Hypercholesterolemia is one of the most important risk variables for cardiovascular diseases (CVDs) [7, 8]. Atherosclerotic cardiovascular diseases (ASCVDs) are the main cause of death in patients with diabetes. In this regard, statins' main function is inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase (HMG-COA-R) in the cholesterol biosynthesis pathway. Consequently, statins prevent cholesterol biosynthesis and decrease the serum level of low-density lipoprotein-cholesterol (LDL-C) [8-12]. Kimura et al showed that atorvastatin decreases serum levels of advanced glycationend products in nonalcoholic steatohepatitis patients with dyslipidemia [13].

Furthermore, in addition to decreasing the serum level of LDL-C, atorvastatin can decrease the serum level of triglycerides but increase the serum level of high-density lipoprotein-cholesterol (HDL-C) [14,15]. Statins have various membrane permeability. Hydrophilic statins cannot enter non-liver cells [16]. Besides, it is a reason for differences in the function of statins. In the non-liver cells, endothelial cells of the blood vessels, lipophilic statins can also reduce inflammation and vascular complications via inhibition of activity GTPases Ras and Rho [17]. In recent years, evidence has shown that statin is associated with an increased risk of developing type 2 diabetes [18]. Based on the tests of patients using statins to prevent CVDs, in 2012, Food and Drug Administration (FDA) warned that the use of statins was associated with an increase in the levels of serum fasting blood glucose (FBS) and glycosylated hemoglobin (HbA1c) [19, 20]. It has been shown that statins can cause the onset of type 2 diabetes through impaired insulin secretion and insulin resistance [20]. Studies have shown that some of the effects of statins on insulin resistance are caused by activating the inflammasome and stimulating inflammatory pathways [21-23]. The data linking atorvastatin with glucose metabolism and lipid profile regarding type 2 diabetes and pre-diabetes patients to show the underlying mechanisms is limited. We hypothesized that atorvastatin had influenced biochemical variables. Therefore, in the current study, we

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aimed to evaluate the effects of atorvastatin consumption on biochemical variables in patients with type 2 diabetes and pre-diabetes.

Materials and Methods

Study design

Samples were prepared randomly from patients with type 2 diabetes mellitus and pre-diabetics referring to Endocrinology Department as well as the healthy individuals referring to the medical diagnostic laboratory (Babol, Iran). Healthy subjects were selected under the supervision of an endocrinologist. Also, we included 80 individuals, and they were divided into five groups: i) Healthy subjects without diabetes mellitus (control group), ii) Patients with type 2 diabetes mellitus use atorvastatin, iii) Patients with type 2 diabetes mellitus do not use atorvastatin, iv) pre-diabetes use atorvastatin, v) pre-diabetes who do not use atorvastatin.

The number of subjects in group (iv) was 12, but the number of patients and participants in other groups was 17. In groups (iii) and (v), patients with type 2 diabetes mellitus and pre-diabetes did not receive statins after being selected by the endocrinologist. In groups (ii) and (iv), patients with type 2 diabetes mellitus and pre-diabetes used atorvastatin 20 mg/day for three months. After three months, blood samples were prepared. Blood samples from each subject were taken at a rate of 5 ml in a serum collection tube, and then the serum was isolated for the measurement of biochemical variables. Data of variables such as age, weight, height, and blood pressure were taken from the profile of these individuals. Also, variables such as FBS, cholesterol, triglyceride, LDL-C, HDL-C, and HbA1c levels were used to assess the status of diabetics and pre-diabetes.

Moreover, the subjects in the control group did not have a specific disease and a history of diabetes and FBS, cholesterol, triglyceride, LDL-C, and HDL-C values were in the normal range. The inclusion criteria were: taking atorvastatin 20 mg/day, type 2 diabetes mellitus (FBS < 126 mg/dl), pre-diabetes (FBS 100-125 mg/dl), diabetes for 3 years and not receiving insulin. The exclusion criteria were: women who were pregnant or breastfeeding, individuals with active infections such as hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and tuberculosis, history of cancer, heart attack in the last six months, or peripheral coronary artery disease, being under the treatment of chronic disease that requires steroids such as prednisone, smoking cigarettes and consuming alcohol, women taking contraceptives, indigestion and chronic diarrhea, failure of important organs such as liver, lung, kidney, heart and brain, anemia and diabetic nephropathy.

