Rice Bran Oil Compared to Atorvastatin for Treatment of Dyslipidemia in Patients with Type 2 Diabetes

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Abstract

Objective: To compare the effect of rice bran oil versus statins (atorvastatin drug) on blood glucose, glycosylated hemoglobin (HbA1C) and serum lipid profiles in patients with type 2 diabetes. The safety of the tested rice bran oil and atorvastatin were investigated. Fatty acids contents of RBO, olive and sesame oil were also assessed.

Materials and Methods: Forty four eligible patients with type 2 diabetes and moderately hyperlipidemic were randomly and equally allocated into two groups, rice bran oil (RBO) group and atorvastatin group. The RBO group received a low-calorie diet and consumed 30 g / day RBO oil as salad dressing and for use as main cooking oil for 6 months. The Atorvastatin group received a low-calorie diet and 40 mg/day of atorvastatin drug for 6 months. At baseline and after 6 months of study intervention, blood glucose, glycosylated hemoglobin (HbA1C), serum lipid profiles; hepatic, renal and inflammatory biomarkers were estimated.

Results: Results showed significant increase in fasting and postprandial blood glucose, HbA1C and liver transaminases (alanine transaminase ALT and aspartate transaminase AST) in the atorvastatin group while a significant reduction was shown in RBO group. Moreover, significant reductions in lipid profile levels, blood urea, serum uric acid and erythrocyte sedimentation rate (ESR) were observed in both RBO and atorvastatin groups after 6 months of the study intervention.

Conclusion: The use of rice bran oil together with dietary modifications may have implications in lowering fasting and postprandial blood glucose, suppressing serum lipid levels, reduce the TC/HDL-C ratio and therefore reducing the risk of cardiovascular disease. Moreover, RBO exerts a hypooricemic action and anti-inflammatory effects. The findings obtained from the current study reinforce the use of RBO as an alternative natural potent hypolipidemic agent safer than atorvastatin drug that may induce side effects in some cases in patients intolerant to statins.

Introduction

The increasing worldwide prevalence of diabetes mellitus increases the risk of heart disease and stroke. This will substantially increase burden of cardiovascular death rate morbidity and mortality due to atherosclerotic heart disease [1]. The World Health Organization (WHO) estimates that CVD will continue to dominate mortality trends in the future and in 2015, there will be about 20 million CVD deaths [2].

Type 2 diabetes is characterized by insulin resistance and often accompanied with cardiovascular risk factors, including dyslipidemia, obesity and hypertension. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most potent class of drugs used as lipid-lowering agents. Statins have been shown to decrease the mortality from coronary artery disease and decrease the incidence of myocardial infarction, stroke and peripheral vascular disease [3].

Several clinical trials have been made to emphasize the safety and tolerability of statins. The most important adverse effects associated with statins are asymptomatic increases in liver transaminases [4] and myopathy [5]. Besides, other adverse effects associated with statin therapy are relatively mild and often rare [6]. Regarding these adverse effects and high cost of this class of drugs, many statin-intolerant patients seek alternative lipid-lowering therapies to manage their dyslipidemia.

Dietary oil intake has an important influence on blood lipid concentrations [7]. Rice bran oil (RBO), an unconventional oil is recently introduced onto the Egyptian market for human use. It is believed to be a healthy vegetable oil in Asian countries. It is...
characterized by a balanced fatty acids meeting American Heart Association (AHA) recommendations. It exerts hypolipidemic activity in relation to more commonly used vegetable oils rich in linoleic acid [8]. Many researches suggested that rice bran oil’s cholesterol-lowering properties are explained by its unsaponifiable components with nutraceutical value more than by its fatty acid composition [9]. The unsaponifiable fractions mainly composed of phytosterols (γ-oryzanol), triterpene alcohols, tocopherols and tocotrienols have high antioxidant property [10]. In addition, RBO contains up to 20% saturated fatty acids (SFA) and equal amounts of monosaturated fatty acids (MUFA) and polysaturated fatty acids (PUFA) [11].

Rice bran oil has performance properties competitive to other widely used oils. Its taste and performance is complementary to salad, cooking, and frying applications as it has a high smoke point [12].

The aim of this study was to compare the effect of rice bran oil versus atorvastatin drug on blood glucose, glycosylated hemoglobin and serum lipid profiles in patients with type 2 diabetes. The safety of the tested rice bran oil and atorvastatin were studied. Fatty acids content of RBO, olive and sesame oil were also assessed.

