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Effects of Paleolithic Diet on Glucose Control in Adults: A Systematic Review and Meta-analysis of Controlled Clinical Trials

Mohammad Mohammadi; MSc[1,2], Hamed Mohammadi; MSc[3,4], Ehsan Ghaedi; BSc[5], Nahid Ramezani-Jolfaie; MSc[1,2*] & Amin Salehi-Abargouei; PhD[1,2]

[1] *Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*
[2] *Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*
[3] *Food Security Research Center, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.*
[4] *Students' Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran.*
[5] *Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.*

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SYSTEMATIC REVIEW and META-ANALYSIS ARTICLE

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****Corresponding author:***
Ramezani.n.j@gmail.com
PhD candidate in Nutritional Sciences, Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Postal code: 1449614535
Tel: +98-35- 31492136

ABSTRACT

Background: Although the results were conflicting, the Paleolithic diet (PD) was proposed to be effective in improvement of metabolic status. We aimed to conduct a systematic review and meta-analysis on the randomized controlled clinical trials (RCTs) evaluating the effects of PD on glycemic markers. **Methods:** Online databases such as PubMed, Scopus, Web of Science, and Google Scholar were searched up to December 2017 without any restrictions. The weighted mean difference (WMD) was also calculated using random effects model. **Results:** Eventually, eight good quality studies were included in the present systematic review and meta-analysis. The pooled analysis showed that although adherence to the PD led to reduction of fasting blood glucose (FBG) concentrations, it was no statistically significant (WMD = -0.31, 95% CI: -0.70, 0.07, *P* = 0.11). Moreover, compared with the control diets, the PD consumption did not significantly affect other glycemic markers such as 2-h post-prandial blood glucose (2h PBG), insulin, homeostasis model assessment for insulin resistance (HOMA-IR), and Hemoglobin A1c (HbA1c). **Conclusions:** Adherence to the PD had no significant effect on the glycemic markers, but reduction was observed in FBG levels.

Keywords: *Paleolithic diet; Glycemic markers; Systematic review; Meta-analysis*.

Introduction

Type 2 diabetes mellitus (T2DM), one of the most serious current health problems, is a chronic metabolic disease characterized by persistent hyperglycemia due to deficiencies in

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insulin production and/or insulin resistance (IR) (Ahangarpour *et al.*, 2017). The prevalence of diabetes was estimated to be 9 percent in 2014 among adults (WHO, 2014). Based on the predictions from world health organization (WHO), the global prevalence of T2DM will rise from 171 million in 2000 to 366 million people by 2030 (Parham *et al.*, 2014). Prolonged increased glucose level in T2DM causes many micro-vascular and macro-vascular complications such as neuropathy, retinopathy, nephropathy, and cardiovascular disorders. It also increases mortality and morbidity among the patients (Ahangarpour *et al.*, 2017, Chan and Tang, 2015).

It has been recommended that the fasting blood glucose (FBG), 2-h post-prandial blood glucose (2h PBG), and hemoglobin A1c (HbA1c) could be considered as the standard glycemic markers for the assessment of T2DM and pre-diabetes status (Carson *et al.*, 2016). Moreover, homeostasis model assessment, as a useful clinical index, has been widely used to evaluate the insulin resistance (HOMA-IR) (Qu *et al.*, 2011).

Diet modification is considered as one of the cornerstones in T2DM management, but we are faced with paucity of evidences about the appropriate approach for controlling hyperglycemia (Association, 2016). Moreover, there is uncertainty concerning the caloric intake from carbohydrate, fat, and protein for patients with T2DM (Evert *et al.*, 2014). A wide variety of dietary patterns must be investigated to manage glycemic control and T2DM and to protect against its complications.

Today, the dietary pattern taken by our ancestors during the Paleolithic era has been focused by many researchers (the 'Old Stone Age,' 2.5 million–10,000 years ago). Anthropologic evidence from fossils, archeological evidence, and existing hunter-gatherer tribes around the world revealed that the ancient hunter-gatherer humans had Paleolithic diet (PD) (Whalen *et al.*, 2017). This diet is described as a mainly plant food-based diet, with a wide variety of vegetables, roots, nuts, fruits, lean meat, fish, and eggs but not grains, dairy products, processed foods, sugars, and added salt (Jönsson *et al.*, 2009). The PDs are naturally lower in sodium content while higher in potassium, antioxidants, vitamins C and E, carotenes, micronutrients, and fiber (Cordain, 2002, Österdahl *et al.*, 2008).

