Effects of isoflavones on lipid and apolipoprotein levels in patients with type 2 diabetes in Heilongjiang Province in China

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In this study, we examined the association between soy isoflavones and lipid profiles, apolipoprotein levels in patients with type 2 diabetes in China. The study population was composed of 120 cases (80 women with type 2 diabetes and 40 healthy women). Objects in treatment group received isoflavones 435 mg/day for 2 months, then lipid profiles were analyzed by the colorimetry method and apolipoprotein levels were determined by immune turbidimetric method. And all the indexes were determined after oral glucose tolerance test. The levels of total cholesterol, triglyceride and LDL-C significantly reduced and the levels of HDL-C and apolipoprotein A1 significantly raised in the treatment group after intervention (p<0.05). After oral glucose tolerance test, the level of total cholesterol was lower at postprandial 6 h than at empty stomach in treatment group, it had significantly difference (p<0.05). LDL-C levels in the treatment group not only decreased after intervention, but was also significantly lower at postprandial 4, 6 h than in non-intervention group. The ratio of apolipoprotein A1/apolipoprotein B at postprandial 2 h was the highest after treatment in isoflavone group. Supplementation with 435 mg/day of isoflavones exerted favorable effect on the blood total cholesterol, LDL-C levels and the ratio of apolipoprotein A1/apolipoprotein B in Chinese type 2 diabetes women.

Key Words: isoflavones, lipid profiles, apolipoprotein, type 2 diabetes, China

Type 2 diabetes has become a global public health challenge. In Southeast Asia, the prevalence has increased three- to fivefold over 30 years and is projected to rise higher.1,2 Diabetic dyslipidemia is a cluster of lipid and apolipoprotein abnormalities, which include elevated triacylglycerol-rich lipoproteins (TRLs), an excess of small dense low density lipoprotein-cholesterol (LDL) particles (independent of the concentration of LDL-cholesterol) and reduced concentrations of both high density cholesterol (HDL-C) and the major HDL apolipoprotein, apolipoprotein A1 (ApoA1).3,4 Reduction of LDL-C is the first target of lipid-altering therapy in diabetes, secondly is the elevated typical dyslipidemia triglycerides and reduced HDL-C. This is mainly because some studies often find LDL-C to be the strongest predictor of coronary heart disease risk, not only because of a larger evidence base for LDL-C lowering.5,6 Lifestyle change, nutrition therapy, and improved glycemic control have some impact on lipids in patients with diabetes and in metabolic syndrome, the levels of LDL-C in most of them reduce 0.6 to 0.9 mmol/L5,7 and levels of triglycerides reduce 0.2 mmol/L or less.8,9 As TRL and LDL particles contain a single molecule of apolipoprotein B (ApoB), the concentration of ApoB in plasma may be a better indicator of cardiovascular risk than the simple measurement of LDL-cholesterol.10-13 The ApoB:ApoA1 ratio was better than traditional lipid and apolipoprotein levels as a predictor of CVD in large case–control studies14,15 and in people treated with statins.16 These analyses indicate that the standard lipids should be replaced by assessment of ApoB and ApoA1, particularly in people with diabetes.17-19 The search case–control study showed that ApoB levels were elevated in type 2 diabetes compared to nondiabetic controls independent of LDL-C.20,21 For that reason, measurement of ApoB in addition to LDL-C may help reclassify CVD risk in type 2 diabetes patients with borderline LDL-C levels and also determine when lipid-lowering treatment should be considered.

Isoflavones are phytoestrogens present abundantly in soybean, associated with various beneficial health properties such as anti-estrogenic, reducing hormone dependent cancers and bone resorption. It shows healing properties in relation to cardiovascular diseases, renal diseases, osteoporosis and diabetes. However, because the doses of isoflavones from soy products used in animal or in vitro studies are much higher than those in the soy products regularly consumed by humans, the health benefits of soy for type 2 diabetes have been found in epidemiological studies to be limited and inconsistent.22-25 Whether the effects of isoflavones on lipid profiles and apolipoprotein levels differ between non-intervention and isoflavones treatment on patients with type 2 diabetes remains to be determined. The aim of the present study was to investigate two hypotheses: one is that isoflavones have observable effects on lipid profiles and apolipoprotein levels, such as TG, TC, LDL-C, HDL-C and ApoA1, ApoB, the other one is that these effects are modified by different oral glucose tolerance in the patients with type 2 diabetes of Chinese population.

