The effect of garlic intake on glycemic control in humans: a systematic review and meta-analysis

Shaghayegh Emami[1,2], Mohammad Hossein Rouhani[1], Leila Azadbakht[1,3,4]
Shaghayegh Emami1,2, Mohammad Hossein Rouhani1, Leila Azadbakht1,3,4

[1]Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran; [2]School of Kinesiology and Health Science, Faculty of Health, York University, Toronto, Ontario, Canada; [3]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [4]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran - E-mail: l-azadbakht@sina.tums.ac.ir

Summary. *Objective:* To conduct a systematic review and meta-analysis of the effects of garlic intake on glycemic control in humans. *Methods:* We searched MEDLINE, EMBASE, EBSCO, and Science Direct as international data bases, and IranMedex, Magiran, and SID as local databases for studies on effect of garlic intake on glycemic control in humans published until March 2015. Our search included MeSH and non-MeSH terms. The quality of included studies was assessed using the Jadad scale. *Results:* Ten articles were eligible for current meta-analysis. The results showed that garlic intake could decrease fasting blood sugar (FBS) (P<0.001). To overcome the heterogeneity, studies were categorized into five subgroups. Accordingly, consumption of garlic as a food decreased FBS in comparison with garlic supplements (P=0.01). In addition, in comparison with healthy, diabetic, and hypercholesterolemic participants, garlic intake significantly reduced FBS in diabetic patients with hypercholesterolemia (P=0.001), and studies which had dependent design (cross-over or before-after) showed that garlic intake could decrease FBS (P<0.001). We could not observe any significant result through different subgroups of duration of intervention. Moreover, the results showed that garlic intake could decrease post prandial blood glucose (PPBG) (P=0.031), but could not significantly decrease Hemoglobin A_1C (HbA$_1$C) (P=0.1). *Conclusion:* The current analysis revealed that consumption of garlic as a food could significantly decrease FBS especially in patients suffering from both diabetes and hypercholesterolemia. However, it is suggested that garlic intake regardless of its source (food or supplement) might improve PPBG levels in humans.

Key words: garlic, allium sativum, glycemic control, diabetes, meta-analysis

Abbreviations

FBS: fasting blood sugar, PPBG: postprandial blood glucose, HbA$_1$C: hemoglobin A$_1$C

Introduction

Diabetes mellitus (DM) is an important common disease characterized by hyperglycemia that can cause retinopathy, nephropathy, and neuropathy (1). Incidence and prevalence of DM have dramatically increased in recent decades globally (2). The worldwide prevalence of diabetes inall age-groups was 2.8% in 2000 and is estimated to be 4.4% by 2030 (3). Diabetes prevalence has had a remarkable upward trend since 2005 in Iran, and more than four million Iranian diabetic adults were registered in 2011 (4). Good glycemic control can markedly reduce morbidity and mortality rate of diabetes (5). Post prandial blood glucose (PPBG), hemoglobin A$_1$C (HbA$_1$C), and fasting blood sugar (FBS) are used to assess glycemic control (6).

Diet plays an important role in control of diabetes. Plant-based foods such as vegetables and fruits considerably improve exaggerated post-prandial spikes in glucose, triglycerides, and inflammatory biomarkers concentration (7). Among subtypes of vegetables, garlic (Allium sativum) consumption has favorable effects on serum lipids (8), hypertension (9), and risk of cancer (10) according to several meta-analyses. These favorable biological effects of garlic are attributed to effective compounds like hydrogen sulfide and allicin (11-13), which have conflicting effects on risk of diabetes. A meta-analysis study shows the anti-diabetic effect of garlic components intake in rats, and suggests that consumption of effective components of garlic, including S-allylcysteinesulfoxide, S-methylcysteine-sulfoxide, and diallyltrisulfide may effectively reduce plasma glucose concentrations (14), but human studies are inconsistent. Some human studies showed that garlic intake couldsignificantly reduce FBS and PPBG (15, 16); however, other human studies have reported non-significant effects (17). Nevertheless, there is no meta- analysis study to pool the reported effect of garlic consumption on indicators of glycemic control among humans. Regarding to these inconsistencies, it is important and interesting to quantitatively review the effect of garlic intake on glycemic control.

We conducted a systematic review and meta-analysis to summarize the effect of garlic intake on glycemic control (FBS, HbA₁C, and PPBG) among humans.