Studies of extant hunter-gatherer people around the world such as Kitava, Papua New Guinea showed low prevalence of degenerative diseases among them (Metzgar *et al.*, 2011). It was also indicated that this diet could be appropriate to prevent insulin resistance and glucose intolerance (Lindeberg *et al.*, 2003). Therefore, research topics such as the clinical importance of PD pattern and models of disease prevention were discussed in the literature.

Although a number of randomized controlled clinical trials (RCTs) have been recently published on the effects of PD, we are still faced with lack of research evidence regarding its clinical benefits. Studies which systematically reviewed the current evidences are also scarce. Therefore, the aim of present systematic review and meta-analysis of published RCTs was to evaluate the effect of the PD pattern on the glycemic indices and to quantify its possible hypoglycemic effects.

Materials and Methods

Search strategy: This study was designed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Picot *et al.*, 2012). An in-depth search was carried out to identify the related published literature throughout the databases of PubMed, ISI Web of Science, Scopus, and Google Scholar databases up to December 2017 using the following key words: "Paleolithic diet", "Paleolithic nutrition", stone age diet", "stone age nutrition", "caveman diet", "caveman nutrition", "Hunter-Gatherer diet", "Hunter-Gatherer nutrition", Paleolithic-type diet", Paleolithic-type nutrition".

Study selection: Titles and abstracts of all articles retrieved from the initial search were evaluated independently by two reviewers (Mohammadi M and Mohammadi H). The original studies were included if they met the following inclusion criteria: (1) applied a randomized-controlled clinical trial design; (2) were conducted among human adults (aged $\geq$ 18 years); (2) investigated the impact of the PD on glycemic status; and (3) reported the sufficient information on serum glycemic biomarkers in both Paleolithic and control diet. Articles that did not meet the inclusion criteria were excluded using a screen check list with a hierarchical approach. Exclusion criteria were: (1) uncontrolled trials; (2) participants aged < 18 years; (3) use of other interventions such as exercise along with the PD; (4) experimental studies; and (5) reviews, letters, editorial articles, or case reports. In the case that several papers reported similar data, we used the study with the largest population group.

Data extraction: The required data were extracted from the eligible studies: first author's name; publication year; research design; gender and age of participants; sample size, duration of intervention, as well as the type of intervention and control diets. Furthermore, the mean and standard deviation (SD) of indices related to glycemic control and insulin resistance were extracted at baseline and end of study. The extracted data were checked by three independent researchers (Mohammadi M, Mohammadi H and Ramezani-Jolfaie N) and rechecked by other authors to diminish the possible errors.

Quality assessment: A systematic assessment of bias was conducted on the included studies using the Cochrane criteria by two reviewers (Mohammadi M and Mohammadi H) (Higgins and Green, 2011). The quality of all included studies was assessed by the following items: adequacy of sequence generation, allocation concealment, blinding, illuminating of dropouts (imperfect outcome data), selective outcome reporting, and other potential causes of bias. Based on the Cochrane Handbook recommendations, a judgment of "yes" was considered as low risk of bias, "no" was perceived as high risk of bias, and "unclear" was taken as blurred or unidentified risk of bias. If RCTs had low risk in two risk domains or two to four risk domains, they were considered to have fair and high quality, respectively.

Data analysis: For each glycemic control index, we calculated the mean (SD) at the baseline and after the intervention for the PD and control groups. To calculate the pooled effect size for FBG, 2h PBG, insulin, HOMA-IR, and HbA1c, we used the random effects model. Between-study heterogeneity was evaluated using Cochran's Q test and I-square (I^2). To evaluate the possible effects of individual studies on the final results, an influence analysis was conducted (Tobias, 1999). We also used Begg's rank correlation test and Egger's regression asymmetry test to evaluate the publication bias. Statistical analysis was performed using STATA, version 11.2 (Stata Corp, College Station, TX). The statistical significant values were defined as P values <0.05

