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Is the use of pomegranate an effective approach in reducing blood glucose? A meta-analysis

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Abstract
Aims: In the light of this information, this study was conducted to determine the effect of the use of pomegranate on blood glucose, insulin level, and HbA1c value.
Methods: Randomised controlled clinical trials were reviewed on Pubmed, ISI Web of Sciences and Google Scholar databases. 7 randomised controlled trials were included in meta-analysis.In order to test existence of heterogeneity, Cochran's Q test and I2 test statistics were applied. According to heterogeneity of test results, fixed effect and random effects meta-analysis models were used. Hedges' G test statistics was used to show the common effect between pomegranate and placebo groups in meta-analysis.
Results: When the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on reducing the blood glucose, this value was found to be -0.0322 (95% CI:-0.251 to 0.187). When the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on insulin level, this value was found to be -0.129 (95% CI:-0.408 to 0.151). When the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on HbA1c, this value was found to be 0.250 (95% CI:-0.440 to 0.940).
Conclusions: As a result of this meta-analysis, it was observed that the use of pomegranate was an effective approach in reducing blood glucose and insulin concentration. However, it was determined that the use of pomegranate was not an effective approach on HbA1c value.

Keywords: Pomegranate, blood glucose, insulin level, HbA1c value, meta-analysis

1. Introduction
Pomegranate which is a fruit special to Middle East, has been used in traditional medicine for centuries [1]. Owing to substances it contains, pomegranate has anti-oxidant, anti-inflammatory, anti-infective, anti-atherogenic, anti-carcinogenic, and anti-hyperglycaemic effects [2-8].
Pomegranate has been used for prevention and treatment of a wide range of diseases such as cancer, cardiovascular diseases, diabetes, Alzheimer's disease, arthritis, and cerebral ischemia. Furthermore, it is stated in a systematic review that pomegranate can also be used for treatment of metabolic syndrome thanks to its active compounds [9, 10].
In analysis of compounds in pomegranate; it was observed that it contained compounds such as flavonoids, proanthocyanidins, ellagitannins, gallotannins, phenolic acids, sterols, triterpenoids, and alkaloids [4, 11, 12]. It was proved in previous studies that polyphenols had anti-oxidant and anti-inflammatory effects [13]. In addition, it was observed that pomegranate arils are rich in raw fibre, pectin, and sugar [11].
According to *in vivo* and *in vitro* studies, it is reported that pomegranate and its juice have effects such as increased insulin sensitivity, α-glucosidase inhibition, reducing cholesterol, and therapeutic hypoglycemic effect [14, 15]. Moreover, in some studies, pomegranate is also reported to have effects on oxidative state and blood pressure [7, 8, 16, 17].
In a previous study on patients with type 2 diabetes, it was reported that at the third hour after taking pomegranate juice, blood sugar levels of the patients decreased [18]. Similarly in another study, it was revealed that consumption of pomegranate of 200 mL by patients with type 2 diabetes for 6 weeks reduced blood glucose level significantly [17]. In another study, on the other hand, it was reported that the use of pomegranate of 45 g by patients with type 2 diabetes 3 times a day did not have any effect on blood glucose and HbA1c value [19].
In a systematic review, factors related to pomegranate and type 2 diabetes were described and it was concluded that there was still a wide information gap with regard to the use of

pomegranate for clinical management of type 2 diabetes [20]. In the light of this information, this study was conducted to determine the effect of pomegranate on blood glucose, insulin level and HbA1c.

2. Methods

2.1 Criteria for considering studies and Literature search

Randomised controlled clinical trials published between 2005 and 2018 were reviewed on databases of Pubmed, ISI Web of Sciences and Google Scholar using the key words 'Pomegranate and blood sugar'. 17.600 results found upon the review were examined and a total of 14 randomised controlled trials were reached.

2.2 Study selection and data extraction

The inclusion criteria for studies reviewed were; 1) being a randomised controlled trial conducted on human beings, 2) the existence of a placebo group simultaneously with the group using pomegranate, 3) Consumption of pomegranate by the pomegranate group for at least one week, 4) the presence of average and standard deviation values for fasting glucose, insulin concentrations, and HbA1c values. A total of 7 studies meeting these criteria were included in meta-analysis. Fasting glucose, insulin concentrations and HbA1c results measured at the end of pomegranate application were based on for the statistics (Figure 1).