Materials

Subjects. In a double, blind, randomized trial, eighty patients with type 2 diabetes who met with the research criteria were divided into diabetes mellitus non-intervention group (DM-NIG) and isoflavones dose group (Iso-G). As the same time, forty normal subjects joined this protocol and were taken as control group (CG). These patients came from Daqing Chinese medicine hospital and the first affiliated hospital of Heilongjiang Chinese Medicine University of Heilongjiang province in China. The women who received hormone replacement therapy (androgen, estrogen, progesterone, and respectively related synthetic drugs)
or who took medication (selective serotonin reuptake inhibitors, such as escitalopram oxalate, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydro-chloride, paroxetine and sertraline hydrochloride) or health functional foods containing isoflavones or sophoricosides, known to have influence on estrogen levels were excluded. The subjects who had a history of cancer within 5 years, liver and kidney diseases or thyroid disorder, or who had an allergy to soybeans were also excluded. Furthermore, subjects cured with cholesterol lowering drugs within 2 months were excluded. All subjects provided written informed consent for participation in the study. The research protocol was approved by the Ethical Committee of the Heilongjiang Center for Disease Control and Prevention.

It is important to point out the presence of about 145 mg of soy isoflavones in each capsule (aglycone equivalents) of which genistein and daidzein comprised 52.2% and 47.8%, respectively, as evidenced by high performance liquid chromatography (HPLC) analysis, addition to 5 μg of Vitamin D, providing 100% of the daily recommended dose. The placebo capsules were identical in size and color, contained starch and Vitamin from the active formulation. Isoflavones and placebo supplied by Heilongjiang Datong Company and supervised by Heilongjiang Society for Nutrition. The treatment code was allocated randomly. The randomization number with treatment assignment for the individual subject was blinded for the duration of the trial. The subjects received either three isoflavones or three placebo capsules daily for 2 months. The total dose of isoflavone was thus about 435 mg/day. Isoflavones dose in this study was either more or less compared with previous studies. We chose the dose was due to that we found isoflavones at the dose of 435 mg/day could significantly improve the levels of some antioxidant indicators, such as SOD, GSH-PX and GSH-ST of hyperlipidemia patients in our previous research. At the same time, some scholars had found that antioxidants could reduce the oxidation of lipid and glucose, so we guessed whether soy isoflavones at the current dose had effect on the blood lipid index in patients with type 2 diabetes. During the supplemental period, isoflavones intake from foods was restricted to less than 10 mg/day. The subjects received education on food sources of isoflavones by a dietician.

**General characteristics and anthropometric measures.**

The information on the general characteristics of the subjects was collected through face to face interviews. The anthropometric data were gathered using standard methods. The body weight (kg) and height (cm) were measured to the nearest 0.1 kg and 0.1 cm, respectively. The body mass index (BMI) was calculated by dividing the body weight (kg) by the squared height (m²). The waist and hip circumferences were measured twice with a flexible steel metric tape to the nearest 0.1 cm.

**Table 1.** Baseline characteristics of the participants with type 2 diabetes and the controls (mean ± SD)

| Groups   | Age (years old) | Height (cm) | Weight (kg) | Body mass index (kg/m²) | Waist circumference (cm) | Hip circumference (cm) | Wait to hip ratio | Fasting blood glucose level (mmol/L) | Glycosylated serum protein level (µg/L) |
|----------|----------------|-------------|-------------|-------------------------|--------------------------|------------------------|-----------------|-------------------------------------|--------------------------------------|
| CG       | 46.5 ± 13.8    | 162.36 ± 2.81 | 62.52 ± 3.71 | 23.70 ± 0.89           | 89.45 ± 3.13             | 95.37 ± 3.09           | 0.94 ± 0.05     | 5.01 ± 0.36                         | 162.3 ± 28.36                        |
| DM-NIG   | 48.5 ± 13.1    | 164.58 ± 3.71 | 62.49 ± 2.84 | 23.07 ± 0.72           | 87.95 ± 2.04             | 95.98 ± 2.11           | 0.92 ± 0.03     | 10.33 ± 2.32                        | 234.5 ± 65.32                        |
| Iso-G    | 54.87 ± 8.97   | 161.08 ± 3.03 | 63.38 ± 2.48 | 24.43 ± 0.87           | 90.45 ± 3.18             | 97.81 ± 2.10           | 0.92 ± 0.02     | 9.86 ± 4.53                         | 238.64 ± 57.25                       |

Experimental conditions and treatment procedures are given in Materials and Methods. Graph depicts (mean ± SD).