Methods

Search strategy and inclusion criteria

We searched MEDLINE (www.pubmed.com), EMBASE (www.elsevier.com/online-tools/embase), EBSCO, and Science Direct (www.sciencedirect.com/science/journals) as international data bases, and IranMedex (www.iranmedex.com), Magiran (www.magiran.com), and SID (www.sid.ir) as local databases, and included the studies that were published until March 2015and had following keywords: "garlic" or "allyl sulfide" or "allium sativum" in the title, keywords or abstract. Search strategy was without language and time restrictions.

Exclusion criteria

Studies with cohort, cross-sectional or case–control design, review articles, and also studies in which garlic tablets were used in companion with other foods or drugs as an intervention, and net garlic effect was not assessed were excluded. Inclusion and exclusion criteria were checked through titles, abstracts, and, if necessary, full-texts.

Assessment of methodological quality

The Jadad scale was used to evaluate the methodological quality of eligible randomized clinical trials (RCTs) (18). This scale consists of three items: randomization (0-2 points), blinding (0-2 points), and withdrawals and dropouts (0-1 point).

Data extraction

Study characteristics (including first author's name, publication year, sample size, study design, study duration, dose and type of intervention), participants' information (sex and age), baseline and final concentrations or changes, and also standard error (SE) or standard deviation (SD) of FBS, HbA₁C, and PPBG were extracted from eligible studies. The units of biochemical values were converted to conventional units (e.g., for FBS, 1 mmol/L was converted to 18.02 mg/dL).

Data synthesis and analysis

When SDs were not directly available, they were calculated from SEs. STATA (version 11; StataCorp, College Station, TX) was used for performing statistical analyses. Effect sizes (changes), SE of changes, weighted mean differences and 95% CIs were calculated for FBS, HbA₁C, and PPBG values. Overall effect was calculated by using random effects model due to the high between study variations. Between studies heterogeneity was tested with the I^2 statistic. Subgroup analyses were performed in order to find the source of between studies heterogeneity. Random-effects model was selected for detecting the between subgroup heterogeneity.

Publication bias was assessed with the Begg's test. Also sensitivity analysis was performed to evaluate the effect of each study on the effect size.

Results

A total of 4384 articles were initially identified, and finally 11 studies included in qualitative review (figure1). All studies were randomized clinical trials (RCTs). Characteristics of eligible studies included in qualitative review have been presented in Table 1.8 studies had participants suffering from at least one of the diseases such as diabetes, hypercholesterolemia, and obesity (15, 16, 19, 20, 23-26), but participants of the other 3 studies were healthy (17, 21, 22). 7 studies used garlic tablets as their interventions (15-17, 20, 23, 25, 26), and 4 studies used garlic as a food for that purpose (19, 21, 22, 24). Although 7 studies showed that garlic intake had a significant hypoglycemic effect (15, 16, 19, 22-25), the other 4 studies did not show that (17, 20, 21, 26).We could not include the result of the one study (19) in quantitative analysis because duration of intervention in this study was considerably different from other studies. The mentioned study showed that garlic consumption can reduce post prandial blood glucose (PPBG) in diabetic patients. Consequently, 10 studies were included in quantitative review (15-17, 20-26) and 13 effect sizes were extracted.

According to the Jadad scale for assessment of methodological quality of eligible RCTs,among 10 studies included in meta-analysis, 5 studies had high quality (scores ≥ 3) (15-17, 23, 25) and the other 5 studies had low quality (scores ≤ 2) (20-22, 24, 26).