2.3 Assessment of risk of bias

All the studies independently, using a collaboration tool recommended by the Cochrane Handbook 5.1 [21]. There were six points that had to be evaluated: random allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and ''other".

2.4 The GRADE method

Methodological qualities of all studies were evaluated using the below criteria: 1) randomisation, 2) double-blind, 3) separation of groups in randomisation, 4) ensuring privacy during grouping, and 5) producing random numbers. A score was given for each field addressed in the design of the study and total Jadad score ranged between minimum 0 and maximum 5 [22]. The studies having a score of ≥ 4 were considered high quality and those having a score of <4 were considered low quality studies. All 7 studies included in meta-analysis were considered as high quality with the score of ≥ 4.

2.5 Data synthesis and statistical analysis

A heterogeneity test was used to determine whether the effect size was substantially different from the studies in meta-analysis. In order to test existence of heterogeneity, Cochran's Q test and I^2 test statistics were applied. According to heterogeneity of test results, fixed effect and random effects meta-analysis models were used. Hedges' G test statistics was used to show the common effect between pomegranate and placebo groups in meta-analysis.

3. Results

3.1 Study selection

Randomised controlled clinical trials published between 2005 and 2018 were searched on databases of Pubmed, ISI Web of Sciences and Google Scholar. 17.600 studies were identified from the electronic databases using search strategy. We searched electronic databases using the key words 'Pomegranate and blood sugar'. 7 RCTs [24-30] that met all inclusion criteria and data quality standards (Figure 1). Study characteristics

3.2 Study characteristics

As the numbers of sample in the studies were added, 161 patients from Pomegranate group and 154 patients from placebo group were included in the meta-analysis. All the studies were double-blinded, randomized controlled trial. Table 1 shows basic features of the 7 studies selected for the meta-analysis.

3.3 Risk of bias in included studies

Most of the trials are either at unclear or high risk of bias (Table 2).

3.4 Results of individual studies

When the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on reducing the blood glucose, this value was found to be -0.0322 (95% CI: -0.251 to 0.187). (Table 3). It was determined that pomegranate had a statistically significant effect on reducing the blood glucose (Figure 2). In evaluation of 3 randomised controlled trials conducted with patients with Type 2 diabetes, pomegranate was found to have no effects on reducing blood glucose [0.0160 (95% CI: -0.284 to 0.317)] (Figure 3).

When the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on insulin level, this value was found to be -0.129 (95% CI: -0.408 to 0.151). It was found that pomegranate had a statistically significant effect on reducing insulin level (Figure 4).

Similarly, when the standardised average difference value of pomegranate and placebo groups was calculated to evaluate the effect of pomegranate on HbA1c value, this value was found to be 0.250 (95% CI: -0.440 to 0.940). It was found that pomegranate did not have a statistically significant effect on reducing HbA1c value (Figure 5).

4. Discussion

It is reported in i*n vivo* and *in vitro* studies that pomegranate and its juice have effects such as increased insulin sensitivity, α-glucosidase inhibition, reducing cholesterol, and therapeutic hypoglycemic effect [14, 15]. In the light of this information, this study was conducted to determine the effect of pomegranate on blood glucose, insulin level, and HbA1c value.

When analysing studies concerning the effects of pomegranate on fasting plasma glucose, insulin level and HbA1c value, in a study in which patients with type 2 diabetes were given a daily dose of 1.5 mL/kg fresh pomegranate, it was observed in evaluation of blood glucose level that blood glucose level significantly decreased on the measurement at the third hour [18]. In a study comparing individuals with type 2 diabetes using pomegranate (n=8) and healthy individuals (n=9) in terms of fasting plasma glucose, insulin levels, and HbA1c values; individuals included in the study used 2 capsules of pomegranate polyphenol in a day for 4 weeks (POMx, 1 capsule = 753 mg polyphenol). According to the result of the study, there was no significant difference in terms of fasting plasma glucose, insulin level, and HbA1c value [23].

