The Effect of Short-term Treatment with Fennel on Lipid Profile in Postmenopausal Women: A Randomized Controlled Trial

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Objectives: The present trial aimed to assess the effects of Fennel (Foeniculum vulgare Mill.) on lipid profiles.

Methods: In this double blind, randomized and placebo-controlled trial, sixty eligible postmenopausal women were randomly assigned into the fennel and placebo groups. Total blood cholesterol, cholesterol fractions, and triglycerides were tested at the baseline, and after three-month follow-up.

Results: There was no significant difference in triglyceride ($P = 0.679$), total cholesterol ($P = 0.103$), low-density lipoprotein cholesterol (LDL-C; $P = 0.146$) and high-density lipoprotein cholesterol (HDL-C; $P = 0.266$) levels between the two groups. In addition, in both groups, a paired $t$-test showed no significant difference in all mentioned parameters, except for HDL-C, indicating significant borderline improvement ($P = 0.052$) in the fennel group.

Conclusions: The fennel group revealed a very slight positive change in LDL-C, triglyceride and HDL-C. Further studies with longer durations, higher doses, and larger sample sizes are recommended to validate the results. (J Menopausal Med 2018;24:29-33)

Key Words: Foeniculum · Lipids · Postmenopause

Introduction

Menopause, with its notable hormonal profile, is related with unfavorable metabolic changes, particularly in plasma lipoprotein and cholesterol levels and a greater risk of cardiovascular disease. Estrogen treatment, when initiated early in menopause, is also connected with a decline in likelihood of cardiovascular events. Nevertheless, short-term estrogen use can prompt vaginal drying, while long-term usage can elevate the risk of breast cancer, stroke, and cardiovascular sickness. Accordingly, a growing number of postmenopausal women prefer compounds that contain non-hormonal materials like phyto-oestrogens as a more secure alternative. Phytoestrogen has been the subject of increasing attention for its bone-sparing features. Fennel is a type of phytoestrogen which include phenolic compounds such as flavonoids, hydroxycinnamic acids, phenolic acids, tannins and coumarins. There is a paucity nevertheless, there are

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many animal studies that suggest the use of fennel might be effective for improving lipid profile.\textsuperscript{9,10} The main goal of this study is to evaluate the impact of fennel on lipid profile.

Materials and Methods

This is part of a larger study that explores the effect of fennel on bones health and lipid profiles. A first part of the trials was published elsewhere.\textsuperscript{11} It was conducted in compliance with the standards of Declaration of Helsinki and endorsed by Ethics Committee of the Mashhad University of Medical Science.

All participants of the study were enlisted in the health-care center of Imam Reza Hospital in Mashhad, Iran. Inclusion criteria were: (1) postmenopausal status, which was defined as over 40 years of age without any vaginal bleeding for one year; (2) no regular consumption of phytoestrogen or products made of soy (which was defined as digestion more than once a week); and (3) a normal mammogram in the previous year. Exclusion criteria were: (1) use of any fluoride or bisphosphonates; (2) illness or prescriptions influencing bone metabolism; (3) current (or over past 6 months) utilization of estrogen or calcitonin; (4) a history of endometrial or breast cancer; (5) any bone fracture; and (6) regular physical exercise or sensitivity to Fennel (Foeniculum vulgare Mill.). In the following stage, participants signed an informed consent form alongside verbal assurance about voluntary nature of the study and that they could drop out of the study at will. Moreover, assurance was given to participants regarding the confidentiality of data during and after the study. At the baseline, 60 subjects were randomized to fennel or placebo group. Participants were expected to take soft capsule three times a day – (morning, noon and night). Each 100–mg fennel capsule contained a combination of 30% fennel (Standardized to 21–27 mg anethole) and sunflower oil. Active elements of each capsule were Trans-anthol, Methyl chavicol, fenechon and stragol.