Ten articles reported fasting blood sugar (FBS) (15-17, 20-26). The result showed that garlic intake could decrease FBS (-9.14 mg/dL 95% CI: -13.55, -4.74; P<0.001). However, there was a significant between studies heterogeneity (I^2= 85.1; P<0.001). In order to find the source of variation, we categorized the studies into fivesubgroups according to "type of intervention", "study design", "duration of intervention", "health status of participants", and "quality of studies" (Table 2). Accordingly, consumption of garlic as a food, decreased FBS in comparison to garlic supplements (-6.85 mg/dL 95% CI: -12.37, -1.33; P=0.01). Although the heterogeneity in this subgroup was attenuated (I^2= 40.7; P=0.15), another member of this subgroup had significant heterogeneity (I^2= 88.3; P<0.001 for "garlic supplements" subgroup). A significant between subgroup heterogeneity was observed in these
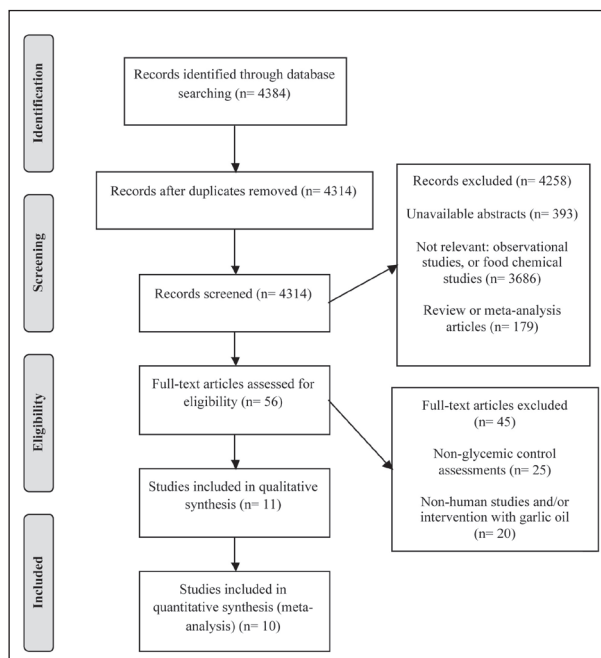

Figure 1. Flow chart of the systematic review and quantitative synthesize

subgroups (P<0.001) (figure2).According to health status of subjects, we defined 4 categories: healthy, diabetic, hypercholesterolemic, and diabetic patients with hypercholesterolemia. We found out that in comparison with healthy, diabetic, and hypercholesterolemic participants, garlic intake significantly reduced FBS in diabetic patients with hypercholesterolemia (-9.56 mg/dL 95% CI: -15.16, -3.97; P=0.001). Although there was no heterogeneity in this subgroup (I^2= 0.0; P=0.398), one of the other members of this subgroup had significant heterogeneity (I^2= 91.2; P<0.001 for "diabetic" subgroup). We did not observe a significant result in "healthy" subgroup. A significant between subgroup heterogeneity was observed in these subgroups (P<0.001). Furthermore, studies which had dependent design (cross-over or before-after) showed that garlic intake could decrease FBS (-7.21 mg/dL 95% CI: -10.75, -3.68; P<0.001). Although the heterogeneity in this subgroup was attenuated (I^2= 21.9; P=0.262), another member of this subgroup had significant heterogeneity (I^2= 90.7; P<0.001 for "independent" subgroup). A significant between subgroup heterogeneity was observed in current subgroup analysis (P<0.001). In addition, studies with low

Table 1. Characteristics of trials included in systematic review

First author (publication year)	Sample size (male: female)	Mean age (y)	Study design	Control	Intervention	Dose of intervention (gram per day)	Duration (day)	Health status of participants
Bakhsh (1984)	4 (NM*)	32.5	Cross-over	Fat-rich diet	Fat-rich diet and garlic	40	7	Healthy
Ardakani (2005)	40 (NM)	47.5	Before-after	_	Tablet (garcin)	0.9	28	Diabetic and hypercholesterolemic
Parastooyi (2005)	50 (11:39)	55	Before-after	_	Garlic powder (garcin)	0.9	42	Diabetic and hypercholesterolemic
Mahmoodi_diabetes (2011)	30 (13:17)	45.2	Before-after	_	Raw garlic	10	42	Diabetic
Mahmoodi_hypercholesterolemia (2011)	30 (11:19)	42	Before-after	_	Raw garlic	10	42	hypercholesterolemic
Mahmoodi_diabetes and hyper cholesterolemia (2011)	25 (8:17)	46.2	Before-after	_	Raw garlic	10	42	Diabetic and hypercholesterolemic
Sobenin_monotherapy (2008)	20 (8:12)	48.2	Parallel	Placebo	Allicore	0.6	28	Diabetic
Sobenin_combined therapy (2008)	40 (18:22)	48.2	Parallel	Placebo	Allicore	0.6	28	Diabetic
Kumar (2013)	60 (NM)	52.5	Parallel	Metformin	Metformin + garlic (allium sativum) capsule	0.5	84	Diabetic and obese
Ashraf (2011)	54 (NM)	47.5	Parallel	Placebo + metformin	Tablet (0.6% allicin)+ metformin	0.9	168	Diabetic
Ebadi (2007)	60 (NM)	46	Parallel	Tablet (vitamin B1)	Tablet (garlic powder + allicin)	2.4	90	Diabetic
Zhang (2001)	41 (16:25)	27	Parallel	Placebo	Garlic powder (garlicin)	1	77	Healthy
Ali (1995)	8 (8:0)	45	Before-after	_	Fresh garlic	3	112	Healthy
Zamaninoor (2006)	24 (13:11)	49.4	Before-after	_	Fresh garlic	20	2	Diabetic