When examining randomised controlled trials on effect of pomegranate on fasting plasma glucose, insulin level, and HbA1c value; in a study, pomegranate group (n=22) consumed pomegranate juice of 250 ml/day a day for 12 weeks and placebo group (n=22) consumed a drink having a similar colour and energy content of 250 ml a day. Upon evaluation of fasting plasma glucose and insulin levels at the end of 12 weeks, it was found that there was no significant change [24]. Similarly in another randomised controlled trial on patients with type 2 diabetes, no significant difference was reported as a result of evaluation of fasting plasma glucose and HbA1c value at the end of 3-month period [25]. In another randomised controlled trial on patients with type 2 diabetes, 80 patients were assigned randomly to pomegranate group (n=40) and placebo group (n=40), and while pomegranate group consumed capsules containing 1000 mg pomegranate twice a day, placebo group used placebo for 8 weeks. At the end of eight weeks, fasting plasma glucose, insulin level and HbA1c were evaluated and it was stated that consumption of pomegranate did not have any effect on the said values [26]. Similar to the studies, the effect of pomegranate on blood glucose in patients with type 2 diabetes was examined in this meta-analysis and pomegranate was observed not to have any effect on reducing blood glucose.

In another randomised controlled double-blind trial with obese individuals; pomegranate group (n=21) used pomegranate extract of 1000 mg (equivalent to approximately 1 L fresh pomegranate juice polyphenol content) per day for 30 days. Placebo group (n=21), on the other hand, used a capsule containing pure microcrystalline cellulose for 30 days. A significant decrease was observed when average serum glucose level and insulin level were evaluated at the end of the study [27].

In another double-blind randomised controlled trial investigating the effect of pomegranate on patients with chronic obstructive pulmonary disease (COPD), pomegranate group (n=15) used pomegranate juice of 400 ml daily for 5 weeks. Placebo group, on the other hand, consumed synthetic orange-flavoured drink of 400 ml daily for 5 weeks. As a result of the study, no significant difference was found in comparison of pomegranate and placebo groups in terms of blood glucose levels [28]. In another randomised controlled double-blind trial, 45 patients with myocardial ischemia were assigned to pomegranate group and placebo group. Pomegranate group (n=26) consumed pomegranate juice of 240 ml daily for 3 months; whereas, placebo group (n=19) used a drink with similar colour and energy content of 240 ml daily for 3 months. As a result of the study, no significant difference was found in analysis of blood glucose and HbA1c value [29]. In another study with patients with metabolic syndrome; pomegranate group used pomegranate juice of 500 mL daily for a period of one week. When examining blood glucose and insulin values as a result of the study, it was reported that there was no significant difference [30].

5. Limitation

In order to minimise risk of bias, only randomised controlled trials were included in meta-analysis. Since there are only a limited number of randomized controlled trials to determine the effect of pomegranate on blood glucose, insulin level, and HbA1c value. Since there is not enough study done for a special patient groups, all studies examining the effect of pomegranate on blood glucose, insulin level, and HbA1c value were included in the metaanalysis.