Materials and Methods

Subjects

A total of 44 eligible patients with type 2 diabetes and moderately hyperlipidemic aged 40–60 years old were recruited into the study for a 6 months trial. Diabetic duration was of 6-10 years. The study subjects had an initial baseline serum fasting blood glucose > 150 mg/dl with no acute complications, serum TC > 220 mg/dl, LDL > 137 mg/dl and TG > 204 mg/dl. Subjects had no evidence of any chronic illness including hepatic, renal, thyroid or cardiac dysfunction. Exclusion criteria included extreme dietary habits such as vegetarianism, severely low fat intake and extreme levels of physical activity. The protocol of the study was approved by the National Research Centre Ethics Committee. In addition an informed consent was obtained from each participant to be included in the study.

Experimental design

This was a randomized, comparison study. Forty four subjects were randomly allocated into two groups, rice bran oil (RBO) group and atorvastatin group. All subjects received a low-calorie diet, 1400 Kcal energy per day for six months, including 26% fat, 17% proteins, and 57% carbohydrates. The atorvastatin group received the low-calorie diet and 40 mg/day of atorvastatin drug daily for 6 months. Subjects in this group were under an antidiabetic regimen of drug (Glucophage). The RBO group received the low-calorie diet and consumed 30 g / day RBO oil as salad dressing and for use as main cooking oil for 6 months. Subjects in this group were not taking any medication known to affect blood glucose or plasma lipid levels (lipid lowering drugs, B-blockers or diuretics). The rice bran oil was produced by the Thai Ideal Oil Limited Company, Bangkok, Thailand. The rice bran oil used had an ISO 9001:2008. Both groups received identical lifestyle education and a therapeutic lifestyle change with some diet restrictions in fat intake. Butter and margarine were strictly avoided. Adherence to the dietary recommendations was assessed by collecting two 24-hour diet recalls at baseline and after 6 months. During the study period, the dietary intake data were analyzed using Nutrisurvey 5, version 2007 to calculate the consumption of calories and the 3 major macronutrients.

The RBO, olive oil and sesame oil were evaluated and compared for fatty acids composition.

Blood sampling and biochemical analysis

Blood samples were drawn after a 12- hours overnight fasting to test the biochemical measurements at baseline and after 6 months of the intervention period. Part of the blood samples were collected in tubes containing EDTA for quantitative colorimetric determination of glycosylated hemoglobin (HbA1C) using ion exchange resin by Stanbio Laboratory (USA) [13]. The remaining blood samples were allowed to clot for 20 min., centrifuged at 4000 rpm for 15 min. to separate the serum.

Fasting and postprandial blood glucose were determined in the fresh serum by using oxidase peroxidase method as described by Trinder [14]. The rest of the serum was stored at - 20°C until used for further analysis of lipid profile, liver function and kidney function tests.

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were determined enzymatically using commercially available kits by Stanbio (USA) as described by Allain et al., [15], Lopes-Virella et al., [16] and Buccolo and David, [17] respectively. Serum low-density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) were subsequently estimated using Friedewald formula [18]:

\[
LDL = TC - HDL - TG/5 \text{ (mg/dL)}
\]

\[
VLDL = TG + 5 \text{ (mg/dL)}
\]

TC/ HDL- C ratio was also calculated.

Hepatic biomarkers, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) were determined according to the colorimetric method described by Reitman and Frankel [19].

Renal function biomarkers including serum creatinine, blood urea nitrogen (BUN) and serum uric
acid were determined using commercially available kits by Stanbio (USA) as described by Fabinay and Eringhausen, [20], Patton and Grouch, [21] and Rebar et al., [22] respectively.

Inflammatory biomarker erythrocyte sedimentation rate (ESR) was also determined in blood samples as described by Bull et al., [23].

Assessment of fatty acids in vegetable oils

Fatty acid methyl esters of the vegetable oils were prepared according to Sheppard and Iverson [24] to be subjected to Gas liquid chromatography (GLC) for fatty acids estimation.

Fatty acids preparation

Fatty acid methyl esters were prepared by treatment of vegetable oils by sulphuric acid/methanol method.