quality also showed that garlic intake could decrease FBS (-7.21 mg/dL 95% CI: -10.75, -3.68; P<0.001) and the heterogeneity in this subgroup was attenuated (I^2= 21.9; P=0.262); however, studies with high quality were not reliable because of their high subgroup heterogeneity(I^2= 90.7; P<0.001). A significant between subgroup heterogeneity was observed in this subgroup analysis (P<0.001).We could not observe any significant result through different subgroups of duration of intervention.

Only 2 studies had reported PPBG (16, 20). The result showed that garlic intake could decrease PPBG (-5.35 mg/dL 95% CI: -10.20, -0.50; P=0.031). There was no heterogeneity between studies (I^2= 0.0; P=0.674) (figure3).
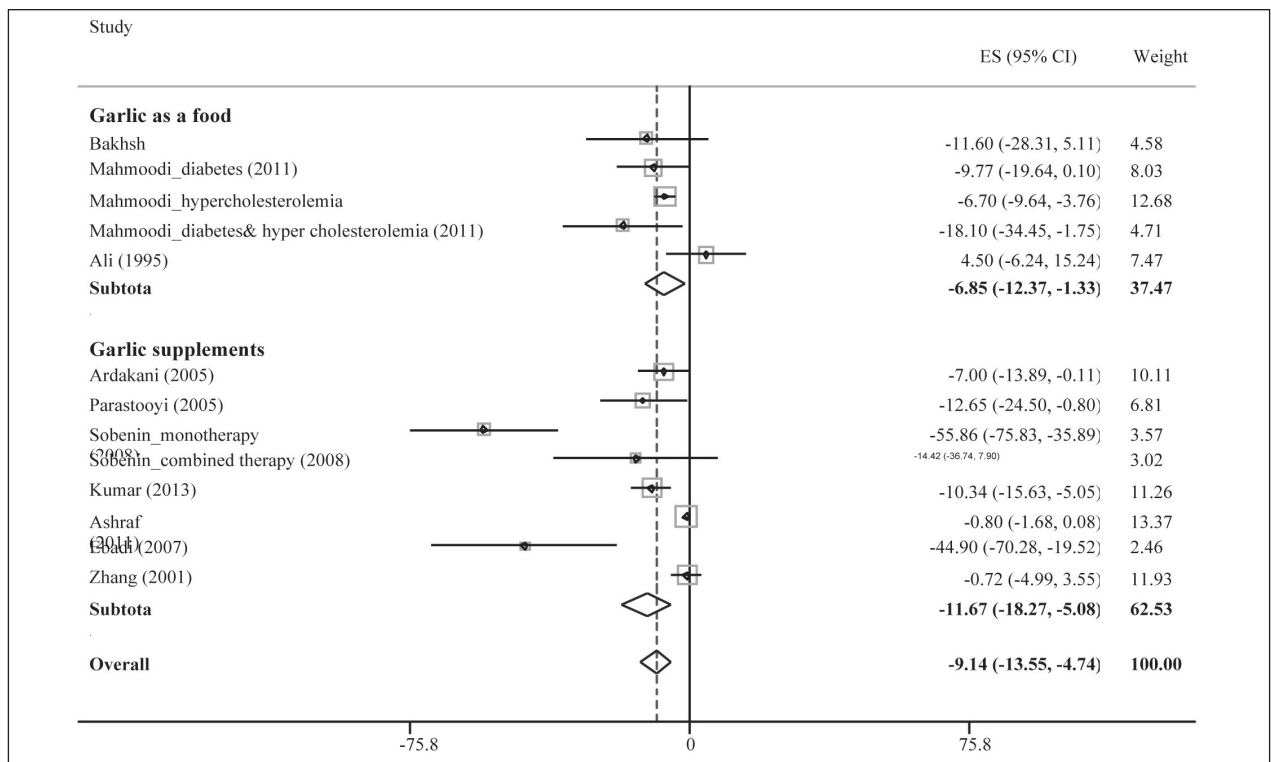
HbA$_1$C was measured in 4 studies (16, 23, 24, 26). The result showed that garlic intake could not significantly decrease HbA$_1$C (-0.16% 95% CI: -0.36, 0.03; P=0.1). There was not a significant heterogeneity between studies (I^2= 42.2; P=0.124).