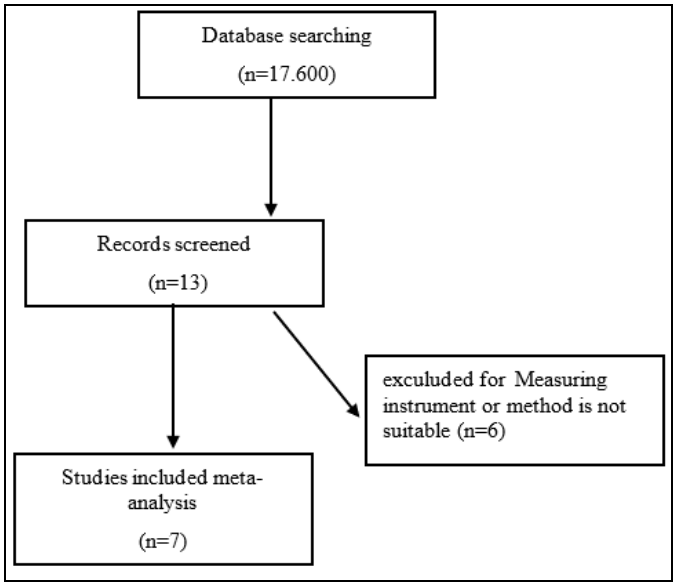

Fig 1: Folow chart of meta-analysis

Table 1: study characteristics of meta- analysis

Study	Sample size		Study design	Applied method	
	Pomegranate	Placebo		Pomegranate	Placebo
Hosseini *et al*, 2016 [27]	21	21	Double-Blinded, Randomized Controlled Trial	1000 mg pomegranate extract daily for 30 days	Capsule containing pure microcrystalline cellulose for 30 days
Faghihimani *et al*, 2016 [26]	40	40	Double-Blinded, Randomized Controlled Trial	2000 mg pomegranate juice daily for 8 weeks	placebo capsules for 8 weeks
Moazzen and Alizadeh, 2017 [30]	15	15	Double-Blinded, Randomized Controlled Trial	500 ml pomegranate juice daily for a week	placebo for the same amount and the same period
Sahrab *et al*, 2015 [25]	22	22	Double-Blinded, Randomized Controlled Trial	250 ml pomegranate juice daily for 12 weeks	250 ml beverage of similar color and energy content juice for 12 weeks
Sahrab *et al*, 2014 [24]	22	22	Double-Blinded, Randomized Controlled Trial	250 ml pomegranate juice daily for 12 weeks	250 ml beverage of similar color and energy content juice for 12 weeks
Summer *et al*, 2005 [29]	26	19	Double-Blinded, Randomized Controlled Trial	240 ml pomegranate juice daily for 3 month	240 ml beverage of similar color and energy content juice for 3 month
Cerda *et al*, 2006 [28]	15	15	Double-Blinded, Randomized Controlled Trial	400 ml pomegranate juice daily for 5 weeks	400 ml of synthetic orange flavored beverage per day for 5 weeks

Table 2: Risk of bias summary of included study

	Random sequence generation (selections bias)	Allocation concealment (selections bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hosseini *et al*, 2016	+	+	?	?	+	?	?
Faghihimani *et al*, 2016	+	+	-	?	+	?	?
Moazzen and Alizadeh, 2017	+	+	?	?	+	?	?
Sahrab *et al*, 2015	+	+	+	?	-	+	+
Sahrab *et al*, 2014	+	+	+	?	-	+	+
Summer *et al*, 2005	+	+	+	+	+	+	+
Cerda *et al*, 2006	+	+	-	?	+	?	?

+: low risk; -: high risk; ?:unclear

Table 3: Comparison of Pomegranate versus Placebo groups in reduction of blood sugar, insulin level and HbA1c

Study	Pomegranate (n)	Placebo (n)	Total (n)	SMD	95% CI
Fasting plasma glucose					
Hosseini *et al*, 2016	21	21	42	-0,572	-1,197 to 0,0529
Moazzen and Alizadeh, 2017	15	15	30	0,408	-0,328 to 1,143
Faghihimani *et al*, 2016	40	40	80	-0,0573	-0,498 to 0,384
Sahrab *et al*, 2015	22	22	44	0,0782	-0,520 to 0,676
Sahrab *et al*, 2014	22	22	44	0,0851	-0,513 to 0,683
Summer *et al*, 2005	26	19	45	-0,104	-0,703 to 0,494
Cerda *et al*, 2006	15	15	30	0,0903	-0,638 to 0,818
Total (fixed effects)	161	154	315	-0,0322	-0,251 to 0,187
Test for heterogeneity: Q=5,0334; df=6; p=0,5395; I^2 =0,00% (95% CI for I^2: 0,00 to 65,78)					
Fasting plasma glucose in Type 2 diabetes mellitus					
Sahrab *et al*, 2015	22	22	44	0,0782	-0,520 to 0,676
Sahrab *et al*, 2014	22	22	44	0,0851	-0,513 to 0,683
Faghihimani *et al*, 2016	40	40	80	-0,0573	-0,498 to 0,384
Total (fixed effects)	84	84	168	0,0160	-0,284 to 0,317
Test for heterogeneity: Q=0,2078; df=2; p=0,9013; I^2 =0,00% (95% CI for I^2: 0,00 to 67,71)					
Insulin Level					
Hosseini *et al*, 2016	21	21	42	-0,746	-1,380 to -0,113
Moazzen and Alizadeh, 2017	15	15	30	0,291	-0,441 to 1,023
Faghihimani *et al*, 2016	40	40	80	-0,0545	-0,495 to 0,386
Sahrab *et al*, 2014	22	22	44	0,000	-0,598 to 0,598
Total (fixed effects)	98	98	196	-0,129	-0,408 to 0,151
Test for heterogeneity: Q=5,5630; df=3; p=0,1349; I^2 =46,07% (95% CI for I^2: 0,00 to 82,06)					
HbA1c					
Faghihimani *et al*, 2016	40	40	80	0,0792	-0,362 to 0,520
Sahrab *et al*, 2015	22	22	44	1,006	0,370 to 1,641
Summer *et al*, 2005	26	19	45	-0,294	-0,895 to 0,307
Total (random effects)	88	81	169	0,250	-0,440 to 0,940
Test for heterogeneity: Q=9,5895; df=2; p=0,0083; I^2 =79,14% (95% CI for I^2: 33,43 to 93,47)					

