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Does a High-Protein Diet Influence C-Reactive Protein Levels in Type 2 Diabetes? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Does a High-Protein Diet Influence C-Reactive Protein Levels in Type 2 Diabetes? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is associated with chronic low-grade inflammation, and one of the most common markers of systemic inflammation is C-reactive protein (CRP). Protein-rich dietary intake has been suggested as a potential method of improving metabolic and inflammatory conditions in patients with T2DM, yet its influence on CRP levels is unknown.

Methods: This meta-analysis and systematic review adhered to the PRISMA guidelines and screened articles through PubMed, Scopus, and Web of Science until November 2025. The selected randomized control trials assessed the effect of a high-protein diet on CRP levels among adults diagnosed with type 2 diabetes mellitus. Ten RCTs that involved 1,231 patients were included. Data were analyzed using a random-effects model, reporting results as WMDs with 95% CIs.

Results: High protein intake resulted in lower levels of CRP relative to controls (WMD = -0.039 mg/L; 95% CI: -0.072 to -0.007; P = 0.016). There was little heterogeneity among the studies included in the meta-analysis (I2 = 7.81%, P = 0.36), and no publication bias existed. Further analysis revealed greater reductions for those aged less than 55 years old, interventions exceeding 6 months in duration, sample size greater than 60 participants, BMI less than 35 kg/m2, and initial CRP greater than 3.5 mg/L. The sensitivity analysis demonstrated that the effect size was highly dependent on a particular study.

Conclusion: Although high protein intake has shown some effect in lowering levels of CRP in patients with type 2 diabetes mellitus (T2DM), this effect seems to be relatively insignificant. It is necessary to conduct further trials that will establish whether this effect is clinically significant at all.

Keywords: High protein diet, C-Reactive protein, Type 2 diabetes, Meta analysis

1. Introduction

T2DM has turned out to be one of the most prevalent metabolic diseases around the world and keeps on causing immense suffering to both health-care systems and patient wellbeing(1). As per estimates from IDF, there were around 536.6 million cases of people with diabetes aged between 20 and 79 years in the year 2021, which will reach 783.2 million by 2045(2). Importantly, more than 90% of these cases are attributed to T2DM (2). Given this rapidly increasing burden, identifying effective lifestyle and nutritional approaches to improve disease management and reduce long-term complications has become increasingly important.

Recent research has focused on the importance of chronic inflammation as part of the pathophysiological processes in type 2 diabetes mellitus (T2DM)(3). Studies have found that inflammation is not only the result of metabolic disorders but is also an active player in the development of insulin resistance and complications(3). Persistent hyperglycemia and metabolic imbalance can trigger oxidative stress, endothelial dysfunction, and inflammatory signaling pathways, collectively worsening cardiometabolic health in individuals with diabetes (3, 4). Inflammatory mechanisms have also been linked to both microvascular and macrovascular complications, highlighting inflammation as a potential therapeutic target in T2DM (5).

Among inflammatory biomarkers, C-reactive protein (CRP) has received particular attention due to its strong association with systemic inflammation and cardiometabolic risk (5, 6). CRP, an acute-phase protein synthesized primarily by the liver, has been shown to correlate with insulin resistance, impaired glucose metabolism, and an increased risk of developing T2DM (7). Moreover, elevated CRP concentrations in individuals with diabetes may reflect a higher inflammatory burden and contribute to adverse cardiovascular outcomes (3, 6).

Alongside pharmacological therapy, medical nutrition therapy remains a cornerstone of T2DM management, and increasing attention has been given to dietary macronutrient composition and its effects on metabolic health (8, 9). Among various dietary strategies, high-protein diets (HPDs), often accompanied by reduced carbohydrate intake, have attracted considerable interest as a potential approach for improving metabolic control in T2DM (8, 10). Previous studies suggest that HPDs may support glycemic control and metabolic regulation through mechanisms such as enhanced satiety, improved body weight management, and better glucose homeostasis (9, 11).

Beyond metabolic effects, dietary protein interventions may also influence inflammatory status, including biomarkers such as CRP, interleukin-6, and tumor necrosis factor-α (8, 12).

Despite growing interest in HPDs, evidence regarding their effect on inflammatory outcomes, particularly CRP concentrations, remains inconclusive (8, 9). While some intervention studies have reported favorable changes in cardiometabolic and inflammatory markers following protein-rich or carbohydrate-restricted dietary interventions in patients with T2DM, others have observed little or no significant effect on CRP levels (7, 9). Such inconsistencies may partly be explained by differences in study design, dietary composition, intervention duration, protein source, and participant characteristics (8). Although the metabolic effects of dietary protein modification in T2DM have been explored previously, evidence specifically addressing the impact of HPDs on circulating CRP concentrations remains fragmented and has not been comprehensively synthesized (7-10). To the best of our knowledge, no previous systematic review and meta-analysis has specifically evaluated the effect of high-protein diets on CRP levels in adults with T2DM based exclusively on evidence from randomized controlled trials.

Given the established role of CRP as a marker of systemic inflammation and its association with cardiometabolic risk in T2DM, even modest changes in CRP may have clinical implications for risk stratification and long-term outcomes (13, 14). However, despite the increasing application of high-protein dietary strategies in clinical practice, their effects on inflammatory biomarkers remain uncertain, particularly in individuals with T2DM who exhibit a heightened baseline inflammatory state (15). Therefore, a quantitative synthesis of randomized controlled trials is warranted to clarify the impact of high-protein diets on CRP levels and to determine their potential role in improving both metabolic and inflammatory profiles in this population.

2. Methods

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) framework followed in the design and reporting of this study (16). The protocol for conducting this review is registered in the PROSPERO database with the register ID: CRD420261413346 (Date of registration: 3 June 2026).

2.1. Search strategy

The research question was formulated according to the PICOS framework. Population (T2DM adults aged 18 and older), Intervention (high protein diet), Comparison (control or any comparative group), Outcome (changes of CRP concentrations), and Study Design (clinical trials). A systematic review search of the PubMed, Scopus and Web of Science databases was conducted up until November 2025. The following MeSH and non-MeSH keywords was used for the systematic literature search: 1) “High protein diet” OR “High Protein Low Carbohydrate diet” OR “Carbohydrate Restricted diet” OR “low carbohydrate diet”; 2) "Type 2 diabetes" OR “T2DM” OR “diabetes”; 3) "Randomized Controlled Trial" OR "clinical trial" OR "controlled trial" OR "intervention" OR "Randomised" OR "Randomized" OR "randomly" OR "placebo" OR "trial" OR "assignment" OR "RCT" OR "cross-over" OR "parallel" OR "single-blind" OR "double-blind" OR "Controlled Clinical Trial". Besides the systematic search, we also performed a hand search of the included studies' references to identify other relevant articles.