Identification of fatty acids methyl ester

GLC analysis of the methyl esters was performed by using Konick equipped with a flame ionization detector (FID). A fused silica capillary column DB-5 (60 m x 0.32 mm. id.) was used. The oven temperature was maintained initially at 50°C for 5 min., and then programmed from 50 to 250°C at a rate of 3°C/min. Helium was used as the carrier gas, at flow rate of 1.1 ml/min. The injector and detector temperatures were 220 and 250°C, respectively. The retention indices (Kovats indices) of the separated fatty acid methyl ester components were calculated using standard fatty acid methyl esters standard (C4-C37, Sigma-Aldrich Co.) as references.

Statistical analysis

The data are presented as means ± SEMs. Statistical Package for the Social Sciences SPSS software for windows (SPSS Inc., Chicago, IL, version 17.0) was used for the statistical analysis. Two independent sample t-test was used to compare baseline data between the RBO and atorvastatin groups and to compare percentage changes before and after the study intervention. Paired t-test was used to compare data from before and after the study intervention between the RBO group and the atorvastatin group. P-Value <0.05 indicated a statistically significant difference for all tests.

Results

Fatty acid profiles of rice bran oil vs olive oil and sesame oil are shown in Table 1. Rice bran oil had a higher proportion of total SFAs, specifically palmitic acid (16:0), than the other vegetable oils. Rice bran oil contained modest proportions of MUFA's and PUFA's, the percent distributions of which were intermediate between olive and sesame oil. Olive oil was relatively high in MUFA's, whereas sesame oil was relatively high in PUFA's.

### Table 1: Comparison of the percentage of fatty acids profile of rice bran oil vs olive oil and sesame oil.

<table>
<thead>
<tr>
<th>Fatty acids (%)</th>
<th>Rice Bran</th>
<th>Olive</th>
<th>Sesame</th>
</tr>
</thead>
<tbody>
<tr>
<td>C14:0</td>
<td>1.21</td>
<td>1.51</td>
<td>6.91</td>
</tr>
<tr>
<td>C16:0</td>
<td>14.46</td>
<td>15.21</td>
<td>13.00</td>
</tr>
<tr>
<td>C18:0</td>
<td>1.95</td>
<td>1.88</td>
<td>5.16</td>
</tr>
<tr>
<td>C20:0</td>
<td>0.67</td>
<td>Trace</td>
<td>0.93</td>
</tr>
<tr>
<td>2 SFA</td>
<td>20.14</td>
<td>15.21</td>
<td>14.51</td>
</tr>
<tr>
<td>C16:1</td>
<td>Trace</td>
<td>1.89</td>
<td>0.30</td>
</tr>
<tr>
<td>C18:1</td>
<td>41.46</td>
<td>70.76</td>
<td>38.36</td>
</tr>
<tr>
<td>C20:1</td>
<td>0.53</td>
<td>Trace</td>
<td>3.87</td>
</tr>
<tr>
<td>ΣMUFA</td>
<td>41.99</td>
<td>72.65</td>
<td>38.66</td>
</tr>
<tr>
<td>C 18:2</td>
<td>36.58</td>
<td>11.16</td>
<td>43.99</td>
</tr>
<tr>
<td>C18:3</td>
<td>1.29</td>
<td>1.02</td>
<td>2.56</td>
</tr>
<tr>
<td>ΣPUFA</td>
<td>37.87</td>
<td>12.18</td>
<td>44.59</td>
</tr>
</tbody>
</table>

SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

The results of the dietary analysis are shown in Table 2. No significant differences in calorie intakes, macronutrient intakes, or macronutrient intakes as a percentage of calories were observed in a comparison of values before and after the study intervention between the two groups.

### Table 2: Average daily intake of energy, protein, fat and carbohydrate in 3-day dietary records in subjects during intervention periods.

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=22)</th>
<th>RBO (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>After 6 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>Kcal/day</td>
<td>1433.3 ± 70.3</td>
<td>1435.6 ± 90.5</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>69.5 ± 6.6</td>
<td>69.2 ± 5.5</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>53.2 ± 4.3</td>
<td>52.8 ± 3.4</td>
</tr>
<tr>
<td>CHO (g)</td>
<td>177.0 ± 7.5</td>
<td>176.1 ± 6.5</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>19.0 ± 1.1</td>
<td>20.0 ± 1.5</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>28.9 ± 2.5</td>
<td>33.0 ± 3.4</td>
</tr>
<tr>
<td>CHO (%)</td>
<td>49.0 ± 2.8</td>
<td>47.0 ± 2.9</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM; *CHO, carbohydrate; %E, % of energy.