Placebos were similar in shape and size but filled with sunflower oil. These capsules were the courtesy of Barij Essence Pharmaceutical Company, who was not directly involved in the study, was in charge of allocation sequencing and packing. Also, both subjects and research group were blind to the treatment,

1. Laboratory methods

Blood samples were collected after 12–hour fast and moved in a cooled container to the laboratory. The levels of plasma total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol (LDL–C) and high-density lipoprotein (HDL) cholesterol (HDL–C) were measured by Hitachi 902 auto–analyzer (Hitachi High Technologies Corporation, Tokyo, Japan) using analytical kits produced by Pars Azmoon Co, (Pars Azmoon, Tehran, Iran).

2. Statistical tests

Kolmogorov–Smirnov test was used to test whether samples had a normal distribution. Paired $t$-tests (within group) was used to compare between the baseline and three–month period, and Student’s $t$-test was used to compare between treatment groups, Statistical tests were two–sided, and a $P$–value < 0.05 was considered statistically significant.

Results

The two groups were similar in variables such as age, history of hysterectomy, body weight, body mass index, and duration of menopause at the baseline, as shown in Table 1. Side effects were observed in 6 subjects in the fennel group and 3 subjects in the placebo group. In the fennel group, subjects complained of allergic rash ($n = 1$), weight gain ($n = 1$), hypertension ($n = 1$) and vaginal bleeding ($n = 2$). Only one patient in placebo group complained of stomachache.

Table 2 showed the lipid levels at baseline and after three treatments. There was no significant difference in profiles lipids triglyceride ($P = 0.679$), total cholesterol ($P = 0.103$), LDL concentrations ($P = 0.104$) and HDL ($P = 0.266$) between groups. Also, in both group, Paired $t$–test showed no significant difference in all mentioned parameters except HDL–C that showed a significant borderline improvement ($P = 0.052$) in the fennel group,
To the best of our knowledge, this is the first study to assess the effects of fennel on lipid profiles among the postmenopausal women. According to the results of this study, the group treated with fennel showed a very slight positive change in LDL-C and triglyceride. Moreover, improved HDL concentration reached the borderline level of statistical significance ($P = 0.052$) after three months. However, no significant difference was found between the two groups on the lipid parameters.

As we know, there is no human study on the fennel effectiveness of on the lipid profiles. Nevertheless, considering that phytoestrogen is an active biological compound in fennel, we referred to studies evaluating the effects of phytoestrogen on the lipid profiles. The phytoestrogens are plant compounds with properties similar to the estrogen.

The major types of phytoestrogens are isoflavones, lignans, flavonoids and coumestans. Soy and red clover have high content of isoflavones. Lignans are mainly found in flaxseed and fennel is a rich source of flavonoids. Hallund et al. evaluated the effect of flaxseed on the lipid profiles only in a randomized, double blind, placebo-controlled clinical trial with a 6-week wash out period in post menopause. The present results demonstrated that the lipid profiles (total cholesterol, LDL–C, HDL–C and triglycerides) were not affected by both treatments. In a recently published meta–analysis, Tokede et al. assessed the effect of soy products on the serum lipids. There was a significant decrease in LDL–C of $–4.83$ mg/dL (95% confidence interval [CI], $–7.34$, $–2.31$), total cholesterol $–5.33$ mg/dL (95% CI, $–8.35$, $–2.30$) and triglycerides of $–4.92$ mg/dL (95% CI, $–7.79$, $–2.04$) in the patients treated with soy. A significant increase was observed in serum HDL–C concentration of $1.40$ mg/dL (95% CI, 0.58, 2.23) in the soy group. The LDL–lowering effect was more exhibited in hypercholesterolemic subjects.

Two animal studies investigated the effect of fennel on the lipid profiles. The first study was conducted by Helal et al. on 30 rats divided into 5 groups of 6. The Group 1 rats were as control. The rats in the Group 2 experienced hyperlipidemia for 3 week that was sacrificed then. The rats in the Group 3 were made hyperlipidemia and then treated by fennel for further 3 weeks. The rats in the Group 5 were