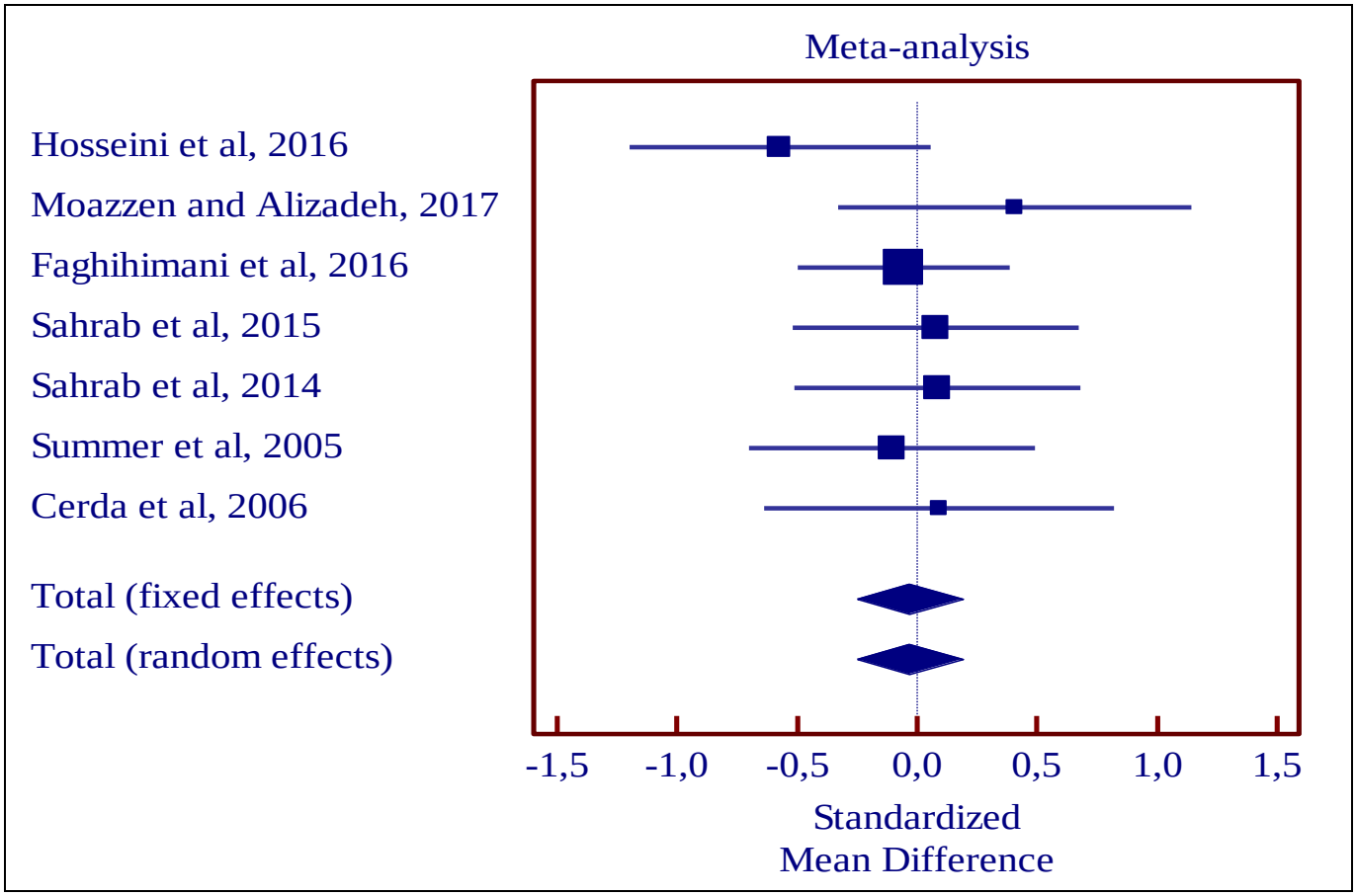

Fig 2: Forrest plot showing changes pomegranate between fasting plasma glucose