The results of sensitivity analysis demonstrated that excluding any other study could not significantly affect overall effect sizes for "FBS" and "PPBG". However, excluding Mahmoodi et al. study on hypercho-

Table 2. Subgroup analyses for evaluating the effect of garlic intake on fasting blood sugar (FBS)

Pooled variable	Categorized by	Subgroups (number of effect size in each subgroup)	Effect size[1]	95% CI	P	I-squared	P for heterogeneity	P for between subgroup heterogeneity
Mean of fasting blood sugar (FBS)	Overall	-	-9.14	-13.55, -4.74	<0.001	85.1	<0.001	-
	Type of intervention	Garlic as a food (5)	-6.85	-12.37, -1.33	0.015	40.7	0.150	<0.001
		Garlic supplements (8)	-11.67	-18.27, -5.08	0.001	88.3	<0.001	
	Study design	Independent (6)	-13.24	-21.52, -4.95	0.002	90.7	<0.001	<0.001
		Dependent (7)	-7.21	-10.75, -3.68	<0.001	21.9	0.262	
	Duration of intervention	≤ 42 days (8)	-13.89	-20.84, -6.94	<0.001	72.5	0.001	<0.001
		> 42 days (5)	-4.25	-10.00, 1.50	0.147	83.8	<0.001	
	Health status of participants	Healthy (3)	-0.68	-6.16, 4.81	0.808	21.1	0.282	<0.001
		Diabetic with hypercholesterolemia (3)	-9.56	-15.16, -3.97	0.001	0.0	0.398	
		Diabetic (6)	-18.00	-28.90, -7.10	0.001	91.2	<0.001	
		Hypercholesterolemic (1)	-6.70	-9.64, -3.76	<0.001	-	-	
	Quality of studies	Low (7)	-7.21	-10.75, -3.68	<0.001	21.9	0.262	<0.001
		High (6)	-9.14	-13.55, -4.74	0.002	90.7	<0.001	

[1]*Random effect models were used for calculating pooled effect size in all cases.*

Study	ES (95% CI)	Weight
Garlic as a food		
Bakhsh	-11.60 (-28.31, 5.11)	4.58
Mahmoodi_diabetes (2011)	-9.77 (-19.64, 0.10)	8.03
Mahmoodi_hypercholesterolemia	-6.70 (-9.64, -3.76)	12.68
Mahmoodi_diabetes& hyper cholesterolemia (2011)	-18.10 (-34.45, -1.75)	4.71
Ali (1995)	4.50 (-6.24, 15.24)	7.47
Subtota	**-6.85 (-12.37, -1.33)**	**37.47**
Garlic supplements		
Ardakani (2005)	-7.00 (-13.89, -0.11)	10.11
Parastooyi (2005)	-12.65 (-24.50, -0.80)	6.81
Sobenin_monotherapy (2008)	-55.86 (-75.83, -35.89)	3.57
Sobenin_combined therapy (2008)	-14.42 (-36.74, 7.90)	3.02
Kumar (2013)	-10.34 (-15.63, -5.05)	11.26
Ashraf (2014)	-0.80 (-1.68, 0.08)	13.37
Isbah (2007)	-44.90 (-70.28, -19.52)	2.46
Zhang (2001)	-0.72 (-4.99, 3.55)	11.93
Subtota	**-11.67 (-18.27, -5.08)**	**62.53**
Overall	**-9.14 (-13.55, -4.74)**	**100.00**

Figure 2. Effect of garlic as a food in comparison with garlic supplements on fasting blood sugar (FBS)

lesterolemic patients (24) could apparently change the overall effect of "HbA₁C" to significant (-0.25% 95% CI: -0.43, -0.08). This may be due to the health status of participants, because HbA₁C does not have considerable changes in patients with hypercholesterolemia. Moreover, we could not detect any evidence supporting publication bias (P=0.360 for "FBS", P=1.000 for "PPBG", and P=0.452 for "HbA₁C", Begg's test).