| Table 1. Baseline characteristics of subjects in the groups |
|---------------------|---------------------|---------------------|---------------------|
| Items               | Fennel group (n = 25) | Placebo group (n = 29) | P value |
| Age (years)         | 56.1 ± 6.5           | 56.2 ± 4.7           | 0.933 |
| Height (m)          | 1.53 ± 5.57          | 1.51 ± 4.71          | 0.206 |
| Duration of menopause (months) | 97 ± 81           | 86 ± 59             | 0.587 |
| Body weight (kg)    | 68 ± 25              | 72.03 ± 11.5         | 0.206 |
| No. of children     | 4.29 ± 1.9           | 3.7 ± 1.7            | 0.334 |
| History of hysterectomy | 1 (4.0%)           | 4 (13.8%)           | 0.354 |
| Cigarette smoking  | 2 (8.0%)             | 0 (0.0%)            |        |

The data is presented as mean ± standard deviation or n (%)

| Table 2. Effect of fennel on lipid parameters in postmenopausal women |
|---------------------|---------------------|---------------------|---------------------|
| Variable            | Fennel group (n = 25) | Placebo group (n = 29) | P value |
| Total cholesterol (mg/dL) |                      |                      |         |
| Start point (0 week) | 236.6 ± 44.7         | 227.83 ± 34.3        | 0.419   |
| End point (12 weeks) | 238.64 ± 40.1        | 222.83 ± 29.69       | 0.103   |
| Paired t-test       | 0.761               | 0.291               |         |
| LDL cholesterol (mg/dL) |                      |                      |         |
| Start point (0 week) | 149.84 ± 35.06       | 133.41 ± 27.34       | 0.060   |
| End point (12 weeks) | 147.16 ± 36.22       | 133.69 ± 30.8        | 0.146   |
| Paired t-test       | 0.630               | 0.950               |         |
| HDL cholesterol (mg/dL) |                      |                      |         |
| Start point (0 week) | 46.6 ± 8.87          | 51.45 ± 9.18         | 0.055   |
| End point (12 weeks) | 48.8 ± 8.97          | 51.55 ± 8.95         | 0.266   |
| Paired t-test       | 0.052               | 0.926               |         |
| Triglycerides (mg/dL) |                      |                      |         |
| Start point (0 week) | 121.36 ± 41.71       | 127.48 ± 52.9        | 0.643   |
| End point (12 weeks) | 118 ± 38.11          | 122.45 ± 40.1        | 0.679   |
| Paired t-test       | 0.649               | 0.378               |         |

LDL: low-density lipoprotein, HDL: high-density lipoprotein
made hyperlipidemia for 6 weeks. The rats in the Group 6 was made hyperlipidemia for 3 weeks and then treated with fennel for 6 weeks. When comparing with the control group, the Groups 4 and 6 showed higher significant decrease ($P < 0.01$) in levels of liver total lipids. They concluded that the fennel might shift liver total lipid value to normal level. The possible mechanism of action of the fennel on reducing lipids could be attributed to its anti-oxidative properties and radical scavenging activity. Fatiha et al. performed the second research on 18 rats with the mean weight of $20 \pm 2$ g divided into three group of six, The Group 1 (control) received intraperitoneal normal saline and water via gavages, The Group 2 was made hyperlipidemia by Triton WR–1339, In the Group 3, the rats was made hyperlipidemia by WR–1339, and then treated with the fennel. The blood samples were collected after scarifying the rats, Then, the samples were immediately centrifuged to separate the plasma for analyzing the lipid parameters (total cholesterol, HDL–C), and LDL–C, triglycerides, apolipoproteins. The second group showed 35%, 50% and 50% decrease in the total cholesterol, triglycerides and LDL–C, respectively. They concluded that administration of methanol extract of fennel might have anti-atherosclerotic and hyperlipidemic effects.

**Conclusion**

There were several limitations in our study. First, the sample size was relatively small and the research units were followed–up only for three month. Seconded limitation of the current study was its failure to control the lifestyle hab- its, like physical activity and diet. However, the subjects were requested not to change their routine diet and physical activity over the study period. Third, we did not calculate the inter- and intra–assay coefficients.

The fennel revealed a very slight positive change in the LDL–C, triglyceride, and HDL concentrations. Further studies with longer durations, higher doses, and larger sample sizes are required to validate the results of this study.

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**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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