Results

Study selection: The electronic search on literature yielded 2722 titles, of which 26 were reviewed in full text considering the criteria of eligibility. Of these studies, 19 papers were excluded for the following reasons: 1) seven studies reported no data related to our target outcomes (Baumgartner *et al.*, 2009, Frassetto *et al.*, 2013, Genoni *et al.*, 2016a, Jonsson *et al.*, 2010, Jonsson *et al.*, 2013, Lee *et al.*, 2017, Singh *et al.*, 2012); 2) six studies reported duplicated results (Andersson *et al.*, 2016, Blomquist *et al.*, 2017a, Blomquist *et al.*, 2017b, Boraxbekk *et al.*, 2015, Sandberg *et al.*, 2012, Stomby *et al.*, 2015); 3) four studies had single-arm design with no control group (Frassetto *et al.*, 2009, Osterdahl *et al.*, 2008, Ryberg *et al.*, 2013, Trexler *et al.*, 2013); 4) one study evaluated the effect of PD along with exercise (Otten *et al.*, 2016b); and 5) one study evaluated the acute effects of following the PD consumption (Bligh *et al.*, 2015). In addition, one additional study (Mellberg *et al.*, 2014) was added after the manual search of references. Eventually, eight eligible studies were included in the present systematic review and meta-analysis (Boers *et al.*, 2014, Chorell *et al.*, 2016, Genoni *et al.*, 2016b, Jönsson *et al.*, 2009, Lindeberg *et al.*, 2007, Masharani *et al.*, 2015, Mellberg *et al.*, 2014, Otten *et al.*, 2016a). The study selection process is shown in **Figure 1**.

Study characteristics: The included studies were published from 2007 to 2016 and were conducted in the United States (Masharani *et al.*, 2015), Australia (Genoni *et al.*, 2016b), Sweden (Chorell *et al.*, 2016, Jönsson *et al.*, 2009, Lindeberg *et al.*, 2007, Mellberg *et al.*, 2014, Otten *et al.*, 2016a), and Netherlands (Boers *et al.*, 2014). Seven trials were designed as parallel-group studies (Boers *et al.*, 2014, Chorell *et al.*, 2016, Genoni *et al.*, 2016b, Lindeberg *et al.*, 2007, Masharani *et al.*, 2015, Mellberg *et al.*, 2014, Otten *et al.*, 2016a) and one study had a crossover design (Jönsson *et al.*, 2009) with follow-up period of two weeks to two years. All studies were comparison trials, in which PD was compared with other dietary patterns. In these studies, guidelines such as Australian guide to healthy eating (AGHE), Nordic nutrition recommendations (NNR), dietary recommendations based on the guidelines of the American Diabetes Association (ADA), dietary recommendations based on the guidelines for a healthy diet of the Dutch Health Council, diabetes diet designed in accordance with current diabetes dietary guideline, and Consensus (Mediterranean-like) diet were applied.

The number of samples in these RCTs ranged from 13 to 61 participants with the mean age of 59 years. The participants had different health status including healthy people, postmenopausal women, patients with type 2 diabetes or ischemic heart disease, and individuals with characteristics of the metabolic syndrome. The characteristics of the included RCTs in the present systematic review and meta-analysis are listed in **Table 1**.

Risk of bias assessment: After evaluating the quality of eight final studies according to the Cochrane collaboration's risk of bias assessment tool, all RCTs were of good quality (Boers *et al.*, 2014, Chorell *et al.*, 2016, Genoni *et al.*, 2016b, Jönsson *et al.*, 2009, Lindeberg *et al.*, 2007, Mellberg *et al.*, 2014, Otten *et al.*, 2016a) except Masharani et al.'s study (Masharani *et al.*, 2015). This study had fair quality, in which no methods of allocation concealment and random sequence generation were reported. Moreover, since blinding was not possible to conduct dietary intervention trials, the blinding of participants and investigators was not considered throughout these studies. Findings of the quality assessment are illustrated in **Table 2**.

Meta-analysis: Six studies (including 210 participants) (Boers *et al.*, 2014, Genoni *et al.*, 2016b, Jönsson *et al.*, 2009, Lindeberg *et al.*, 2007, Masharani *et al.*, 2015, Mellberg *et al.*, 2014) examined the effect of PD pattern on FBG levels. The overall results showed that although adherence to PD led to reduction of FBG concentrations, it was not statistically significant [weighted mean difference (WMD) = -0.31, 95% confidence interval (CI): -0.70, 0.07, P = 0.11; **Figure 2**]. No heterogeneity was found between the studies (Q statistic = 5.78, Cochrane Q test, P = 0.328, I^2 = 13.5%).

Five studies (including 186 participants) reported the effects of PD on serum insulin changes. Their results showed that PD consumption did not significantly affect the insulin levels in comparison with the control diets (WMD = 0.55, 95%CI: -1.81, 2.92, P = 0.647; **Figure 3**). The result of between-study heterogeneity was significant (Cochran's Q test, Q statistic = 18.49, P = 0.001, I^2 = 78.4%); however, due to the limited number of studies, we could not perform subgroup analysis to find the potential sources of this heterogeneity.