All participants in this study provided written informed consent. The study protocol and written consent procedures were approved by the Ethics Committee at the Hormozgan University of Medical Sciences (HUMS.REC. 1395.127). Serum glucose, HbA1c, HDL-C, total cholesterol, triglycerides, and insulin were measured using chimerical kits in the clinical laboratory. Also, we calculated the LDL-C level using the Friedewald equation.

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Statistic analysis

Data obtained from the study was calculated by descriptive statistics (mean, standard deviation), and the relationship between variables and biochemical variables was calculated based on the Pearson correlation coefficient. SPSS Version 24 was used to analyze the obtained results. The analysis of variance (ANOVA) test was used to compare the mean of data. Also, the ROC test was used to assess the sensitivity and specificity of the variables in the diagnosis of diabetes in each of the groups. In the current study, $p < 0.05$ was statistically considered significant.

Results

Table 1 shows the mean and standard deviation of the variables measured in the five groups based on the ANOVA test. All patients with diabetes and pre-diabetes who did not use atorvastatin had significantly higher body mass index (BMI) than healthy subjects. Furthermore, pre-diabetes patients who do not use atorvastatin had significantly higher BMI than those with diabetes who use atorvastatin ($p = 0.001$). The systolic blood pressure level in patients with diabetes and pre-diabetes were significantly higher than in normal subjects ($p = 0.001$). However, the diastolic blood pressure level in healthy subjects was significantly higher than in patients with diabetes and pre-diabetes ($p = 0.016$) the FBS and HbA1c levels in patients with diabetes and pre-diabetes were significantly higher than in the control group. The patients with diabetes and pre-diabetes who used atorvastatin had a significantly lower level of FBS and HbA1c ($p = 0.001$) than those with diabetes and pre-diabetes who did not use atorvastatin. The serum cholesterol and LDL-C levels in diabetics and pre-diabetes were significantly higher than in healthy subjects. The serum cholesterol and LDL-C levels in patients with diabetes and pre-diabetes who use atorvastatin significantly decreased ($p = 0.001$) compared to patients with diabetes and pre-diabetes who do not use atorvastatin. In pre-diabetics, atorvastatin significantly increased the serum HDL-C level. However, in people with diabetes, atorvastatin significantly decreased the serum HDL-C level ($p = 0.001$). The serum triglycerides level in the patients with diabetes and pre-diabetes were significantly higher than in healthy subjects. In patients with diabetes and pre-diabetics, atorvastatin significantly decreased the serum triglyceride level ($p = 0.016$). The serum insulin level in healthy subjects was significantly higher than the patients with diabetes and pre-diabetes. In patients with diabetes and pre-diabetes, atorvastatin significantly increased the serum insulin level($p = 0.003$). Based on the Pearson test, the serum LDL-C level in the control group had a significantly negative correlation with the serum insulin level ($p = 0.008$, $R = -0.6$).

Figure 1 shows the receiver operating characteristic curve (ROC), the ability of atorvastatin in patients with diabetes to alter the measured variables in groups (ii) and (iii). Atorvastatin was able to affect the serum levels of FBS, cholesterol, and insulin with high sensitivity and specificity.

Table 1. Comparison of the mean and standard deviation of variables measured in 5 groups, based on the ANOVA test

Variables	Control group	The diabetic group who received statin	The diabetic group who did not receive statin	The pre-diabetic group who received statin	The pre-diabetic group who did not receive statin	P-value
Age	36 ± 17	*61 ± 9	52 ± 14	*53 ± 8	45 ± 11	0.001
BMI Kg/cm^2	24 ± 2	*28 ± 4	28 ± 3	21 ± 4	*29 ± 4	0.001
Systolic blood pressure mmHg	118 ± 3	*129 ± 10	*127 ± 5	126 ± 9	124 ± 8	0.001
Diastolic blood pressure mmHg	*80 ± 1	79 ± 4	78 ± 3	75 ± 6	75 ± 6	0.016
FBS mg/dl	84 ± 4	*142 ± 44	189 ± 63	*108 ± 9	109 ± 15	0.001
Cholesterol mg/dl	149 ± 20	*155 ± 28	205 ± 38	*168 ± 38	189 ± 38	0.001
LDL-C mg/dl	80 ± 12	*80 ± 25	111 ± 34	*99 ± 46	103 ± 25	0.001
HDL-C mg/dl	46 ± 8	*42 ± 8	43 ± 8	*47 ± 15	44 ± 14	0.001
Triglyceride mg/dl	104 ± 37	*163 ± 109	208 ± 156	*130 ± 54	181 ± 143	0.016
HbA1c %	5.1 ± 1	*7.9 ± 1	8.7 ± 1	*5.3 ± 1	5.6 ± 1	0.001
Insulin µIU/ml	*23 ± 1	*23 ± 1	21 ± 2	*22 ± 2	21 ± 2	0.003