**Table 2.** Levels of lipid profiles and apolipoprotein levels before and after intervention (mean ± SD)

| Groups   | TC (mmol/L) | TG (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) | ApoA1 (g/L) | ApoB (g/L) |
|----------|-------------|-------------|----------------|----------------|--------------|-------------|
| CG       | Before      | 4.71 ± 1.21 | 1.77 ± 1.17    | 2.68 ± 0.74    | 1.45 ± 0.42  | 1.15 ± 0.18  | 0.58 ± 0.14  |
|          | After       | 4.69 ± 1.04 | 1.71 ± 0.7    | 2.69 ± 0.57    | 1.59 ± 0.26  | 1.15 ± 0.16  | 0.61 ± 0.15  |
| DM-NIG   | Before      | 4.98 ± 0.86 | 1.87 ± 1.02    | 2.63 ± 0.38    | 1.52 ± 0.53  | 1.12 ± 0.19  | 0.58 ± 0.17  |
|          | After       | 4.78 ± 0.98 | 1.56 ± 0.88    | 2.57 ± 0.43    | 1.53 ± 0.23  | 1.15 ± 0.14  | 0.59 ± 0.16  |
| Iso-G    | Before      | 5.12 ± 1.21 | 1.97 ± 1.17    | 2.78 ± 0.74    | 1.35 ± 0.42  | 1.05 ± 0.18  | 0.54 ± 0.14  |
|          | After       | 4.79 ± 1.04*| 1.49 ± 0.7*    | 2.39 ± 0.57*    | 1.52 ± 0.56*  | 1.18 ± 0.18*  | 0.63 ± 0.15  |

Experimental conditions and treatment procedures are given in Materials and Methods. Graph depicts (mean ± SD). Asterisk means significant against before intervention (*p<0.05), t test.
at postprandial 1, 2 h than at empty stomach, but it had no obvious changes in Iso-G after OGTT. The level of TC was higher in DM-NIG than in CG at postprandial 6 h. Significantly, it showed that the level of TC was lower at postprandial 6 h than at empty stomach in Iso-G, it had significantly difference \( p < 0.05 \). There were no changes of HDL-C levels after OGTT in each group. The level of LDL-C was higher at postprandial 4, 6 h than at empty stomach in DM-NIG, the change was significantly different \( p < 0.05 \). It was worth mentioning that LDL-C levels in the treatment group were not only decreased after intervention, but also were significantly lower at postprandial 4, 6 h than in DM-NIG.

Levels of ApoA1 in each group after OGTT (mean ± SD) are shown in Fig. 2. In control group, the level of ApoA1 at empty stomach, postprandial 1, 2, 4 and 6 h was 1.13 ± 0.12, 1.11 ± 0.12, 1.11 ± 0.19, 1.10 ± 0.15 and 1.12 ± 0.17 g/L, respectively. In diabetes mellitus non-intervention group, the levels of ApoA1 was 1.04 ± 1.15, 1.07 ± 0.15, 1.07 ± 0.14, 1.13 ± 0.19 and 1.05 ± 0.16 g/L, respectively. In isoflavones dose group, the level of ApoA1 was 1.13 ± 0.18, 1.18 ± 0.19, 1.16 ± 0.11, 1.11 ± 0.16 and 1.12 ± 0.15 g/L, respectively. There was no significantly different of ApoA1 level after OGTT in every group.