Discussion

Thefindings of this systematic review and meta-analysis showed that compared with garlic supplements, garlic as a food, decreased FBS in diabetic patients with hypercholesterolemia. Furthermore, these findings showed that garlic intake could decrease PPBG. However, we could not find any significant effect of garlic intake on HbA₁C.

The result showed that garlic as a food was more effective than garlic supplements. This might be justified by more efficaciesof effective compounds in garlic as a food. Although supplements mostly consist of one or two effective compounds, a combination of different compounds is usually available in different foods. Hence, therapeutic characteristics of a food cannot be attributed to only one or two components, and the interaction of different components may cause these characteristics.

Comparing foods with supplements in order to find out which can be more effective has long been a considerable issue. However, most documents showed that foods might be more helpful compared to supplements. There are several examples in the field of food and nutrition. For instance, according to American Heart Association, soy products are more beneficial than soy isoflavones supplements for health (27). In addition, there was a review article that suggested tomato-based foods could be more effective than lycopene supplementation for improvement of cardiovascular health (28), and thatcould be a supportive evidence for comparing an effective compound taken through food sources with the one taken through supplement sources. Furthermore, consumption of supplements containing high dose and pure components which are extracted from food sources can cause negative effects that do not result from food intakes. For example, even though fish oil supplements intake could significantly increase cardiac and sudden deaths in UK men, consumption of oily fish did not show this effect (29). The results of our systematic review and meta-analysis showed that superiority of foods over supplements was applicable to garlic, and garlic as a food was more effective than garlic supplements for reducing FBS.

In the present meta-analysis, improvement of FBS level was more considerable in patients suffering from both diabetes and hypercholesterolemia in
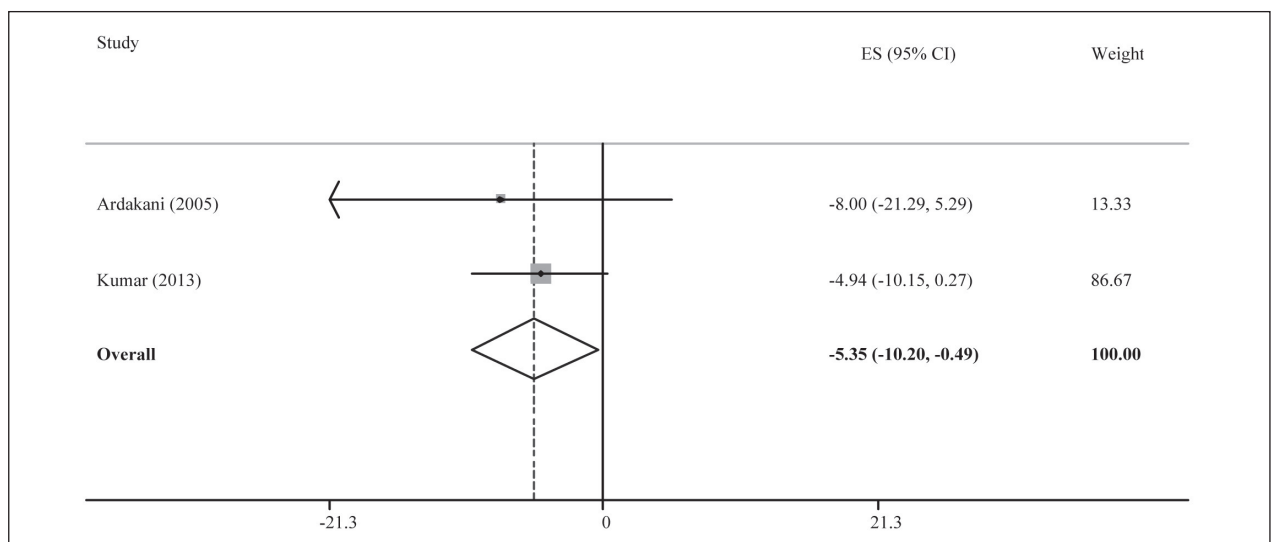

Study	ES (95% CI)	Weight
Ardakani (2005)	-8.00 (-21.29, 5.29)	13.33
Kumar (2013)	-4.94 (-10.15, 0.27)	86.67
Overall	**-5.35 (-10.20, -0.49)**	**100.00**

-21.3   0   21.3

Figure 3. Effect of garlic intake on post prandial blood glucose (PPBG)

comparison with healthy, diabetic, and hypercholesterolemic participants, because first, FBS level is not an issue in healthy or hypercholesterolemic people and second, there is a positive correlation between blood sugar and cholesterol (30). So, FBS level is higher in diabetic patients with hypercholesterolemia in comparison with diabetic patients, and thatwas also shown in tables of Mahmoodi's study (24). Hence, the reduction of FBS level will be more distinguishable in diabetic patients with hypercholesterolemia.