BMI= body mass index; FBS= fasting blood glucose; LDL-C= low-density lipoprotein-cholesterol; HDL-C= high-density lipoprotein-cholesterol; HbA1c= glycosylated hemoglobin
Data are presented as mean ± SD. (*presented as significant, p=0.001)

Atorvastatin significantly decreased the serum levels of FBS and cholesterol in patients with diabetes. However, it increased the serum insulin level slightly in patients with diabetes. Atorvastatin can significantly decrease the serum cholesterol level with a sensitivity of 82%, specificity of 83%, and cut off 177 mg/dl.

Figure 2 shows the ROC curve assessing the sensitivity and specificity of variables between groups (i) and (iii) for predicting the probability of developing diabetes in a healthy person. Moreover, atorvastatin significantly decreased the serum FBS level with a sensitivity of 82%, specificity of 65%, and cut-off of 158 mg/dl. Atorvastatin significantly increased the serum insulin level with a sensitivity of 60%, specificity of 65%, and cut-off of 20 µIU/ml. Variables such as cholesterol and insulin were significantly able to predict passing the healthy phase to the diabetic phase. Cholesterol was significantly able to predict passing the healthy phase to the diabetic phase with a sensitivity of 59%, specificity of 30%, and cut-off of 184 mg/dl.

Furthermore, insulin was significantly able to predict passing the healthy phase to the diabetes phase with a sensitivity of 76%, specificity of 65%, and cut-off of 23 µIU/ml. Figure 3 shows the ROC curve assessing the sensitivity and specificity of variables between groups (i) and (v) for the prediction of the probability of progression from a healthy subject to a pre-diabetes. Variables such as FBS, HbA1c, BMI, cholesterol, and LDL-C were significantly able to predict passing the healthy phase to the pre-diabetes phase. Cholesterol was significantly able to predict passing the healthy phase to the pre-diabetes phase with a sensitivity of 82%, specificity of 60%, and cut-off of 148 mg/dl. FBS was significantly able to predict passing the healthy

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phase to the pre-diabetes phase with a sensitivity of 99%, a specificity of 98%, and a cut-off of 98 mg/dl. In addition, HbA1c was significantly able to predict passing the healthy phase to the pre-diabetes phase with a sensitivity of 64%, specificity of 60%, and a cut-off of 5.2%.

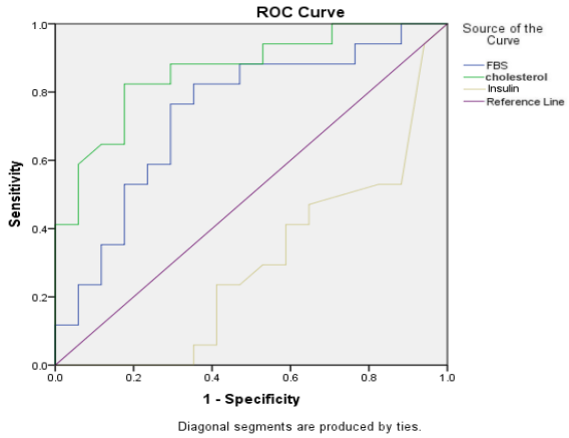

Fig. 1. ROC curve between group (ii) and group (iii)