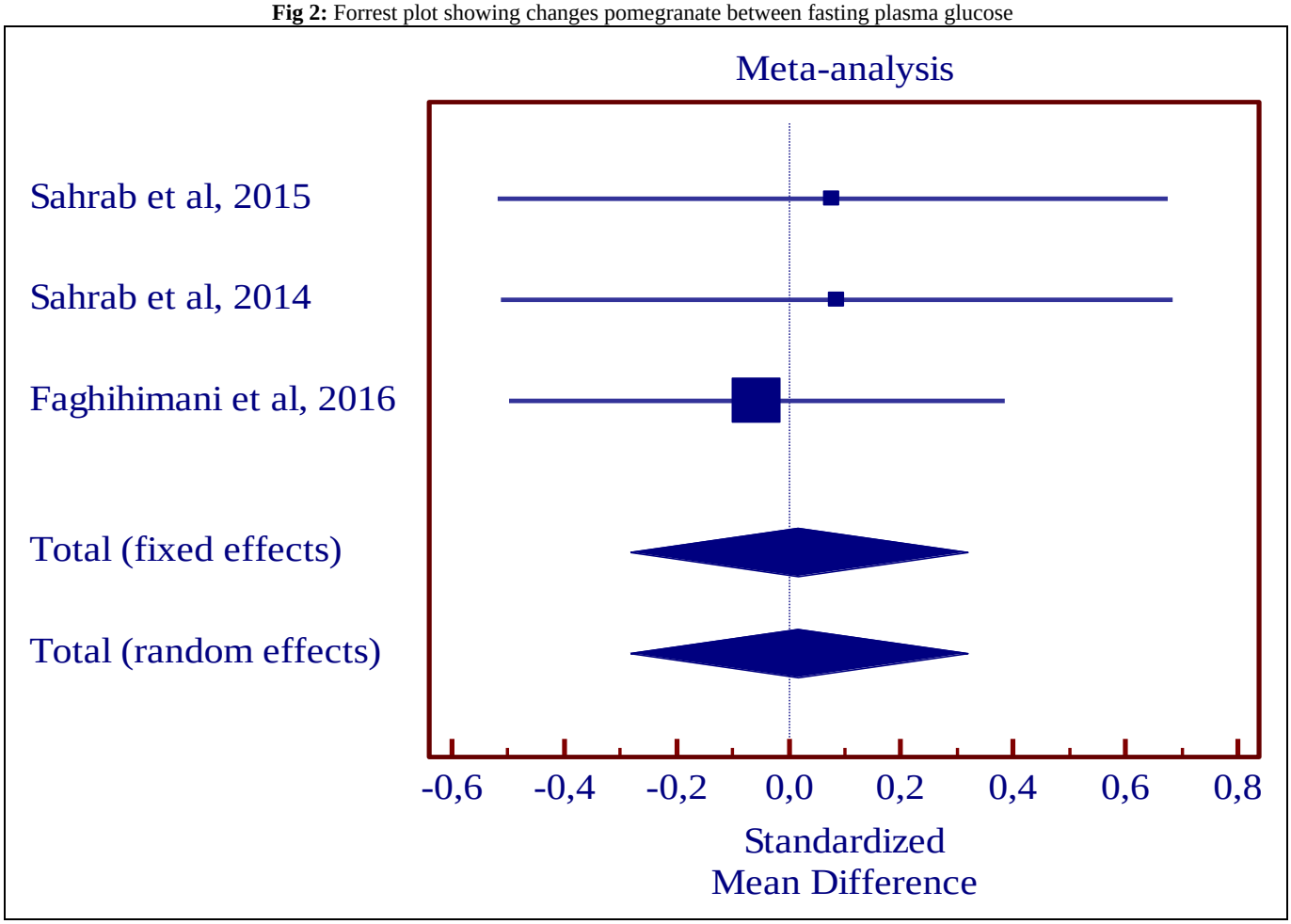

Fig 3: Forrest plot showing changes pomegranate between fasting plasma glucose in type 2 diabetes mellitus