Levels of ApoB in each group after OGTT (mean ± SD) is shown in Fig. 3. In control group, the levels of ApoB at empty stomach, postprandial 1, 2, 4 and 6 h was 0.65 ± 0.12, 0.64 ± 1.12, 0.62 ± 0.17, 0.62 ± 0.12 and 0.60 ± 0.12 g/L, respectively. In diabetes mellitus non-intervention group, the level of ApoB was 0.68 ± 1.15, 0.69 ± 0.14, 0.75 ± 0.18, 0.80 ± 0.18 and 0.88 ± 0.19 g/L, respectively. As can be seen from the results, the level of ApoB in DM-NIG was the highest of all the groups at postprandial 6 h and compared with empty stomach, the difference was significantly \( p < 0.05 \). In isoflavones dose group, the level of ApoB was 0.69 ± 0.18, 0.71 ± 0.15, 0.71 ± 0.13, 0.70 ± 0.18 and 0.65 ± 0.16 g/L, respectively. Compared with empty stomach, the level of ApoB at postprandial 6 h rose significantly \( p < 0.05 \).

Ratio of ApoA1/ApoB in each group after OGTT is shown in Fig. 4. In control group, ratio of ApoA1/ApoB at empty stomach, postprandial 1, 2, 4 and 6 h was 1.85 ± 0.47, 1.87 ± 0.45, 1.87 ± 0.54, 1.86 ± 0.55 and 1.82 ± 0.45, respectively. In diabetes mellitus non-intervention group, ratio of ApoA1/ApoB was 1.64 ± 0.40, 1.63 ± 0.45, 1.63 ± 0.44, 1.65 ± 0.49 and 1.45 ± 0.46, respectively. In isoflavones dose group, ratio of ApoA1/ApoB was 1.63 ± 0.48, 1.73 ± 0.39, 1.86 ± 0.31, 1.61 ± 0.46 and 1.58 ± 0.45, respectively. It showed that after OGTT, obvious changes of the ratio of ApoA1/ApoB had taken place. We can see that the ratio of ApoA1/ApoB was lower at postprandial 6 h than at empty stomach in DM-NIG. Obviously, the ratio of ApoA1/ApoB at postprandial 2 h was the highest (1.86 ± 0.31) after treatment in Iso-G.
were observed. The effects on lipid profiles in patients with diabetes mellitus, this analysis found that, compared with placebo, treatment with isoflavones also significantly improved TC, LDL-C levels and the ratio of ApoA1/ApoB after OGTT. In October 1999, a health claim put forward by the US food and drug administration (FDA) was based on the results of a clinical trial suggesting that at least 25 g of soy protein per day reduced total-C and LDL-C and it approved that products containing soy protein could protective against CHD. Also, the AHA Nutrition committee reevaluated the evidence on isoflavone and CVD and updated its science advisory in 2006. They reported that only 3 studies (among 19 studies) of soy isoflavones showed a reduction in LDL-C; however, no significant changes in HDL-C and TG were observed. Although the evidence for improving lipid profiles and apolipoprotein levels effect of isoflavones on patients with 2 type diabetes is clear from animal or in vitro studies, the results from epidemiological studies have been inconsistent, and we need to consider these inconsistencies further. The primary defect underlying abnormalities in lipoprotein transport in type 2 diabetes is insulin resistance, which leads to increased triglycerides in the fasting and postprandial states, preponderance of small, dense LDL and low concentrations of dysfunctional HDL. Concentrations of LDL-C are most often not remarkably abnormal. Based on this lipoprotein profile, it seems somewhat counterintuitive to prioritize LDL-C lowering in type2 diabetes rather than simply cholesterol content. Also, supplementation with a soy protein containing isoflavones significantly reduced levels of TC, LDL-C and TG and increased levels of HDL-C.(29) In our study, isoflavones supplements (435 mg/day) significantly reduced the levels of TC, TG, LDL-C, while raised the levels of HDL-C two months later. And after OGTT, the levels of TC and LDL-C significantly reduced at postprandial 6 h than at empty stomach, which suggested that isoflavones could improve the lipid profiles of patients with type 2 diabetes. However, other lipid profiles and levels were not affected by the supplementation.