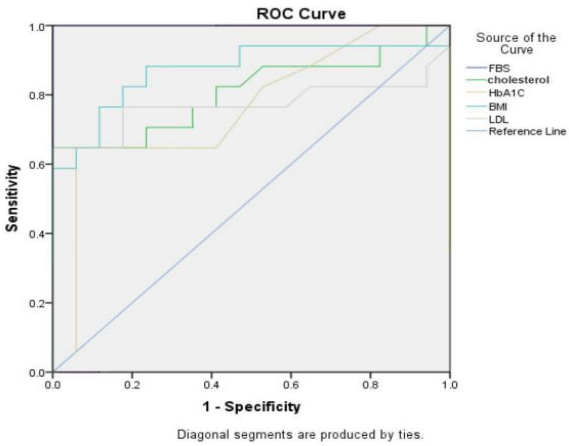

Fig. 2. ROC curve between group (i) and group (iii)

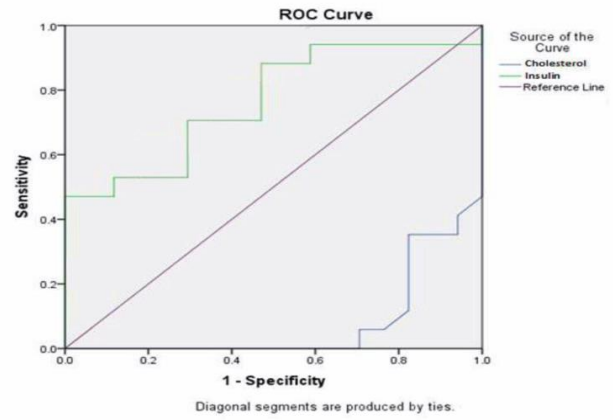

Fig. 3. ROC curve between group (i) and group (v)

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Discussion

Atorvastatin use was associated with decreased values for FBS and HbA1c but increased insulin secretion in diabetes and pre-diabetes patients. In this regard, impaired glucose metabolism is crucial for developing type 2 diabetes mellitus. Also, decreased FBS and elevated insulin concentration might be due to the influence of atorvastatin on glucose metabolism. Furthermore, the current study demonstrated a relationship between atorvastatin use and impaired glycemic traits. The relationship between atorvastatin diabetes and pre-diabetes depends on different confounders, such as age, physical activity, education level, and family history of patients with diabetes. Also, the current study demonstrated that the association between atorvastatin uses was partly dependent on lipid profiles. Patients treated with atorvastatin tend to decrease cholesterol and triglyceride levels compared to non-atorvastatin users. One of the most harmful consequences of pre-diabetes status is the onset of type 2 diabetes mellitus [3]. It was shown that type 2 diabetes enhances cholesterol biosynthesis and reduced cholesterol absorption; thereby, the risk of coronary artery disease will be decreased [24, 37]. It is recommended now that atorvastatin is used as the first choice for primary prevention against cardiovascular complications in patients with type 2 diabetes and other risk variables for CVDs [25]. Cholesterol treatment trialists' Collaboration showed that statin therapy for five years had reduced the incidence of CVDs in patients with diabetes [26]. On the other hand, numerous studies showed that atorvastatin, with an inhibitory effect on the HMG-COA-R activity, significantly reduced serum cholesterol and LDL-C levels [8, 9, 11, 12, 38]. Hence, it can reduce cholesterol and LDL-C levels in diabetic patients. In the current study, the serum cholesterol and LDL-C levels in diabetes and pre-diabetes were higher than in healthy subjects. These results aligned with many studies that mentioned type 2 diabetes increased cholesterol and LDL-C levels [24, 27].

On the other hand, the comparison between diabetes and pre-diabetes use of atorvastatin, compared with diabetes and pre-diabetes who did not use atorvastatin, caused a significant decrease in the serum cholesterol and LDL-C levels. The results have been proven in numerous other studies [28-31]. The serum HDL-C level in patients with diabetes was significantly lower than in healthy subjects. In patients with pre-diabetes, atorvastatin significantly increased the serum HDL-C level. But, in diabetic patients, atorvastatin significantly reduced the serum HDL-C level. Due to this contradiction, we cannot achieve the result of the effect of atorvastatin on HDL-C level, and further studies are needed. The serum triglyceride levels in diabetes and pre-diabetes patients were significantly higher than in healthy subjects. Type 2 diabetes is associated with increased triglyceride levels [27]. In diabetes and pre-diabetes patients, atorvastatin significantly decreased the serum

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triglyceride level (p = 0.016). Therefore, statin reduced the serum triglyceride level in diabetic and pre-diabetic patients.