2.2. Eligibility criteria

In assessing the eligibility of studies included in the present article, two researchers (A.M. and F.A.) screened the title and abstract of the possible studies. Next, the full text of the studies whose titles and abstracts were adequate was reviewed. The difference in opinion was settled by including the opinion of a third researcher (H.B.). Only the original randomized controlled trial whose full text was accessible was included. Human studies done on adults (>18 years of age) with high protein diet, which were informative regarding levels of CRP, were included. Studies in children and adolescents who were treated for less than 4 weeks and whose dietary protein intake was less than 20% were excluded.

2.3 Data extraction

Information relevant to the objectives of this meta-analysis was independently extracted from the eligible studies by two authors (M.H. and A.M.). The extracted data included the first author’s name, year of publication, country in which the trial was conducted, sample size and

allocation to intervention and control groups, as well as details of the high-protein diet intervention, including type, dosage, and duration. Information regarding the control interventions, participants' baseline characteristics and anthropometric measures, and the mean changes and standard deviations (SD) of CRP levels were also collected. Any discrepancies in the extracted data were resolved through discussion to reach consensus, and when necessary, a third reviewer (H.B.) was consulted to adjudicate unresolved disagreements.

2.4 Risk of bias assessment

The risk of bias associated with the included studies was independently assessed by two reviewers (A.M. and M.H.), employing the revised Cochrane Risk of Bias tool for randomized trials (RoB 2)(16). The RoB tool evaluates the possibility of risk in five distinct areas, such as risk of bias due to the randomization process, deviations from the intervention, missing data on the outcome, measurement of the outcome, and reporting of the outcome. All the areas were assessed as having low, some, or high risk of bias (see Table3). An assessment of the risk of bias for each study was performed based on the results obtained from the domains and categorized as high risk if any of the domains was assessed as having a high risk of bias, or where there were two or more domains with some concerns about the bias. In situations where only one domain had some concerns, the study was assessed as having some concerns about the risk of bias. Where all the domains were assessed as having a low risk of bias, it was categorized as having a low risk of bias. Differences between the two reviewers were sorted out by discussion with the third reviewer (H.B.).

2.5 Data synthesis and statistical analysis

Statistical analysis was done using Comprehensive Meta-Analysis program, version 3.0, with a significance level of $P<0.05$. The effect sizes were estimated in terms of weighted mean difference (WMD) accompanied by their 95% confidence intervals. For pooled data analysis, random-effects model (DerSimonian & Laird model) was used(17). The missing standard deviations were imputed through procedures outlined by Hozo et al.(18). Mean differences were calculated as post-intervention minus baseline values in case they were not provided directly in the literature. The standard deviations for the mean changes were calculated by(19):

SD change $= \sqrt{[(\text{SD baseline})^2 + (\text{SD final})^2 - (2 \times R \times \text{SD baseline} \times \text{SD final})]}$, where R is the correlation coefficient.

The presence of heterogeneity was evaluated using the Cochran Q test and the heterogeneity index I^2. The presence of heterogeneity was indicated when the value of I^2 exceeded 50% or $P < 0.05$(19, 20). Sensitivity analysis was conducted through leave-one-out methods to examine the sensitivity of the combined effects of the study findings and the effect of each individual study in determining the overall effect size. Funnel plot asymmetry, Begg's test, and Egger's regression were applied for detecting publication bias, while its potential impact was determined through Duval and Tweedie's Trim and Fill method and fail-safe N(21). Subgroup analyses were performed using a fixed-effect model where appropriate(22).

3. Results

3.1 Study Selection

A systematic review of PubMed, Web of Science, and Scopus produced 1447 total records. After duplicating 436, there was a total of 1011 records that were unique and were screened via titles and abstracts. Ultimately, 23 full-text articles were critically reviewed for eligibility. After critically reviewing the full-text articles 13 studies were excluded for various reasons such as design was not randomized, outcomes or intervention were irrelevant, duplicate publication, or data not available. 10 randomized controlled trials (RCTs) were ultimately included in the meta-analysis. The identification, screening, and selection processes are summarized in the PRISMA flow diagram (Figure 1).