Blood glucose, HbA1c and serum lipid levels are shown in Table 3. Baseline parameters did not differ significantly between the subjects assigned to the two groups. In Atorvastatin group, fasting and 2-h postprandial blood glucose concentrations increased significantly by 7.57% and 3.59% respectively after the study intervention. By contrast, in the RBO group, the fasting and 2-h postprandial blood glucose concentrations decreased significantly by 8.06% and 14.79% respectively after the study intervention. HbA1c increased significantly by 6.27% after the study intervention in the Atorvastatin group. However, HbA1c was significantly reduced by 8.13% after the study intervention than before the intervention in the RBO group.

Atorvastatin and RBO groups showed significant reduction in serum TC concentrations (mean changes: 24.05% and 16.49%, respectively), TG concentrations (mean changes: 28.55% and 12.91% respectively), LDL-C concentrations (mean changes: 31.41% and 18.64% respectively), and the atherogenic ratio of TC/HDL-C ratio (mean changes: 30.62% and 25.15%, respectively) from baseline.
By contrast, HDL-C concentrations showed significant increase in atorvastatin and RBO groups (mean changes: 9.52% and 11.66%, respectively) from baseline.

In the atorvastatin group, VLDL-C decreased by 35.42% after the study intervention. In the RBO group, VLDL-C increased by 3.96% but the change was not significantly different after the study intervention.

A comparison of the percentage change in TC, TG and LDL before and after the study intervention showed a significant difference in their levels between RBO group and atorvastatin group.

As shown in Table 4, the activity of ALT and AST were normal and almost the same in both atorvastatin and RBO groups at baseline. After 6 months of intervention of atorvastatin, it resulted a significant increase in ALT and AST activity by 35.34% and 51.40% respectively but it remained almost unchanged in RBO group. Serum level of creatinine showed non-significant change in both groups before and after the study intervention. Urea levels showed non-significant change in atorvastatin group, while it showed a significant decrease of 14.49% in RBO group. A significant reduction in serum uric acid levels was shown in atorvastatin and RBO groups of 9.46% and 18.13% respectively after the study intervention.

Erythrocyte sedimentation rate (ESR) showed significant decrease of 28.00% and 31.11% during the first and second hour respectively in atorvastatin group. Similarly in the RBO group, ESR showed a significant decrease of 36.17% and 40.86% during the first and second hour respectively.

**Discussion**

Individuals with type 2 diabetes mellitus (T2DM) have an increased risk of mortality, primarily because of cardiovascular disease (CVD). An important risk factor for the development of CVD is dyslipidemia. Many studies have shown that lipid lowering treatments reduce the risk of CVD and death.

Most of the hypolipidemic drugs, currently in use in the treatment of dyslipidemia in type 2 diabetics, have a plenty of side effects [25] and this has further necessitated the search for suitable alternatives. In contrast, natural source as rice bran oil has a hypoglycemic effect [26], effective lipid lowering property [27], in addition to its potent antioxidant activity [28]. The aim of this study was to compare the effects of atorvastatin vs RBO on blood glucose, serum lipid profiles and their safety in type 2 diabetic patients. Atorvastatin drug was chosen in our study as it is the most commonly used drug for treatment of hypercholesterolemia in Egypt.

Atorvastatin is frequently administered for the treatment of dyslipidemia associated with type 2 diabetes mellitus, and used for primary prevention of major cardiovascular events [29]. However, a marked deterioration of glycemic control has been reported in patients with diabetes following atorvastatin therapy for 3 to 4 months in Japanese diabetic patients [30].

The current study, in agreement with earlier reports manifested a significant elevation of HbA1C level in patients treated with atorvastatin [31]. This was accompanied by increased fasting [32] and two hour postprandial glucose blood levels [33, 34].