Kimura et al. showed that atorvastatin Atorvastatin decreases serum levels of advanced glycationend products in nonalcoholic steato-hepatitis patients with dyslipidemia [13]. Regarding the relation between statin and diabetes, Tsuchiya et al. showed that lovastatin was associated with impaired insulin secretion from beta cells in the pancreas by inhibiting the biosynthesis of cholesterol [32]. Nakata et al. showed in adipose tissue that atorvastatin (10 mg/day) had reduced the expression of glucose transporter type 4 (GLUT4) and thereby had decreased insulin sensitivity by inhibiting the synthesis of isoprenoids in the cholesterol biosynthesis pathway. It was accompanied by a significant increase in HbA1c level [33]. In a study performed by Takaguri et al., atorvastatin reduced the transmission of GLUT4 to the plasma membrane and thereby insulin resistance by inhibiting protein isoprenylation [34]. Henriksbo et al. showed in adipose cells that fluvastatin had caused insulin resistance by activatingNod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, thereby activating pro-inflammatory factor interleukin (IL)-1β [21]. Gumprecht et al. showed that atorvastatin (20 mg/day) had significantly increased FBS level [29]. In the current study, the FBS and HbA1c levels in diabetic and pre-diabetic patient groups were significantly higher than in the control group. However, contrary to most other studies, atorvastatin did not significantly affect insulin secretion a. Therefore, it decreased the FBS and HbA1c levels in diabetic and pre-diabetic patients and prevented the promotion of diabetes and the progression of pre-diabetes. In the current study, atorvastatin may contribute to improving insulin secretion and thereby reduce the FBS and HbA1clevels by decreasing serum LDL-C levels.

In the control group, the serum LDL-C levels significantly negatively correlated with the serum insulin level. Fernández-Real et al. showed that insulin caused the increase in the expression of LDLR [35]. It was also shown in the study by Wade et al. that insulin caused the increase of LDL-C degradation in the Hep G2 cell line by increasing LDLR level [36]. According to the mentioned studies, insulin can cause a decrease in serum LDL-C levels by increasing the amount of cellular LDLR. Therefore, based on the current study, atorvastatin can also reduce LDL-C levels by increasing insulin levels. The results of the ROC test between groups (ii) and (iii) showed that if the levels of cholesterol and FBS were lower than 177 mg/dl and 155 mg/dl, respectively, and the level of insulin was greater than 20 µIU/ml, it demonstrates that patient with diabetic. The results of the ROC test between groups (i) and (iii) showed that if the level of cholesterol was greater than 184 mg/dl and the level of insulin was lower than 23 µIU/ml. It indicated diabetic status.

Furthermore, the results of the ROC test between groups (i) and (v) showed that if the levels of cholesterol, FBS, and HbA1c were greater than 148 mg/dl, 98 mg/dl, and 5.2 %, respectively, it indicates the pre-diabetic

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status. In the current study, atorvastatin reduced the levels of FBS and HbA1c. Therefore, atorvastatin cannot contribute to insulin resistance. Despite the positive results, it should be noted that different types of statin therapy, including different types and dosages, might exert different outcomes in type 2 diabetic and pre-diabetic patients. Due to these different actions of each type of statin and each dosage, further study is required.

This study has strengths and limitations: We have data on HbA1c and insulin levels in type 2 diabetes and pre-diabetes patients. Our analysis highlights the greatest influence of atorvastatin on cholesterol and triglyceride levels. This study was restricted to lipid-soluble statin, atorvastatin, at a single dose of 20 mg daily. We did not have data on the effect of other dosages and types of stains.

Conclusion

We examined the effects of atorvastatin on biochemical variables. Atorvastatin might prevent cardiovascular complications in patients with type 2 diabetes and pre-diabetes by reducing LDL-C and triglyceride levels and increasing insulin levels. Also, atorvastatin may prevent the promotion of diabetes status and the progression of pre-diabetes status to diabetes.

Conflict of Interest

The authors do not have any commercial affiliations or potential conflicts of interest associated with this work submitted for publication.

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