Several studies have indicated that ApoA1 and ApoB provide better discrimination of CHD risk than serum LDL-C, HDL-C and triglycerides in cardiovascular disease and CHD prevention.(30) A randomised primary prevention trial of lovastatin also get a similar conclusion in a non-diabetic population.(31) ApoB is essential for the binding of LDL-C particles, allowing cells to internalize LDL-C and thus absorb cholesterol. An excess of ApoB-containing particles highly correlates with the level of non-HDL-C cholesterol and it is a main trigger in the atherogenic process.(32) On the other hand, levels of ApoA1 strongly correlate with those of HDL-C, and expression of ApoA1 may be largely responsible for determining the plasma level of HDL-C, protecting against CVD. Notably, the calculated ApoB/ApoA1 ratio has been consistently reported as a prognostic cardiovascular risk factor superior than LDL-C. Willcox founded that the ratio of ApoA1 and ApoB should on behalf of the comprehensive changes of the two lipoprotein ApoA1 and ApoB, which could be considered to be an important dangerous forecast factors of Diabetic coronary heart disease.(33) And the rising of the ratio of ApoA1 and ApoB is beneficial to type 2 diabetes. Some scholars found that the peak post-load glucose (PPG) was about 1 h in healthy individuals. But in type 2 diabetes patients, blood glucose continues rose slowly, which due to insulin secretion defect and insulin resistance, so PPG reached a peak delayed to 1.5~2 h.(34) Lind found that the ratio of ApoA1/ApoB had positive correlation with insulin sensitivity.(35) Isoflavones could enhance insulin sensitivity, so the ratio of ApoA1/ApoB was highest at postprandial 2 h in Iso-G. To our knowledge, it is for the first time that our study demonstrated the favorable impact of isoflavones on ApoB levels and ApoA1/ApoB ratio in the diabetic population. We found that the ratio of ApoA1/ApoB is the highest at postprandial 2 h after treatment with isoflavones. In general, blood glucose levels reached the highest peak at 1.5 to 2 h after OGTT. Some cell culture experiments found that insulin sensitivity increased at 1~3 h after OGTT, and the adhesion of insulin and fat cells became stronger. Lind found that the ratio of ApoA1/ApoB had positive correlation with insulin sensitivity. Isoflavones could enhance insulin sensitivity, so the ratio of ApoA1/ApoB was highest at postprandial 2 h in Iso-G. These findings were consistent with our results. On the contrary, it was the lowest at postprandial 6 h without treatment. Although the influence of isoflavones on ApoA1 and ApoB was non-significant, but it made the ratio of ApoA1 and ApoB changed.

In conclusion, supplementation with 435 mg/day of isoflavones exerted favorable effect on the blood TC, LDL-C levels and the ratio of ApoA1/ApoB in Chinese women with type 2 diabetes. Further studies are needed to evaluate the clinical implication of these positive effects in women with abnormal blood glucose.

Discussion

This study explored the effects of supplementation of isoflavones on the lipid profiles and apolipoprotein levels related to type 2 diabetes mellitus in the Chinese women. We found that oral supplement of isoflavones at a dose of 435 mg/day for 2 months could decrease the levels of TC, TG, and LDL-C, while increased HDL-C and ApoA1 levels in serum. In addition to improving lipid profiles in patients with diabetes mellitus, this analysis found that, compared with placebo, treatment with isoflavones also significantly improved TC, LDL-C levels and the ratio of ApoA1/ApoB after OGTT.

In our study, isoflavones supplements (435 mg/day) significantly reduced the levels of TC, TG, LDL-C, while raised the levels of HDL-C two months later. And after OGTT, the levels of TC and LDL-C significantly reduced at postprandial 6 h than at empty stomach, which suggested that isoflavones could improve the lipid profiles of patients with type 2 diabetes. However, other lipid profiles and levels were not affected by the supplementation. Further studies are needed to evaluate the clinical implication of these positive effects in women with abnormal blood glucose.
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Abbreviations

| Abbreviation | Description                        |
|--------------|------------------------------------|
| ApoA1        | apolipoprotein A1                  |
| ApoB         | apolipoprotein B                    |
| BMI          | body mass index                    |
| CG           | control group                      |
| DM-NIG       | diabetes mellitus non-intervention group |
| HDL-C        | high density lipoprotein cholesterol |
| HPLC         | high performance liquid chromatography |
| Iso-G        | isoflavone dose group              |
| LDL          | low density lipoprotein cholesterol |
| OGGT         | oral glucose tolerance test         |
| TC           | the serum total cholesterol         |
| TG           | triglyceride                        |
| TRLs         | triacylglycerol-rich lipoproteins   |

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