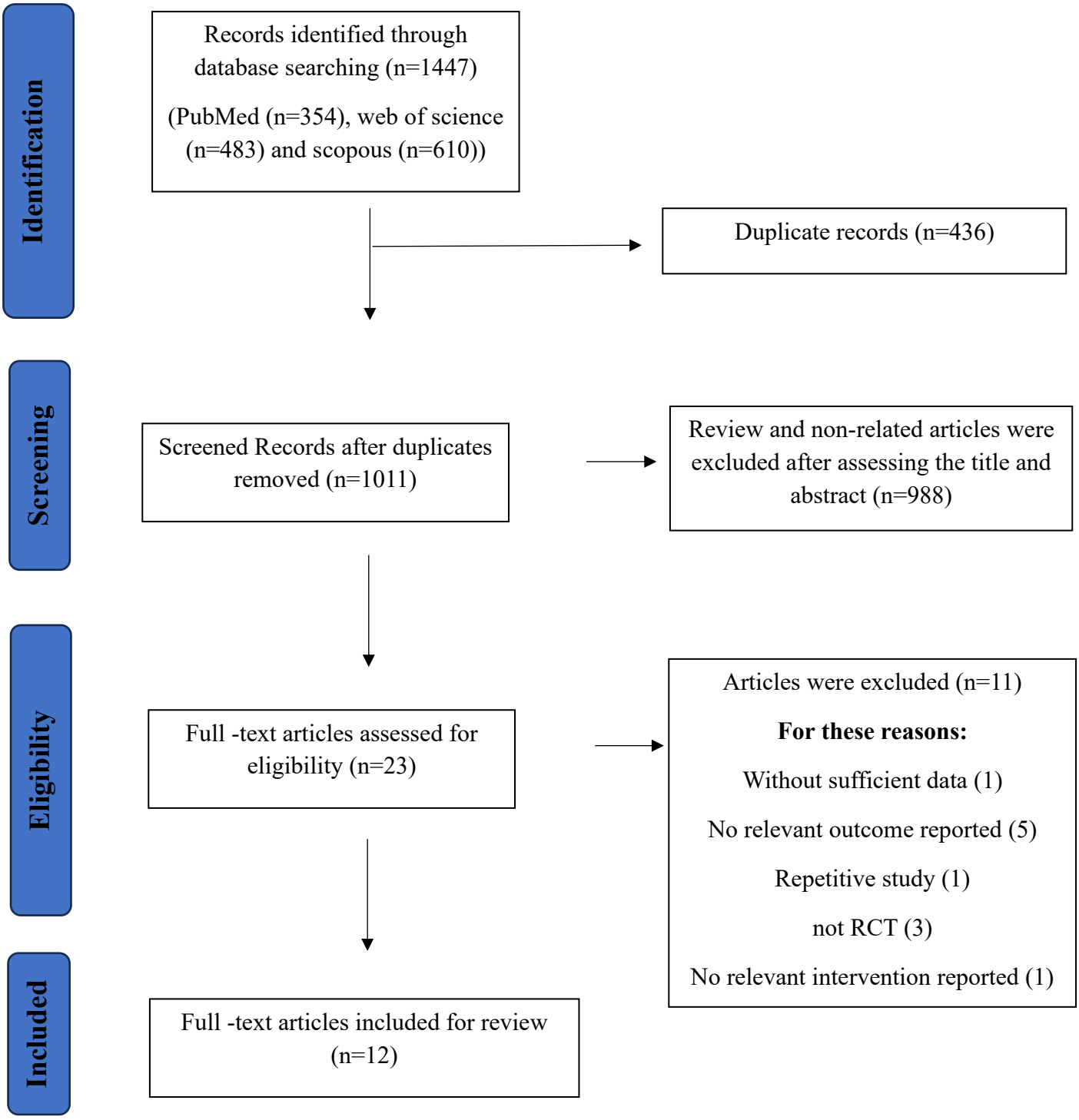


Figure 1: A PRISMA flowchart outlining the study selection proc

3.2 Study Characteristics

This meta-analysis included 10 RCTs examining the effects of the high protein diet on C-Reactive Protein in adults. Trials spanned 2010 to 2024, conducted across diverse regions: Australia(23-28), USA(29), Netherland(30), Egypt(31) and Germany(32). Most used parallel-group randomized designs with employing double-blind methods. Participants were predominantly adults with T2DM. The average age of participants (across studies) was 51(32) to 60.9(23) years old, and the average (baseline) BMI was between 30.7(30) and 36.2 kg/m²(29), representing a range of overweight and obesity classes. Most of the included studies recruited both male and female participants. Trial sample sizes ranged from 28(28) to 446(32). Intervention durations ranged from 12(27) to 104(26) weeks. Outcome included CRP. Table 1 summarizes key study characteristics.

3.3. Meta-analysis results

CRP was reported as an outcome measure in 10 studies with a total of 1231 contributors. The pooled findings from the fix effects model exhibited significant alteration in CRP levels after high protein diet intervention (mean difference (MD): - 0.039 mg\l, 95% CI: -0.072, -0.007, P value: 0.016) (Figure 2) with substantial heterogeneity among the studies (I^2 = 7.81 %, P value = 0.36).

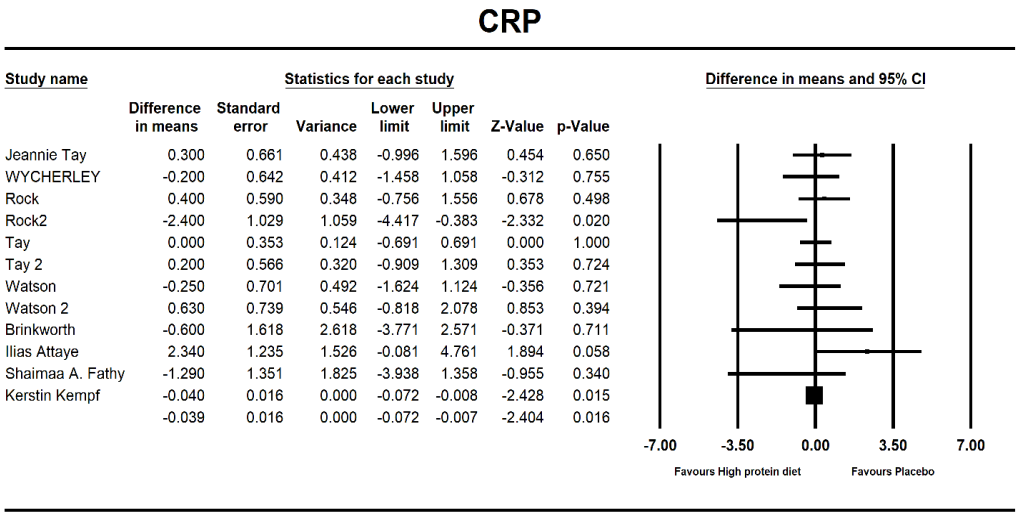


Figure.2. Forest plot of randomized controlled trials that compares the effects of the intervention (high protein diet) and the control (Placebo) groups on C-Reactive Protein. Effects are presented

as means and standard error (SE) for within-group change from baseline and standardized (Std) mean differences with Random 95% CI.

3.4. Sensitivity analysis

Leave-one-out sensitivity analysis was carried out to determine the influence of each trial on the effect size. Effect size for the impact of high-protein intake on CRP was found to be sensitive to 1 study(32). Omission of this study from the meta-analysis produced significant changes in results (see Figure3).