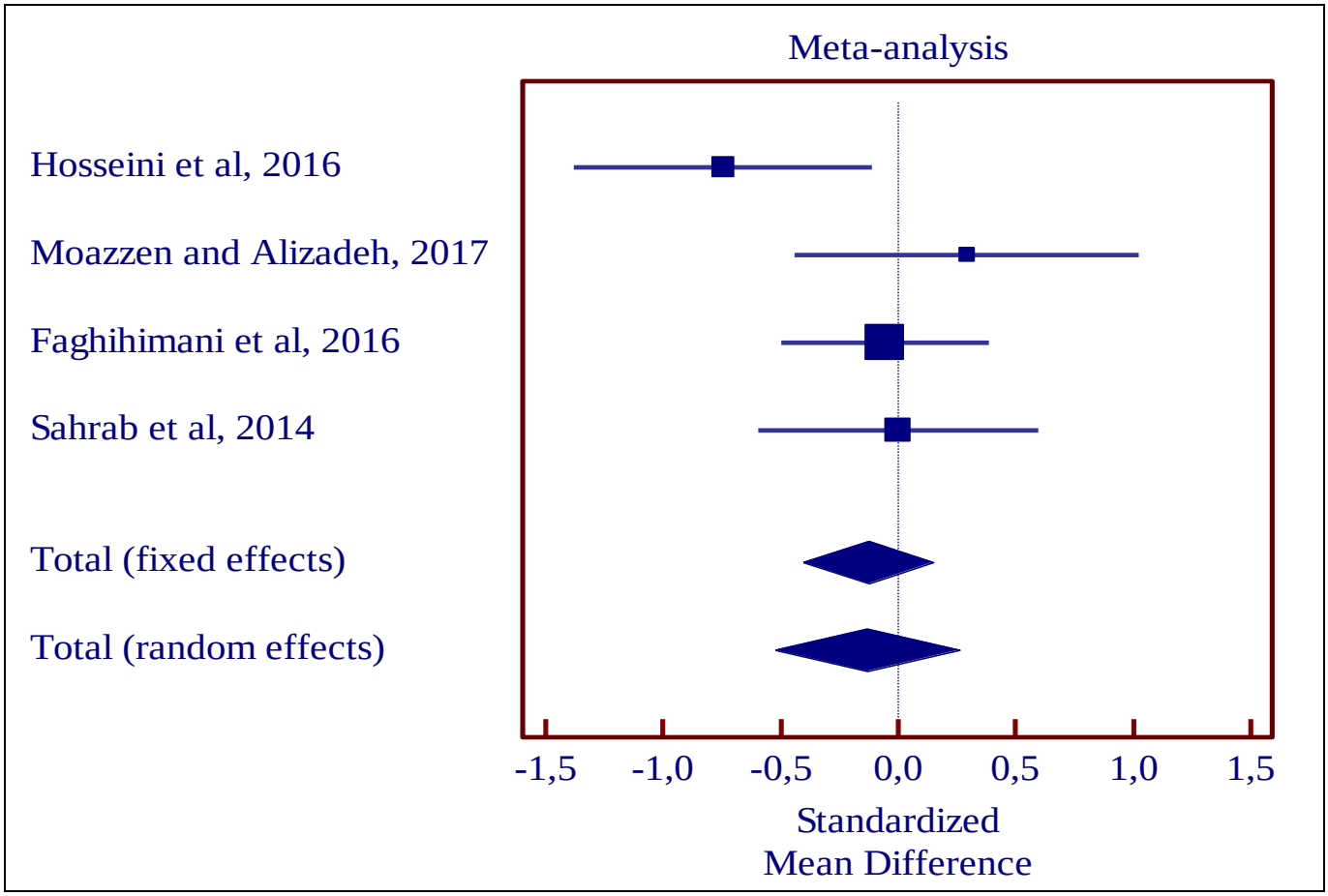

Fig 4: Forrest plot showing changes pomegranate between insulin levels

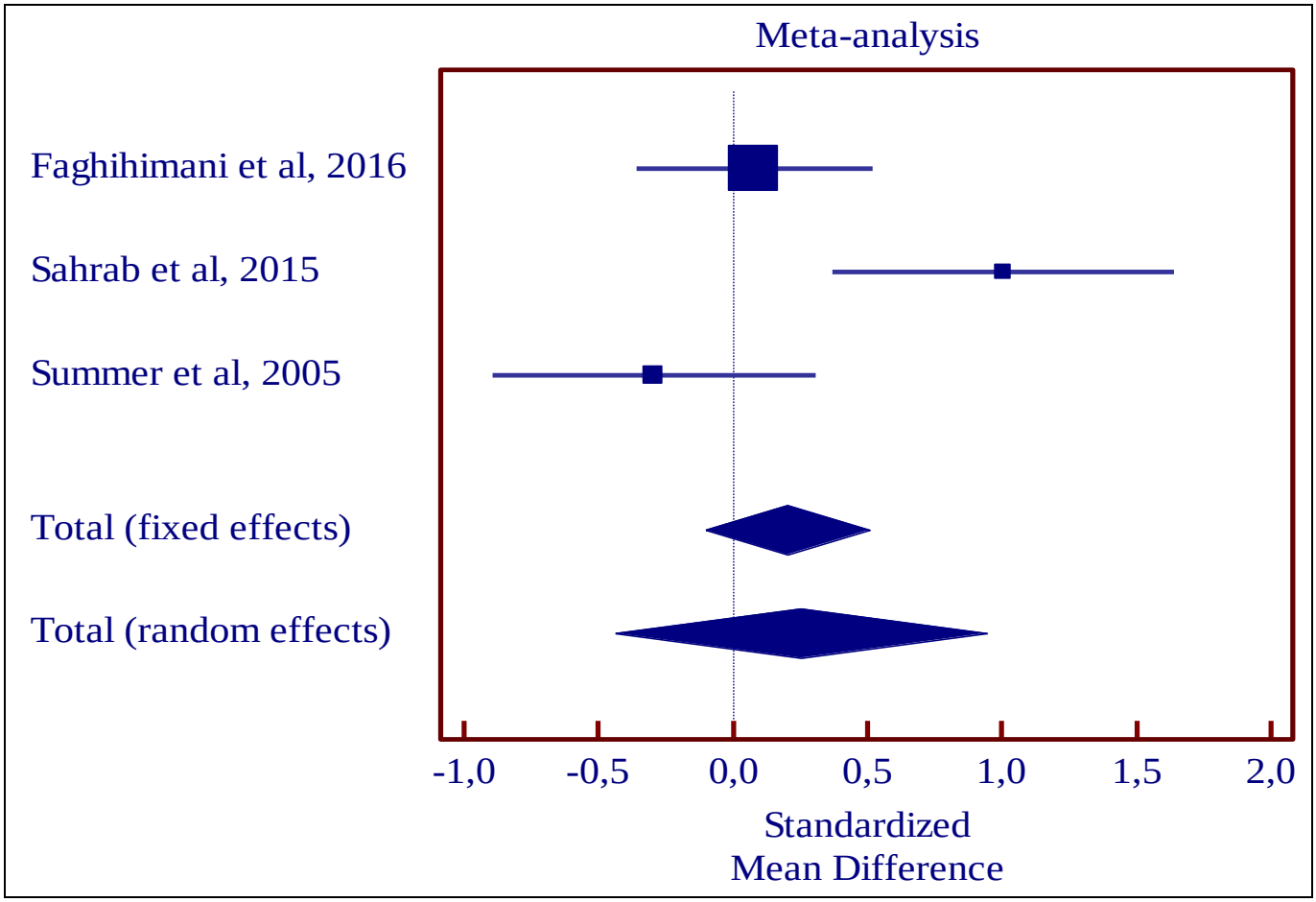

Fig 5: Forrest plot showing changes pomegranate between HbA1c

6. Conclusion

As a result of this meta-analysis, it was determined that pomegranate was effective in reducing fasting plasma glucose but it did not have a significant effect on patients with type 2 diabetes. Furthermore, it was found that pomegranate was effective in reducing insulin concentration but it did not have a significant effect on HbA1c value. It is recommended to increase the number of randomised controlled trials with special patient groups and to conduct meta-analysis studies with special patient groups in the future in order to identify the effect of pomegranate on blood glucose, insulin level, and HbA1c value.

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