The overall result of meta-analysis of four studies (including 131 participants) (Boers *et al.*, 2014, Chorell *et al.*, 2016, Jönsson *et al.*, 2009, Lindeberg *et al.*, 2007) over the effects of the PD adherence on HOMA-IR showed no significant change (WMD = -0.33, 95%CI: -0.76, 0.09, P = 0.126; **Figure 4**) and no between-study heterogeneity (Cochran's Q test, Q statistic = 4.42, P = 0.219, I^2 = 32.2%).

Other outcomes such as HbA1c and 2h PBG were also reported in a few of studies; no significant results were observed after conducting the meta-analysis (HbA1c: WMD = -0.26, 95%CI: -0.73, 0.20, P = 0.274; 2h PBG: WMD = -1.49, 95%CI: -3.16, 0.16, P = 0.077). Furthermore, no heterogeneity was observed among the studies (HbA1c: Cochran's Q test, Q statistic = 0.05, P = 0.977, I^2 = 0%; 2h PBG: Cochran's Q test, Q statistic = 3.30, P = 0.069, I^2 = 69.7%).

Sensitivity analysis and publication bias: The sensitivity analysis was conducted for all parameters to assess the contribution of each study on the overall estimate. The results did not change after excluding any other study.

We found no evidence of publication bias in studies evaluating the effect of PD consumption on the levels of FBG (Begg's test, P = 0.707; Egger's test, P = 0.997), insulin (Begg's test, P = 0.806; Egger's test, P = 0.534), HOMA-IR (Begg's test, P = 0.308; Egger's test, P = 0.071), and HbA1c (Begg's test, P = 0.296; Egger's test, P = 0.154).

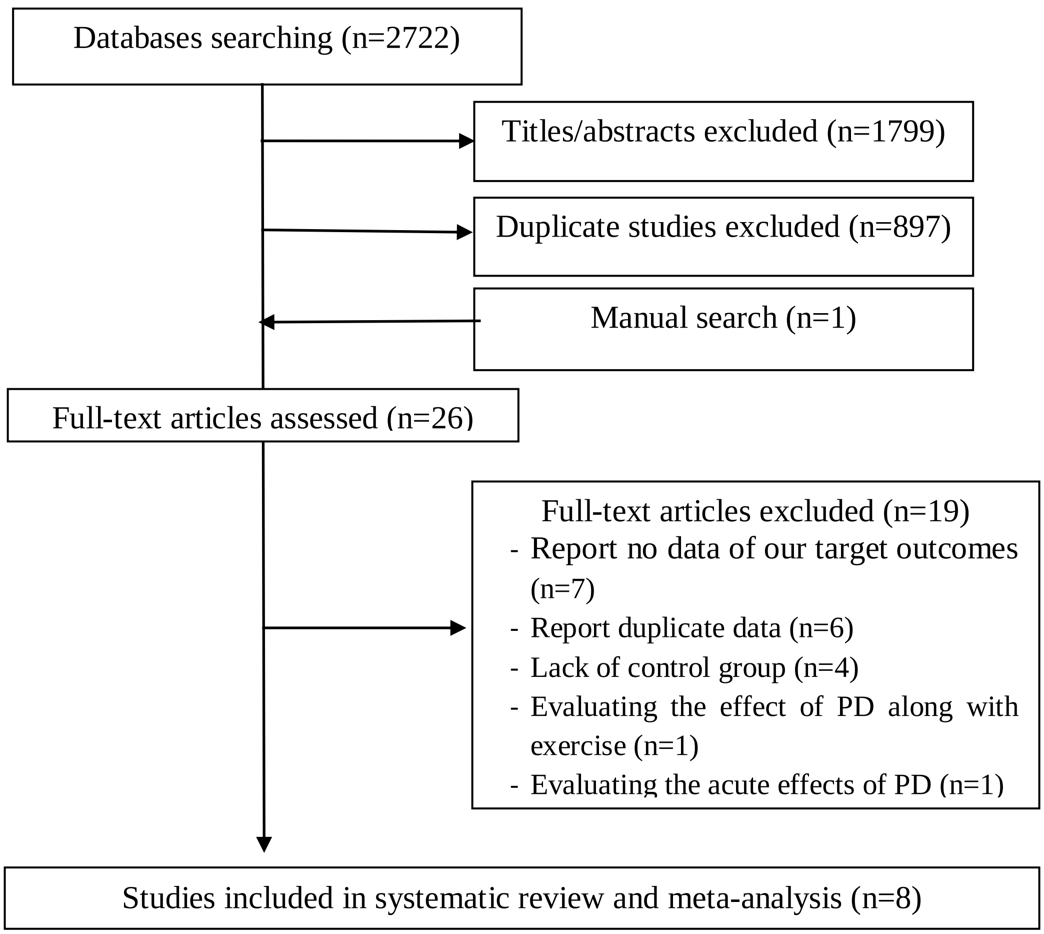

Figure 1. Flow chart representing study selection process.