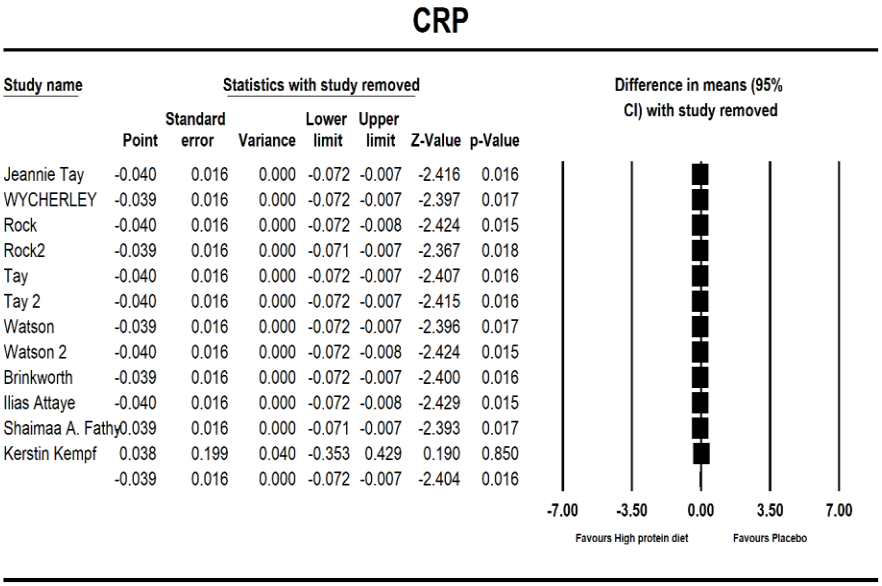


Figure 3. Forest plot of the Leave-one-out sensitivity analysis of the effects of the intervention (high protein diet) and the control (Placebo) groups on C-Reactive Protein. Effects are presented as means and standard error (SE) for within-group change from baseline and standardized (Std) mean differences with Random 95% CI.

3.5. Results from subgroup analysis

The results of the subgroup analyses are provided in Table 4. We stratified the studies based on the age (year), duration (weeks), BMI, sample size and baseline CRP. The subgroup analysis presented that high protein diet could significantly reduce CRP in patients below than 55 years old (WMD: -0.04 mg\l, 95%CI: -0.072, -0.008, P-Value: 0.015), intervention duration more than 6 month (WMD: -0.04 mg\l, 95%CI: -0.072, -0.008, P-Value: 0.015), sample size more than 60 (WMD: -

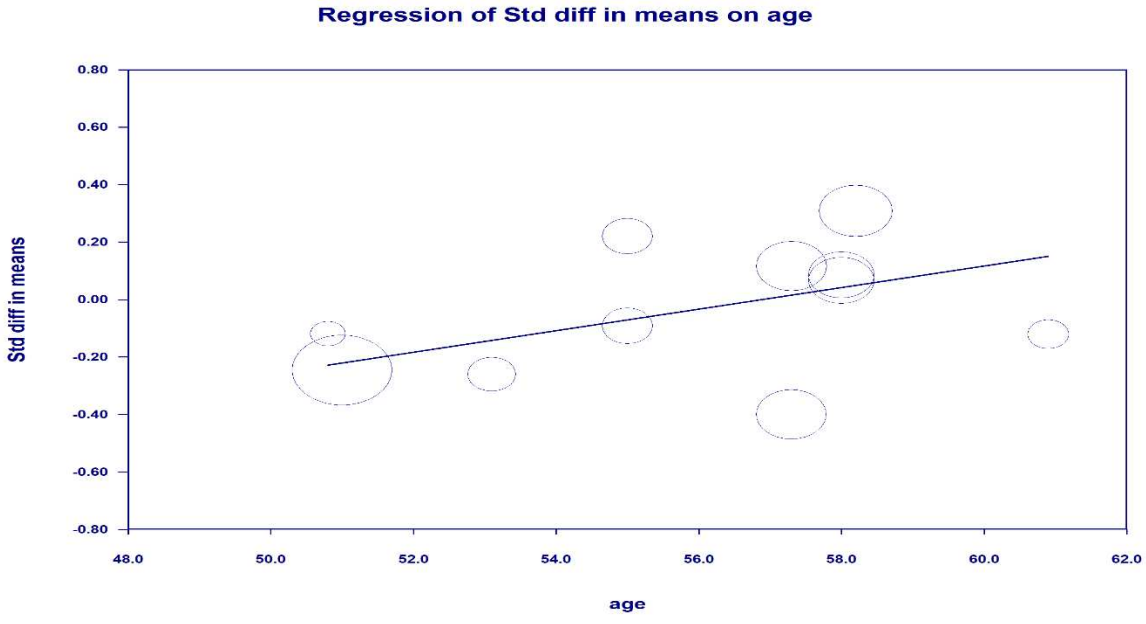
194 0.039 mg\l, 95%CI: -0.072, -0.007, P-Value: 0.017), baseline BMI lower than 35 (WMD: -0.039
195 mg\l, 95%CI: -0.071, -0.007, P-Value: 0.017) and baseline CRP higher than 3.5 (WMD: -0.04
196 mg\l, 95%CI: -0.073, -0.008, P-Value: 0.014).

197 **3.6. Meta-Regression**

198 Univariate meta-regression was conducted in an attempt to find sources of heterogeneity for the
199 association between consumption of a high-protein diet and CRP level in patients with diabetes.
200 These covariates include age, baseline CRP, BMI, duration of intervention, and sample size.

