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File: ■ Pomegranate (*Punica granatum*, Lythraceae)
■ Type 2 Diabetes
■ Glycemic Control

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RE: Pomegranate Seed Oil Decreases Blood Glucose and Increases GLUT-4 Expression in People with Type 2 Diabetes

Khajebishak Y, Payahoo L, Alivand M, et al. Effect of pomegranate seed oil supplementation on the GLUT-4 gene expression and glycemic control in obese people with type 2 diabetes: A randomized controlled clinical trial. *J Cell Physiol*. November 2019;234(11):19621-19628. doi: 10.1002/jcp.28561.

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, which is caused by defects or abnormalities in insulin-secreting cells, insulin binding receptors, and glucose transporters. Glucose transporter type 4 (GLUT-4) plays a major role in regulating blood glucose levels and glucose metabolism. Pomegranates (*Punica granatum*, Lythraceae) have antidiabetic, antioxidant, and anti-inflammatory properties, and different parts of the fruit are being studied for potential benefits in people with diabetes and other chronic diseases. Pomegranate seed oil (PSO) contains up to 80% punicic acid, a fatty acid that is reported to have effects similar to the antidiabetic thiazolidinedione drugs. The purpose of this randomized, double-blind, placebo-controlled trial was to evaluate the effect of PSO on insulin resistance, GLUT-4 expression, and glycemic indices in people with obesity and T2DM.

The trial was conducted at the Tabriz University of Medical Sciences in Tabriz, Iran from January to April 2018. Patients were included if they had T2DM for more than six months, had fasting blood glucose (FBG) ≥126 mg/dL, were 30-50 years of age, and had a body mass index (BMI) of >30 to <40 kg/m^2. Patients were excluded if they were pregnant or lactating; were taking insulin, thiazolidinediones, or weight loss drugs; were taking supplements containing omega-3 fatty acids, antioxidants, vitamin A, vitamin D, or vitamin B6; or took omega-3 fatty acids in the month before starting the study. Patients were randomly assigned to the PSO group or the placebo group. The PSO group consumed three capsules, each containing 1 g of PSO, daily for eight weeks. The placebo group consumed three capsules, each containing 1 g of paraffin. The PSO was supplied by Saruneh Company (Urmia, Iran) and contained about 45% punicic acid. The PSO was formulated into soft gel capsules by Zahravi Pharmaceutical Company (Tabriz, Iran). The source of the placebo capsules was not identified. Patients were instructed to

consume the capsules with their main meals and to maintain their usual diet and physical activity during the trial.

Body weight and height were measured at the start and end of the trial. Fasting blood samples were collected at the start and end of the trial. Blood was analyzed for FBG and insulin. Homeostatic model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated to assess insulin resistance and insulin sensitivity. Peripheral blood mononuclear cells were isolated from whole blood for measurement of GLUT-4 gene expression.

A total of 60 patients were enrolled, and data from 52 patients were included in the analysis. Four patients in each group did not complete the trial. Reasons for the withdrawals were not provided. There were no significant differences in baseline characteristics between the two groups. Mean FBG in the PSO group decreased significantly from 161.46 ± 34.44 mg/dL to 143.50 ± 24.2 mg/dL after the intervention (P=0.000). The decrease in FBG was significantly greater in the PSO group compared to the placebo group (P= 0.008). Mean QUICKI scores improved in the PSO group from 0.30 ± 0.02 to 0.31 ± 0.03 after the intervention (P=0.039). However, this change was not statistically significant compared to the placebo group. GLUT-4 gene expression increased by a mean factor of 6.63 in the PSO group. In the placebo group, GLUT-4 expression increased by a mean factor of 1.65. The PSO group had a significantly greater increase in GLUT-4 expression compared to the placebo group (P<0.05). There were no statistically significant changes within or between the two groups for blood levels of insulin or HbA1c or for HOMA-IR scores.

This is the first study to investigate the effects of PSO supplementation on GLUT-4 gene expression in obese people with type 2 diabetes. PSO at a dose of 3 g/day for eight weeks decreased FBG and increased expression of GLUT-4 but did not affect blood insulin levels or models of insulin resistance and insulin sensitivity. The authors explain that PSO increased insulin levels and improved insulin sensitivity in animal studies. They suggest that long-term PSO supplementation may be needed to see improvements in insulin sensitivity in this population. The authors attribute the antidiabetic effects of PSO to punicic acid. They recommend that future trials should measure blood levels and absorption of punicic acid to understand more about PSO's mechanisms of action in T2DM.

The authors declare no conflict of interest.

—*Sandra Jean, MS*

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