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**Table 3: Blood glucose, HbA1C and serum lipid levels in subjects before and after intervention periods either with Atorvastatin or RBO.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>After 6 months</th>
<th>Change(%)</th>
<th>Baseline</th>
<th>After 6 Months</th>
<th>Change(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>$150.27 \pm 1.87$</td>
<td>$177.64 \pm 1.86^*$</td>
<td>-17.47</td>
<td>$151.09 \pm 1.52$</td>
<td>$188.71 \pm 2.35^*$</td>
<td>-28.16</td>
</tr>
<tr>
<td>PP blood glucose(mg/dL)</td>
<td>$256.10 \pm 5.5$</td>
<td>$275.30 \pm 6.3^*$</td>
<td>-7.49</td>
<td>$258.21 \pm 7.5$</td>
<td>$220.01 \pm 8.3^*$</td>
<td>-17.49</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>$7.65 \pm 0.25$</td>
<td>$8.13 \pm 0.28^*$</td>
<td>-6.72</td>
<td>$8.49 \pm 0.28$</td>
<td>$7.80 \pm 0.29^*$</td>
<td>-8.13</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>$234.7 \pm 3.60$</td>
<td>$180.32 \pm 3.08^*$</td>
<td>-24.05</td>
<td>$235.68 \pm 2.52$</td>
<td>$196.82 \pm 2.90^*$</td>
<td>-16.49</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>$227.95 \pm 4.31$</td>
<td>$253.16 \pm 6.38^*$</td>
<td>-27.55</td>
<td>$225.41 \pm 3.53$</td>
<td>$196.27 \pm 3.29^*$</td>
<td>-16.49</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>$37.27 \pm 1.46$</td>
<td>$25.36 \pm 1.03^*$</td>
<td>-35.42</td>
<td>$29.82 \pm 0.99$</td>
<td>$21.00 \pm 0.88$</td>
<td>-3.96</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>$146.32 \pm 2.43$</td>
<td>$100.36 \pm 2.77^*$</td>
<td>-37.04</td>
<td>$148.50 \pm 2.30$</td>
<td>$120.82 \pm 2.55^*$</td>
<td>-18.64</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>$34.45 \pm 1.06$</td>
<td>$37.73 \pm 1.02^*$</td>
<td>-9.52</td>
<td>$35.50 \pm 1.06$</td>
<td>$39.64 \pm 1.18^*$</td>
<td>11.66</td>
</tr>
<tr>
<td>Tg/HDL-C ratio</td>
<td>$6.89 \pm 1.72$</td>
<td>$4.78 \pm 0.92^*$</td>
<td>-30.82</td>
<td>$6.64 \pm 1.66$</td>
<td>$4.97 \pm 0.83^*$</td>
<td>-25.15</td>
</tr>
</tbody>
</table>

Values are expressed as means ±SEM. 1 Values with asterisk (*) are significantly different from baseline values (p < 0.05). 2 Values with sharp (#) are significantly different from Atorvastatin group (p < 0.05). 3 HbA1C glycosylated hemoglobin. 4 TC, total cholesterol; TG, triglyceride; VLDL-C, very low density lipoprotein; LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; Tg/HDL-C, ratio of total cholesterol to HDL-C.

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**Table 4: Liver and kidney function tests of Atorvastatin and RBO groups.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Atorvastatin (n =22)</th>
<th>RBO (n =22)</th>
<th>Change(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>$37.15 \pm 0.95$</td>
<td>$50.32 \pm 1.99^*$</td>
<td>-35.94</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>$36.36 \pm 0.71$</td>
<td>$55.05 \pm 3.08^*$</td>
<td>-35.40</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>$0.69 \pm 0.03$</td>
<td>$0.70 \pm 0.24$</td>
<td>-1.14</td>
</tr>
<tr>
<td>Blood Urea (mg/dL)</td>
<td>$39 \pm 1.6$</td>
<td>$36 \pm 2.1$</td>
<td>-2.56</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>$7.08 \pm 0.12$</td>
<td>$6.41 \pm 0.13^*$</td>
<td>-9.46</td>
</tr>
<tr>
<td>ESR(#)</td>
<td>$153.62 \pm 1.46$</td>
<td>$136.52 \pm 1.03^*$</td>
<td>-17.08</td>
</tr>
<tr>
<td>First hour (mm/hr)</td>
<td>$52 \pm 2.2$</td>
<td>$36 \pm 2.6^*$</td>
<td>-28.00</td>
</tr>
<tr>
<td>Second hour (mm/hr)</td>
<td>$90 \pm 2.9$</td>
<td>$62 \pm 3.4^*$</td>
<td>-31.11</td>
</tr>
</tbody>
</table>

Values are expressed as means ±SEM. 1 Values with asterisk (*) are significantly different from baseline values (p < 0.05). 2 ALT, alanine transaminase. 3 AST, aspartate transaminase, 4 ESR, Erythrocyte Sedimentation Rate.
Because HbA1C levels are a sensitive indicator for glycemic control, our results strongly suggest that atorvastatin causes glucose intolerance that may lead to decreased insulin sensitivity and modestly increase the risk of developing diabetes mellitus [35]. These baneful metabolic effects of atorvastatin occur despite its beneficial effect to improve lipid profile.