Even though the current study suggested that garlic intake could decrease PPBG, it cannot be considered as a reliable result due to the fact that only two studies had reported PPBG. Accordingly, more studies are needed to investigate the effect of garlic intake on PPBG in humans. However, Moradabadi et al showed that garlic extract decreased PPBG in diabetic rats (31). The mechanism responsible for garlic's ameliorative effects on PPBG and FBS could be increased insulin secretion and sensitivity (16). Garlic can elevate the transportation of blood glucose to the peripheral tissues, and thereby increase insulin response which enhances the conversion of the inactive form of glycogen synthetase to its active form that results in augmentation of conversion of blood glucose into glycogen (32). Garlic may also elevate insulin release from its bound form (33).

We could not find any significant effect of garlic intake on HbA_1C, while some human studies declared that garlic intake could significantly decrease HbA_1C (23). This might be due to inadequate study durations. According to WHO report, HbA_1C can reflect average plasma glucose over the previous 56 to 84 days (34). However, most of studies included in this systematic review and meta-analysis had measured HbA_1C earlier than 56 days after their interventions; and this resulted in interaction of before and after intervention diets and consequentlyattenuated the effect of garlic as an intervention on HbA_1C.Therefore, it is recommended that future studies consider the range of time recommended by WHO for their investigations.

According to our results, the heterogeneity between studies was high in most cases. Some variables such as type of intervention, study design, duration of intervention, health status of participants, and quality of studies seemed to be the most probable sources of heterogeneity, so we ran several subgroup analyses based on these variables. Despite the differences between cross-over and before-after studies, we considered them as one subgroup that was"dependent design", because we only had one cross-over study.In addition, it was not possible to include all probable sources of heterogeneity, such as gender and age of participants due to the fact that with more subgroup analyses, the number of studies in each subgroup would be decreased. Moreover, we could not include the dose of intervention as a source of heterogeneity regarding to the high variety of garlic tablets used in studies. Consequently, more precise studies are recommended in purpose of presenting more reliable results.

The most important strength of the current study is that it is the first systematic review and meta-analysis conducted to summarize the effect of garlic intake on glycemic control (including FBS, PPBG, and HbA_1C) in humans. According to the fact that scientists are interested in finding new ways to control diabetes, this study can suggest a non-chemical way to control diabetes besides the idea for future studies. The other strengths include various subgroup analyses, and searching not only international but also local databases.

There were some limitations for this study. First, the number of studies which assessed the effect of garlic intake on PPBG was not enough to conduct a comprehensive systematic review and meta-analysis. Second, there wasno study with appropriate duration of intervention for investigating the effect of garlic intake on HbA_1C. In other words, studies that reported the effect of garlic intake on HbA_1C were not long-term enough to assess the precise effect. Hence, more sufficiently long-term studies are required to investigate the effect of garlic intake on PPBG and HbA_1C.

Conclusion

In conclusion, the results revealed that consumption of garlic as a food could significantly decrease FBS especially in patients suffering from both diabetes and hypercholesterolemia. However, it is suggested that garlic intake regardless of its source (food or supplement) might improve PPBG levels in humans.

Teaching points

- Garlic intake (food + supplements) decreases fasting blood sugar (FBS).
- Consumption of garlic as a food decreases FBS in comparison with garlic supplements.
- Garlic intake shows more FBS reduction in diabetic patients with hypercholesterolemia.
- Garlic intake decreases post prandial blood glucose (PPBG).
- Garlic intake does not significantly decrease Hemoglobin A_1C (HbA_1C).

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Correspondence:
Leila Azadbakht, PhD
Department of Community Nutrition
School of Nutrition and Food Science
Isfahan University of Medical Sciences
PO Box 81745 Isfahan - Iran
Tel: +98 311 792-2719
Fax: +98 311 6682509
E-mail: l-azadbakht@sina.tums.ac.ir