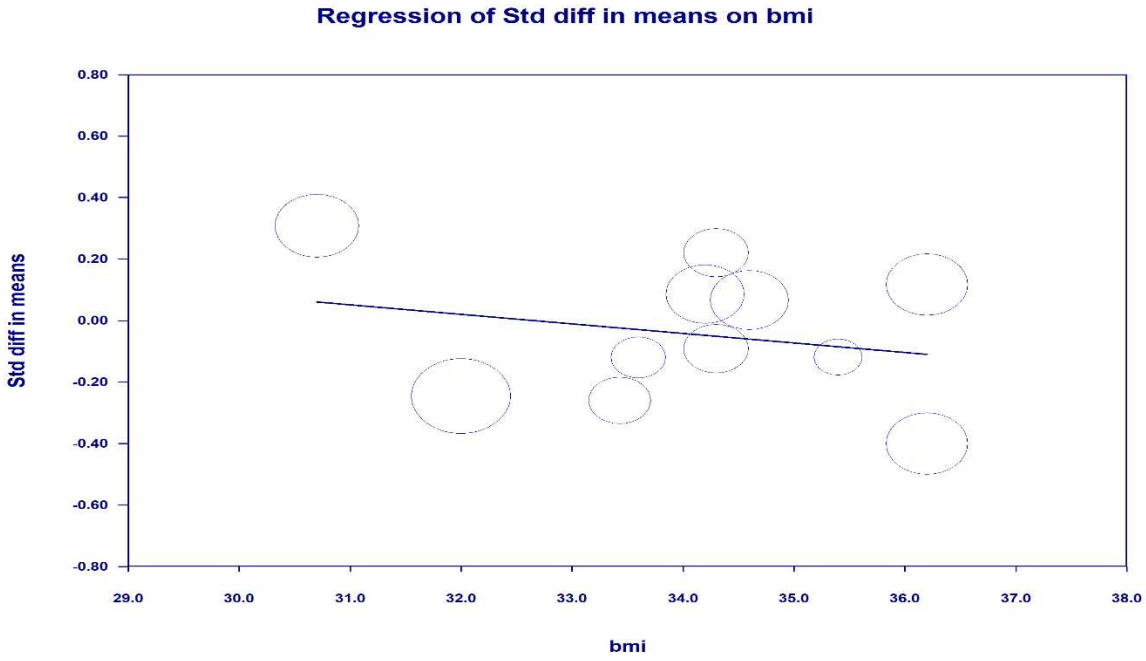
201 The analysis showed that none of the examined covariates were statistically significant moderators.
202 Specifically: age (coefficient = 0.0375, 95% CI: -0.0049 to 0.0799, p = 0.0828), baseline CRP
203 (coefficient = -0.0605, 95% CI: -0.1274 to 0.0064, p = 0.0763), BMI (coefficient = -0.0310, 95%
204 CI: -0.1218 to 0.0598, p = 0.5035), intervention duration (coefficient = -0.0012, 95% CI: -0.0069
205 to 0.0044, p = 0.6655), and sample size (coefficient = -0.0006, 95% CI: -0.0016 to 0.0004, p =
206 0.2618). The R^2-like numbers were as follows: 0.59 for age, 0.57 for initial CRP level, 0.00 for
207 BMI, 0.00 for diabetes duration, and 0.23 for sample size, implying that age and initial CRP levels
208 explained a substantial amount of variation in the effect estimates, while BMI and duration
209 explained virtually nothing (Figure 4, Panels A-E).

210 A.Association between the mean difference of CRP and mean age of the participants

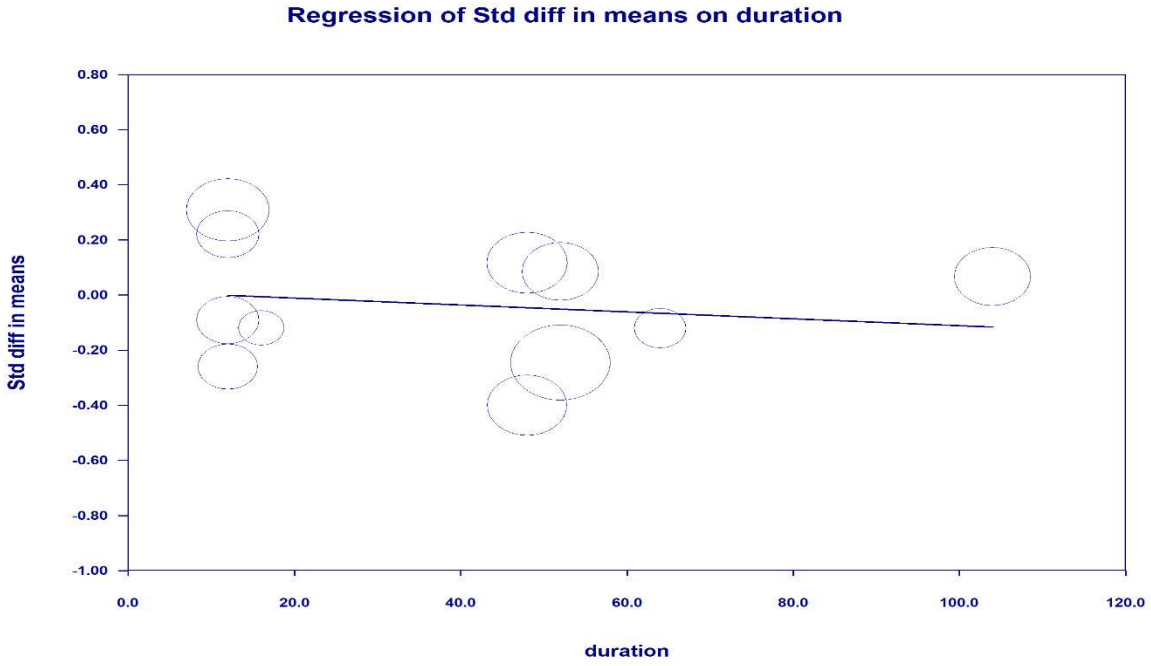


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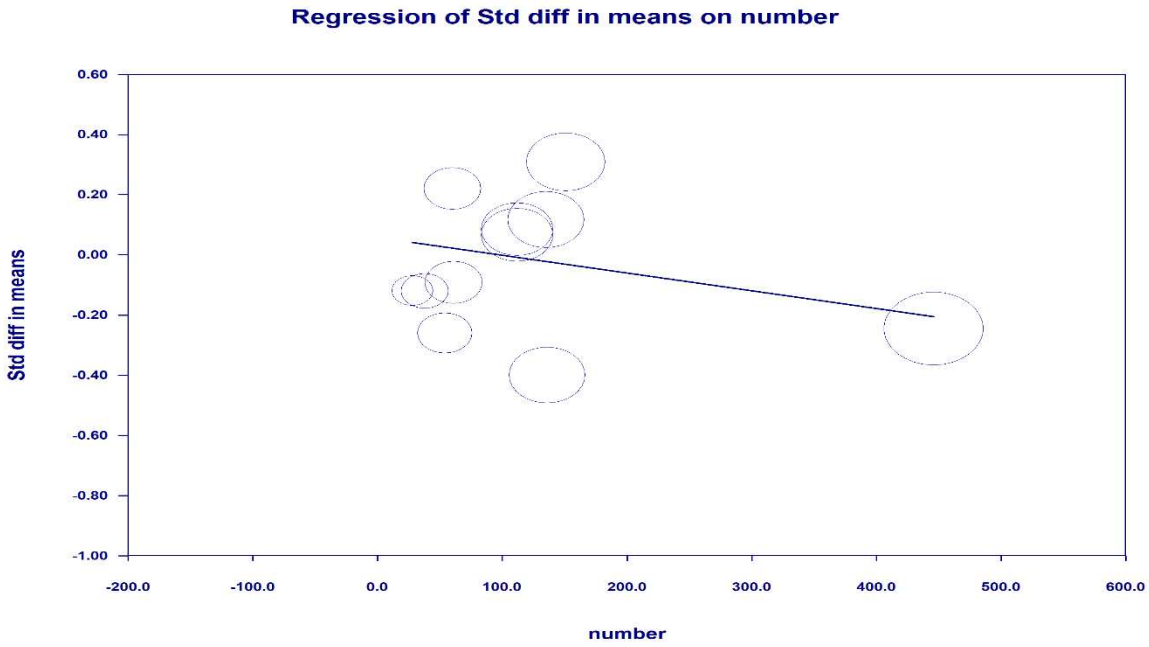
B. Association between the mean difference of CRP and mean BMI of the participants