In the contrary, a significant reduction of HbA1C level was shown in RBO group. This was also accompanied by a significant decrease in fasting and two hour postprandial blood glucose levels. According to our results, we found that there is an appreciable amount of oleic acid in RBO which could be the cause of blood glucose reduction. Our results are in accordance with previous studies that emphasized the role of monounsaturated fatty acids content of RBO in decreasing postprandial plasma glucose, increasing insulin sensitivity and suppressing the hyperinsulinemic response in rats with T2DM [36, 37, 38].

Tocotrienol rich fraction (TRF) in rice bran oil (RBO) has also been shown to lower the blood glucose level in patients and preclinical animal models [26]. Further TRF may be a useful antioxidant effectively caused decrease in glycyslated hemoglobin (Hba1C) in diabetic rats [39]. Furthermore, Oryzanol content in RBO can be considered as a novel antinociceptive agent and can be used as a possible therapeutic option in the treatment of neuropathic pain associated with diabetes mellitus [40].

In our present study, we speculated that the improvement of the glycemic status in RBO group may have been resulted from the high MUFA and tocotrienol content in RBO. RBO could therefore provide a new adjuvant therapeutic line for better control of diabetes. The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [41]. Atorvastatin was used in this study in order to understand how far RBO hypolipidemic effect is comparable to that drug. Atorvastatin and RBO were evaluated for their anti-hyperlipidemic activity by estimating serum triacylglyceride (TG), total cholesterol (TC), very low density lipoprotein-cholesterol (VLDL), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein-cholesterol (HDL) levels.

In the present study, both atorvastatin and RBO significantly improved the lipid profile, each in different aspects, in groups of patients with type 2 diabetes.

RBO and its specific components (unsaturated fatty acids, triterpene alcohols, phytosterols, tocotrienols, alpha-tocopherol and γ-oryzanol) have been shown by many studies to have an effect on lipid metabolism [42]. RBO improves the plasma lipid pattern of rodents, rabbits, non-human primates and humans, reducing total plasma cholesterol, triglyceride concentration and increasing the high density lipoprotein cholesterol level [43, 10].

The amount of linoleic acid in RBO is rather moderate among the vegetable oils (36.58% of total fatty acids), but it is still a rich source. RBO also contains a relatively high proportion of oleic acid (41.46%). Conjugated linoleic acid (CLA) and oleic acid have been shown to offer a host of beneficial effects for the body. They can regulate blood glucose levels and serum lipids, help to lose weight, prevent cardiovascular disease, lower high blood pressure and reduce inflammation [44, 45]. These results are supported by the recommendation of the American Diabetes Association that patients with type 2 diabetes should consume vegetable oil containing abundant amounts of oleic acid to improve hyperlipidemia and prevent heart related diseases [46, 47]. RBO also contains a detectable amount of a linolenic acid 1.29%. This amount may be enough to increase the content of (n-3) highly polyunsaturated fatty acids such as eicosapentaenoic and docosahexaenoic acids in tissue phospholipids compared with other vegetable oils [48].

Many researchers have implicated the rich unsaponifiable compounds of the RBO mainly composed of sterols such as yoryzanol, triterpene alcohols and tocotrienols as being responsible for its hypolipidemic effect [49], as well as for its antiatherogenic property [50].

The reduction in the TC and LDL level by RBO may be associated with the presence of phytosterols which act either by influencing the absorption of dietary cholesterol from the gut or enhancing the conversion of cholesterol to fecal bile acids [10]. The presence of γ-oryzanol (cyclodecatrienol), a geranyl ester of triterpene alcohol with a similar structure to cholesterol, may compete with the binding sites of cholesterol, thereby impaired uptake of cholesterol into enterocytes by withdrawal cholesterol from the system [51]. Oryzanol has an effect on lowering plasma non-HDL-C and raising plasma HDL through a greater extent to increase fecal excretion of cholesterol and its metabolites [1].