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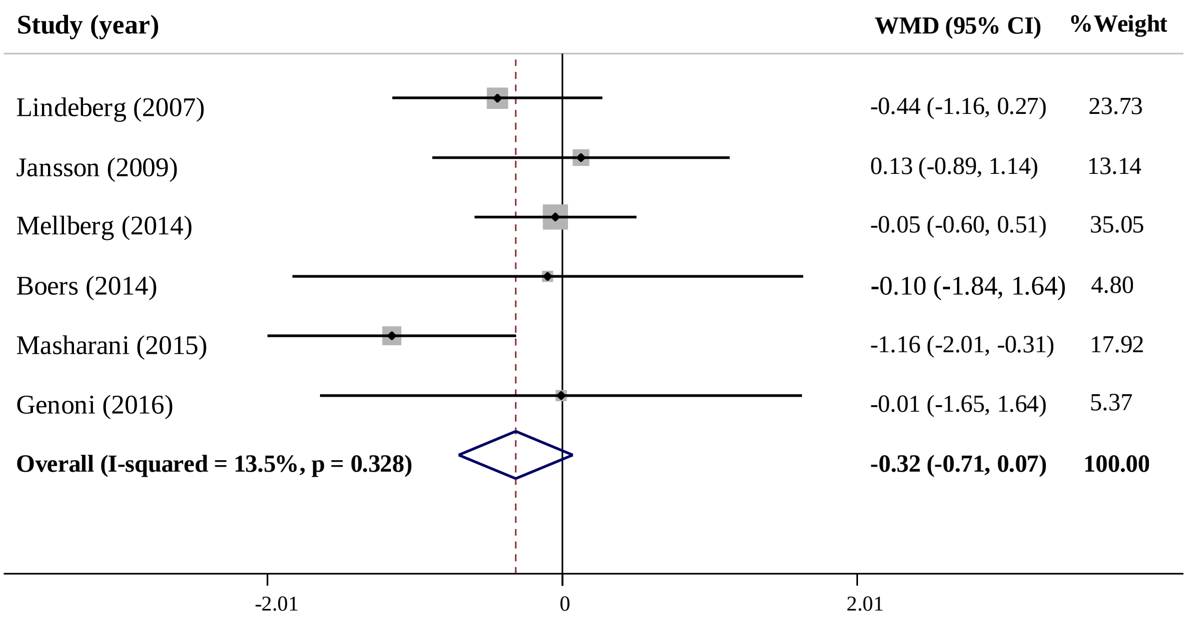

Figure 2. Forest plot of RCTs representing weighted mean difference in glucose change between the Paleolithic diet and control groups for all included studies.