C. Association between the mean difference of CRP and mean Duration of the studies



D. Association between the mean difference of CRP and mean Sample size of the studies



E. Association between the mean difference of CRP and baseline values of CRP in the intervention group

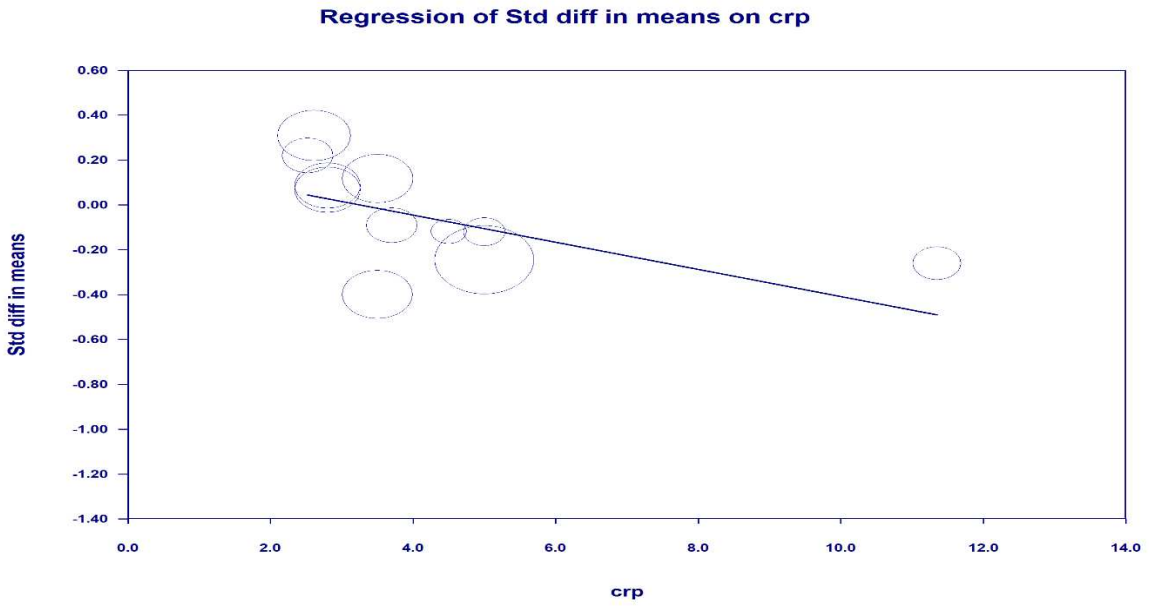


Figure4. Meta-Regression of the association between the mean difference of CRP and mean age, BMI, duration, baseline values of CRP and sample size of studies

Based on these results, it appears that the impact of a high protein diet on CRP concentrations does not depend on the investigated clinical and demographic variables.

3.7. Publication bias

The funnel plot showing the effect of high protein diet on CRP is illustrated in Figure S1. The findings of Begg's rank correlation test, Egger's linear regression test, "fail-safe N" test, and correlated effect size are presented in Table 5.