Moreover, tocotrienols, one of the essential components of RBO have been suggested to lower TC concentrations in the blood, thought inhibiting the HMG-CoA reductase activity in the biosynthetic pathway of cholesterol [52]. Many studies indicate that tocotrienols have cardioprotective properties in humans [53] by improving postischemic ventricular function and reducing myocardial infarct size [54]. Furthermore, the reduction in the TC level by RBO may be due to the presence of high amount of Oleic acid which belongs to the class of MUFAs [55].

The reduction in the TG level by RBO may be associated with the presence of triterpene alcohols and phytosterols which lower the circulating levels of...
cholesterol and TG due to the possible structural similarity of cycloartenol and cholesterol [56]. Another probable mechanism may involve an increase in the lipoprotein lipase (LPL) enzyme which is capable of breaking down plasma TGs of TG-rich lipoproteins, including chylomicrons and LDL [57]. Furthermore, our study shows that RBO has the ability to reduce the atherogenic ratio of TC / HDL-C concentration to a great level (25.15%). This finding is in agreement with the earlier reports [58, 59].

Statins are highly effective cholesterol-lowering agents, and have been shown to reduce atherosclerosis-related mortality in patients with diabetes [60].

Atorvastatin is a potent inhibitor of hydroxymethylglutaryl-CoA reductase, which decreases all major LDL subspecies in plasma by upregulating LDL receptor activity [61]. Atorvastatin also reduces the secretion of apo B. This is believed to account for its TG-lowering effect, which is more profound at higher doses [62].

Hepatic dysfunction is a risk factor for statins as the predominant route of elimination for the majority of this class of drugs occurs via the bile after metabolism by the liver [63].

In the present study, ALT and AST elevations occur in diabetic patients by 6 months drug intervention of atorvastatin. Many studies confirm our results [64]. Therefore, despite the beneficial effect of atorvastatin in achieving significant levels of TC, LDL cholesterol reduction and significant level of HDL cholesterol elevation, it may lead in some cases to a hepatotoxic effect as occurs with high atorvastatin doses (80 mg/kg), whereas the lower dose (20 mg/kg) seems to cause mild liver injury [65]. Moreover, atorvastatin may induce pancreatitis [66] and cholestasis [67]. Statin-associated myalgia is an important clinical problem that will likely become more prevalent owing to the ever-expanding indications for statin use [68]. In general, statins are well tolerated and serious adverse events including muscle toxicity are rare [69].

Serum creatinine was not significantly affected in diabetic patients receiving atorvastatin in our study. Same results have been shown in a previous study [70].

Epidemiological studies confirmed a positive association between raised SUA levels and risk of CHD or CVD in the general population [71]. Our results showed that atorvastatin significantly lowered serum uric acid levels. It exerts a hypouricemic action by affecting uric acid metabolism [72].

In the present study, atorvastatin induced reduction in erythrocyte sedimentation rate (ESR). A previous study provided evidence that atorvastatin has fast and early anti-inflammatory effects [73]. Similarly, our findings demonstrate that RBO reduced ESR. Scientific research suggests that Phytosterols and linoleic acid content in RBO provide antioxidant and anti-inflammatory effects [74].

Furthermore, our results showed that blood urea nitrogen level was significantly lowered in diabetic patients by 6 months dietary intervention involving consumption of RBO. Same results have been previously demonstrated by [75].

In conclusion, it could be suggested that the 6-months dietary intervention involving consumption of RBO, has advantages in terms of lowering fasting and postprandial blood glucose, suppressing serum lipid levels and improving the cardiovascular risk profile. Some components of RBO, possibly in the unsaponifiable fraction, may have exerted a greater effect on plasma lipids relative to other vegetable oils than can be ascribed to the fatty acid composition of the oil itself. Our findings show that RBO and atorvastatin exert similar and substantially beneficial effects on serum lipid profile, significant reduction of TC, TG, LDL cholesterol and TC / HDL-C ratio levels and increase in HDL cholesterol level, coupled with a hypouricemic action and anti-inflammatory effects. Despite beneficial improvement in lipid profile, atorvastatin treatment resulted in significant increase in blood glucose and glycosylated hemoglobin levels. Furthermore, it may induce in some cases a hepatotoxic effect, pancreatitis and cholestasis as it may occur with high atorvastatin doses or its consumption for long term. The use of rice bran oil together with dietary and lifestyle modifications may have implications for reducing the risk of cardiovascular disease. Therefore, the findings obtained from the current study reinforce the use of RBO as a natural potent hypolipidemic agent in type 2 diabetic patients safer than atorvastatin drug.

References


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