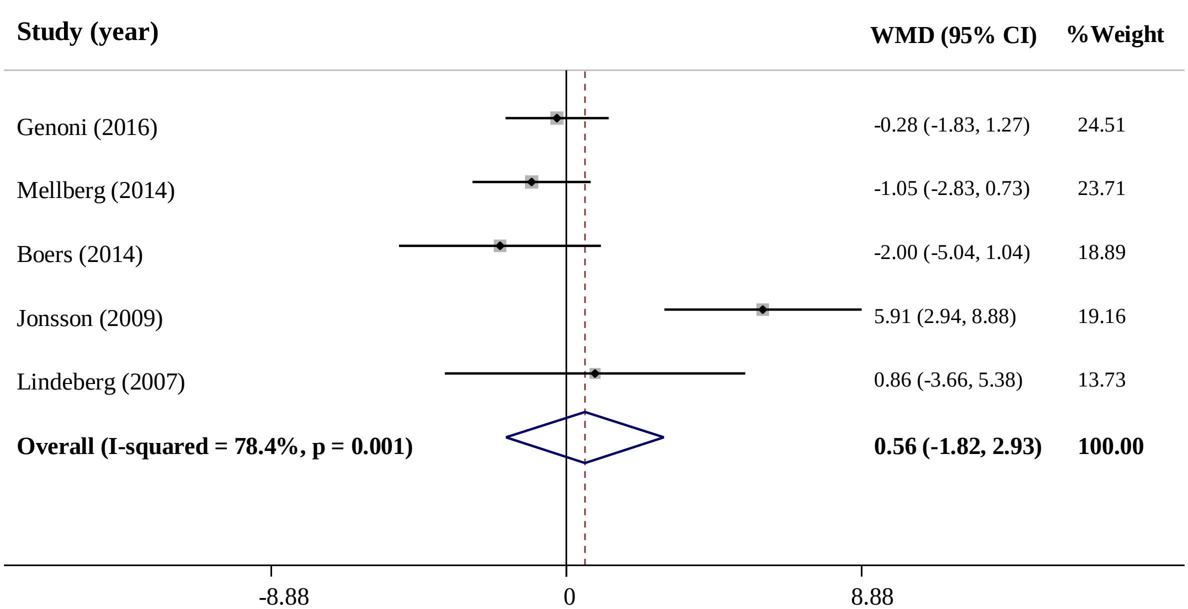

Figure 3. Forest plot of RCTs representing weighted mean difference in insulin change between the Paleolithic diet and control groups for all included studies.

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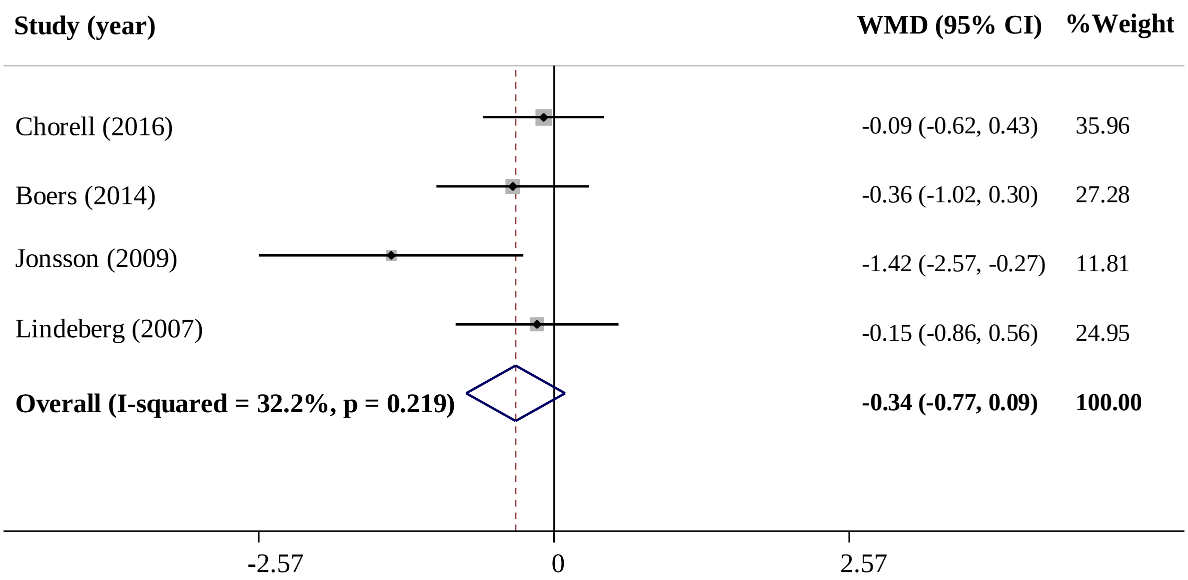

Figure 4. Forest plot of RCTs representing weighted mean difference in HOMA-IR change between the Paleolithic diet and control groups for all included studies.

Table 1. Characteristics of included randomized controlled clinical trials in the systematic review