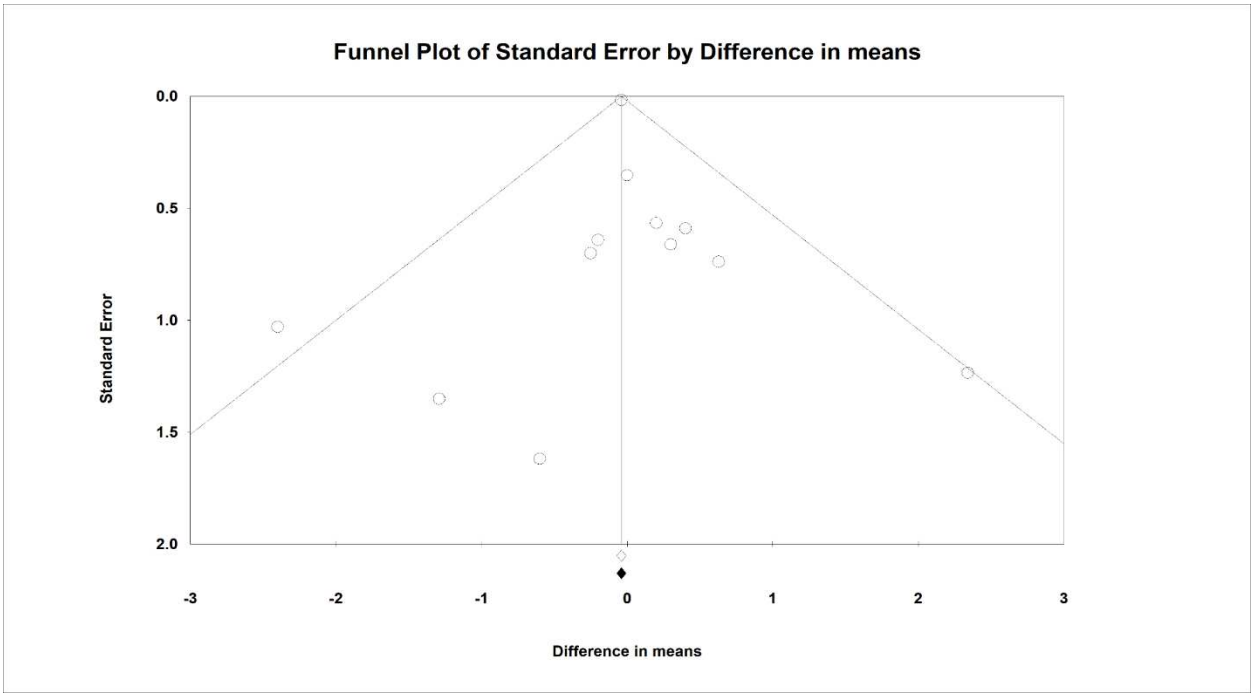


Figure S1. Funnel plots for publication bias assessment of the intervention (high protein diet) and the control (Placebo) groups on C-Reactive Protein. Effects are presented as means and standard error (SE) for within-group change from baseline

To assess the potential publication bias in the meta-analysis of the effect of a high-protein diet on CRP levels in patients with diabetes, Begg's rank correlation test and Egger's linear regression test were performed. Begg's test (Kendall's Tau = -0.015, z = 0.06, p = 0.94) and Egger's test (intercept = 0.04, 95% CI: -0.70 to 0.79, t = 0.13, df = 10, p = 0.89) showed no evidence of significant publication bias. Additionally, the fail-safe N test revealed that 0 missing studies would be needed to nullify the effect, suggesting that the observed effect sizes are robust.

In addition, a trim-and-fill analysis was performed. In this case, no studies needed to be added, and the combined effect size did not change from the original one in the random-effects model. This is another way of proving that there is no publication bias in this case.

4.Discussion

The most important result in this systematic review and meta-analysis was that high-protein diet decreases serum C-reactive protein (CRP) concentrations in patients with type 2 diabetes mellitus (T2DM) compared with controls (MD: -0.039 mg/L; 95% CI: -0.072 to -0.007; p=0.016). Although the magnitude of the effect is low, it is statistically significant. According to the GRADE system, there is high-quality evidence in support of our results. To our knowledge, this is among the few studies in meta-analysis which quantified the anti-inflammatory effects of a high-protein diet on patients with T2DM.

Comparison with Existing Literature

The findings reported herein support existing literature on how macronutrient intake may alter systemic inflammation, which is central to the physiology of type 2 diabetes mellitus(33-36). While previous meta-analyses of high-protein diet intake in relation to inflammation have been conducted, most of them have centered on either weight loss or improvement in glycemia, with the change in CRP concentration used as a secondary variable, and provided conflicting findings(37). The findings from this current meta-analysis, however, indicate that lowering CRP concentration does not depend on any weight loss, as evidenced by significant differences found even when baseline BMI was less than 35 kg/m^2.

Interpretation of Subgroup Analyses

Subgroup analysis showed a few notable findings. First, the intervention had more impact on those less than 55 years old and on individuals whose baseline CRP exceeded 3.5 mg/L. It implies that persons with higher levels of inflammatory burden might benefit from the intervention to a greater extent(38). Second, interventions which lasted for more than six months led to statistically significant results; shorter studies had no effect, which means that long-term dietary compliance is essential in order to have any effect on inflammation(39). Third, studies having over 60 participants showed significant results; therefore, smaller trials lacked power to show such changes. Of interest is the fact that BMI at baseline did not change the effect, thus showing that

the anti-inflammatory effect of high protein diets was not due to their adiposity-reducing properties(40).

Heterogeneity and Meta-Regression

There was little heterogeneity noted in the analysis ($I^2 = 7.81\%$, $p = 0.36$) and is quite impressive for an analysis involving diet intervention studies. The low heterogeneity makes us more confident about the pooled effect. Univariate meta-regression revealed that no covariate was significant in moderation such as age, baseline CRP, BMI, intervention length, or sample size. Yet, the analogous value of R^2 revealed that 59% and 57% of the between-study heterogeneity were accounted for by age and baseline CRP respectively and thus these two variables appear clinically significant even though they did not reach statistical significance (age $p = 0.0828$; baseline CRP $p = 0.0763$).

Sensitivity Analysis and Publication Bias

From the leave-one-out sensitivity analysis, it emerged that the combined effect size was sensitive to one study. The exclusion of the study made significant changes to the outcome; therefore, the effect size is not fully robust against the inclusion/exclusion of all the studies. It is worth noting that this finding does not nullify the result, although future reviews can take further measures.

Luckily, there were no small study effects, and no signs of asymmetry on the funnel plot based on the results obtained from the tests for publication bias using Begg's test ($p = 0.94$), Egger's test ($p = 0.89$) and trim and fill analysis (zero missing studies). The fact that the Fail-Safe N analysis was conducted indicates the robustness of the result obtained.

Biological Plausibility

There are several ways through which high-protein diets can exert their anti-inflammatory effects in individuals with T2DM. Firstly, the consumption of meals rich in proteins increases glucagon-like peptide-1 (GLP-1) secretion after eating, and this acts directly to produce an anti-inflammatory effect on the endothelial cells and inhibit the activation of nuclear factor kappa-B (NF-κB)(41). Secondly, by substituting carbohydrate foods with proteins in the diet, there is less postprandial hyperglycemia, and hence AGE formation and oxidative stress that induce the production of CRP by hepatocytes is prevented(42). Furthermore, high protein intake can increase insulin sensitivity and decrease insulin resistance, which is one of the significant factors behind the development of

inflammation in the context of T2DM. Increased insulin sensitivity could lead to decreased levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, which stimulate CRP production in the liver(11). Additionally, certain amino acids found in protein-containing foods might have a direct effect on the immune system and act as antioxidants. For instance, arginine may help to improve the functioning of endothelium due to higher levels of nitric oxide, whereas cysteine and glutamine are involved in antioxidant response processes. The use of diets that contain high amounts of protein is known to improve endogenous antioxidant activity by means of producing glutathione in order to minimize oxidative stress-induced inflammation(43-45). Furthermore, changes in the lipid profile and decreasing concentration of free fatty acids in blood vessels can inhibit the activation of NF-κB and other inflammatory reactions(46). Lastly, new data suggests that the diet consisting of large quantities of protein affects the composition of gut microflora and the integrity of intestinal wall. These factors might lead to decreasing levels of metabolic endotoxemia and, consequently, overall inflammation. In general, these processes might lead to CRP reduction, irrespective of the initial BMI level of participants(47-49).