First author (year)	Country	Number & sex (F/M)	Mean age (y)	RCT design	Duration (days)	Intervention diet	Control diet	Reported data	Notes about participants
Genoni (2016)	Australia	Intervention 22F Control 17F	Intervention 47 Control 47	Parallel	28	Paleolithic diet CHO: 27.8%, Fat: 39.8%, Pro: 26.8%	Australian Guide to Healthy Eating CHO: 40.6%, Fat: 32.6%, Pro: 21.7%	FBG Insulin	Healthy women
Chorell (2016)	Sweden	Intervention 31F Control 24F	Intervention 60 Control 61.1	Parallel	180	Paleolithic diet CHO: 30%, Fat: 40% Pro: 30%	Nordic Nutrition Recommendations CHO: 55-60%, Fat: 25-30%, Pro: 15%	HOMA-IR	Postmenopausal non-smoking women with a BMI ≥ 27 kg/m^2
Otten (2016)	Sweden	Intervention 25F Control 16F	Intervention 61 Control 62	Parallel	180	Paleolithic diet CHO: 30%, Fat: 40% Pro: 30%	Nordic Nutrition Recommendations CHO: 55-60%, Fat: 25-30%, Pro: 15%	2h PBG	Postmenopausal non-smoking women with a BMI ≥ 27 kg/m^2
Masharani (2015)	USA	Intervention 14NR Control 10NR	Intervention 58 Control 56	Parallel	21	Paleolithic diet CHO: 58.2%, Fat: 27%, Pro: 18.5%	A diet based on recommendations by the American Diabetes Association CHO: 54.4%, Fat: 28.8%, Pro: 20.3%	FBG HbA1c	Patients with type 2 diabetes
Mellberg (2014)	Sweden	Intervention 34F Control 27F	Intervention 59.5 Control 60.3	Parallel	720	Paleolithic diet CHO: 30%, Fat: 40% Pro: 30%	Nordic nutrition recommendations CHO: 55-60%, Fat: 25-30%, Pro: 15%	FBG Insulin	Postmenopausal non-smoking women with a BMI ≥ 27 kg/m^2
Boers (2014)	Netherlands	Intervention 13F/5M Control	Intervention 52 Control 55.4	Parallel	14	Paleolithic diet CHO: 32%, Fat: 41% Pro: 24%	Healthy reference diet CHO: 50%, Fat: 29% Pro: 17%	FBG Insulin HOMA-IR	Subjects with characteristics of the MetS

Jonsson (2009)	Sweden	3F/10M	64	Crossover	90	Paleolithic diet CHO: 32%, Fat: 39% Pro: 24%	Diabetes diet designed in accordance with current diabetes dietary guideline CHO: 42%, Fat: 34% Pro: 20%	FBG Insulin HbA1c HOMA-IR	Patients with type 2 diabetes
Lindeberg (2007)	Sweden	Intervention1 4M Control 15M	Intervention6 5 Control 57	Parallel	84	Paleolithic diet CHO: 40.2%, Fat: 26.9%, Pro: 27.9%	Consensus (Mediterranean-like) diet CHO: 51.7%, Fat: 24.7%, Pro: 20.5%	FBG 2h PBG Insulin HbA1c HOMA-IR	Ischemic heart disease patients with waist circumference >94 cm and increased blood glucose or known diabetes

F: female, M: male, NR: not reported, CHO: carbohydrate; Pro: protein, FBG: fasting blood glucose, 2h PBG: 2-h post-prandial blood glucose, HOMA-IR: homeostasis model assessment for insulin resistance, HbA1c: Hemoglobin A1c, MetS: metabolic syndrome

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Table 2- Risk of bias assessment for included randomized controlled clinical trails

	Genoni (2016)	Chorell (2016)	Otten (2015)	Masharani (2015)	Mellberg (2014)	Boers (2014)	Jonsson (2009)	Lindeberg (2007)
Random sequence generation (selection bias)	+	+	+	?	+	+	+	+
Allocation concealment (selection bias)	?	?	?	?	?	?	?	?
Blinding of participants and personnel (Performance bias)	-	-	-	-	-	-	-	-
Blinding of outcome assessment (Detection bias)	-	+	+	-	+	+	+	+
Incomplete outcome data (Attrition bias)	+	+	+	+	+	+	+	?
Selective reporting (Reporting bias)	+	+	+	+	+	+	+	+
Score	3	4	4	2	4	4	4	3
Overall quality	Good	Good	Good	Fair	Good	Good	Good	Good

Discussion

To best of our knowledge, the present systematic review and meta-analysis is the first study that assessed the effect of PD pattern on the glycemic control. Our meta-analysis of eight RCTs showed that this dietary pattern had no significant effects on glycemic markers, although reduction was observed in FBG levels.

The PD recommends avoidance of processed food, refined sugars, legumes, dairy, grains, and cereals. Instead, it advocates for the consumption plant foods including fruit, vegetables, nuts, roots and grass-fed meat, wild fish, and “healthy” saturated fat (O'dea, 1984). It was reported that PD could improve the insulin sensitivity and prevent insulin resistance (Lindeberg *et al.*, 2003). This pattern may be more satiating among patients with T2DM; this can be resulted from significant increase in plasma glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide, and peptide YY (PYY) following the PD consumption. The changes of these hormone levels were associated with a higher satiety score (Bligh *et al.*, 2015). Moreover, the higher protein content and amount of fruit and vegetable caused by its high contents of water (Davy *et al.*, 2008), may promote the satiating effect of the Paleolithic dietary pattern (Beasley *et al.*, 2009).

In comparison with regular diabetes diet, PD was lower in cereals, dairy products, potatoes, beans, and bakery foods but higher in fruits, vegetables, meat, and eggs. Therefore, it seems that this diet has lower total energy, carbohydrate, dietary glycemic load, fiber, and saturated fatty acids, but higher unsaturated fatty acids and dietary cholesterol (Klonoff, 2009). Moreover, PD provides higher amounts of protein, which can promote the weight loss compared with high-carbohydrate diets and consequently lead to favorable effects on risk reduction for metabolic diseases (Lasker *et al.*, 2008). However, it must be noted that in absence of changes in weight or energy intake, the PD is as efficient in improving the glucose, insulin, or HOMA-IR as a standard diet. Thus, even very short deficits in energy balance can improve the metabolic parameters (Gannon *et al.*, 1996).

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Previous meta-analysis reported that PD, compared with control diets, resulted in greater short-term improvements for FBG (20.16 mmol/L; 95% CI: 20.44, 0.11 mmol/L) (Manheimer *et al.*, 2015). However, only four studies with short duration were included in this review; therefore, the results are probably unreliable.

Lack of a significant decrease in levels of FBG, insulin, and HOMA-IR in our study may be partly explained by the fact that most of the participants had normal glucose tolerance at the baseline, which could reduce the possibility of improving the metabolic status (Mellberg *et al.*, 2014). Indeed, most studies over the effect of PD on insulin and insulin sensitivity were conducted among participants with a more pronounced metabolic dysfunction. This indicates an improvement in the glucose tolerance and cardiovascular risk markers (Jönsson *et al.*, 2010).

Glucose tolerance did not improve after reduction of carbohydrate intake in earlier dietary investigations (Noakes *et al.*, 2006, Pittas *et al.*, 2006). Diets with low glycemic load such as PD pattern can reduce the metabolic consequences of glucose intolerance; for example, they can delay the manifestation of diabetes, without necessarily improving the glucose tolerance (Gannon and Nuttall, 2006, Reaven, 2005). The potential impact of high protein intakes over long term periods as well as its association with hyperinsulinemia and insulin resistance require further investigations (Rietman *et al.*, 2014). However, weight loss may be a more significant modifier of metabolic syndrome risk compared with the type or quantity of protein intake (Hill *et al.*, 2015).

Some limitations exist in the present systematic review and meta-analysis that must be mentioned. First, there were not many studies on the PD and therefore, the total meta-analysis sample size was small. Second, the included trials were conducted among the individuals with different metabolic characteristics (i.e., patients with T2DM, postmenopausal, ischemic heart disease, metabolic syndrome, and healthy people). In addition, the intervention duration was various in different studies which might lead to different results. On the other hand, the results of most studies were not adjusted for confounding factors such as physical activity (Bassuk and Manson, 2005, Boulé *et al.*, 2001) and smoking (Eliasson, 2003), which were associated with glycemic indices. This meta-analysis had several strengths. It evaluated the effect of PD on several glycemic markers. Additionally, a comprehensive and systematical search was conducted to find all the relevant published literatures and subsequently Egger's test and Begg's test showed that the findings were not affected by publication bias.

Conclusions

The PD had no significant effect on glycemic markers; therefore, it is difficult to make strong conclusions about the long term benefits of this diet considering the short duration of interventions and small sample sizes of the included studies. Accordingly, additional studies are required to assess the anti-hyperglycemic effect of the PD in patients with hyperglycemia. Since avoidance of refined and extra sugars and processed, energy-dense food is in accordance with the available guidelines, more RCTs with more patients in longer period of time are required to determine its beneficial effects over other dietary advices.

Authors' contributions

Salehi-Abargouei A and Mohammadi M designed the research; Mohammadi M and Mohammadi H conducted the systematic search and study selection; Mohammadi M, Mohammadi H and Ramezani-Jolfaie N extracted data; Salehi-Abargouei A and Mohammadi M analyzed data; Mohammadi M, Mohammadi H and Ghaedi H wrote the manuscript; Salehi-Abargouei A and Ramezani-Jolfaie N edited the manuscript and all authors read and approved the final manuscript.

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Conflict of interest

The study was funded by Nutrition and Food Security research center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. There is no conflict of interest to report for present study.

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