Strengths and Limitations

Here are several significant strengths of this meta-analysis. First, the quality of evidence has been assessed as high, and there was minimal statistical heterogeneity (I^2=7.81%). Publication biases were tested using Begg's test, Egger's test, fail-safe N, and trim-and-fill approach. The results of all these analyses have proved that no bias existed. Furthermore, subgroup analysis has revealed clinically relevant responder groups (patients <55 years old, CRP >3.5 mg/L at baseline, intervention >6 months). Finally, 10 RCTs conducted from 2010 to 2024 across five regions of the world were included.

Limitations must also be addressed. Firstly, the relatively small number of clinical trials (n = 10) used meant that the results of meta-analysis and regression could be affected, and Type II errors are common in this scenario. Secondly, considerable heterogeneity was seen in regard to duration of interventions (12 to 104 weeks), types of proteins, and control group's diet plans. Thirdly, there was a high risk of participant's blinding bias, which is very difficult to control in clinical trials of diet. Fourthly, even though statistically significant, the overall size of the effect observed (-0.039 mg/L reduction in mean) was clinically minor. Nevertheless, such a change in the population on the whole might result in decreased morbidity for the heart in terms of cardiovascular disorders in

large cohorts of people. Fifthly, generalization would be somewhat impossible because of the nature of participants recruited (overweight/obese adults with T2DM from high-income countries).

Implications for Clinical Practice and Future Research

Clinically, a prescription for a high protein diet (about 25% to 30% of daily calories or 1.2-1.5 grams per kg body weight) can be suggested as a complementary treatment for lowering systemic inflammation among adult patients with T2DM, especially those with high baseline CRP (CRP >3.5 mg/L) and younger age (<55 years old). Care must be taken to consider the effects on renal function, since prolonged exposure to high protein diet can be harmful to diabetic nephropathy patients(50).

Areas for future investigation would be: (1) large-scale longitudinal (> 1 year), RCT with standardized CRP testing; (2) direct comparison of animal versus plant protein source; (3) mechanistic evaluation with measurement of GLP-1, oxidative stress biomarkers, and gut microbiota analysis; and (4) investigation in subjects with chronic kidney disease to establish safety limits.

5.Conclusions

The meta-analysis based on 10 RCTs proves the effectiveness of a high protein diet in reducing CRP among type 2 diabetic adults, showing low heterogeneity and absence of publication bias. The subgroup analysis shows that younger individuals, those with a longer duration of the intervention (>6 months), and those with higher baseline CRP respond better. Nonetheless, there are limitations with regard to the magnitude of the result, which appears to be highly dependent on the specific studies included in the analysis.

6.Decelaration

Author contributions

A.M. conceived the study. A.M. and H.B. wrote the proposal. A.M. carried out the literature search. A.M. and F.A. carried out the literature screening. A.M. and M.H. carried out data extraction and independent reviewing. A.M. and M.H. accompanied the quality evaluation of included studies. A.M. conducted data analysis and interpretation. A.M., H.B., M.H. and F.S.H.J wrote the

manuscript. A.M., H.B., and M.S. conducted the critical revision of manuscript. All authors read the manuscript and approved it.

Conflict of interest statement

The authors of this article declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

The data sets generated or analyzed during the present study are not publicly accessible due to the regulations of the Research Center for Biochemistry and Nutrition in Metabolic Diseases of Mashhad University of Medical Sciences. However, they can be accessible from the corresponding author upon logical request.

Consent for Publication

Not applicable.

7.References

1. Huang Q, Li Y, Yu M, Lv Z, Lu F, Xu N, et al. Global burden and risk factors of type 2 diabetes mellitus from 1990 to 2021, with forecasts to 2050. Frontiers in Endocrinology. 2025;Volume 16 - 2025.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
3. Shah MS, Brownlee M. Molecular and Cellular Mechanisms of Cardiovascular Disorders in Diabetes. Circulation Research. 2016;118(11):1808-29.
4. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiological reviews. 2013;93(1):137-88.
5. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001;103(13):1813-8.
6. Watanabe Y, Suzuki D, Kuribayashi N, Uchida D, Kato M, Ohashi H, et al. A randomized controlled trial of two diets enriched with protein or fat in patients with type 2 diabetes treated with dapagliflozin. Scientific Reports. 2021;11(1):11350.
7. Stanimirovic J, Radovanovic J, Banjac K, Obradovic M, Essack M, Zafirovic S, et al. Role of C-reactive protein in diabetic inflammation. Mediators of inflammation. 2022;2022(1):3706508.
8. Alzahrani AH, Skytte MJ, Samkani A, Thomsen MN, Astrup A, Ritz C, et al. Effects of a Self-Prepared Carbohydrate-Reduced High-Protein Diet on Cardiovascular Disease Risk Markers in Patients with Type 2 Diabetes. Nutrients. 2021;13(5).
9. Azadbakht L, Atabak S, Esmaillzadeh A. Soy Protein Intake, Cardiorenal Indices, and C-Reactive Protein in Type 2 Diabetes With Nephropathy: A longitudinal randomized clinical trial. Diabetes Care. 2008;31(4):648-54.
10. Malaeb S, Bakker C, Chow LS, Bantle AE. High-protein diets for treatment of type 2 diabetes mellitus: a systematic review. Advances in Nutrition. 2019;10(4):621-33.
11. Dong J-Y, Zhang Z-L, Wang P-Y, Qin L-Q. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. British Journal of Nutrition. 2013;110(5):781-9.
12. Sánchez-Rosales AI, Guadarrama-López AL, Gaona-Valle LS, Martínez-Carrillo BE, Valdés-Ramos R. The Effect of Dietary Patterns on Inflammatory Biomarkers in Adults with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022;14(21).
13. Zaidi S, Mohammad A, Ahmad I, Singla S, Singla B, Kumawat S, et al. Inflammation and Cardiovascular Risk: A Systematic Review of High-Sensitivity CRP as a Prognostic Indicator. Cureus. 2026;18(2):e103348.
14. Ghafoury R, Malek M, Ismail-Beigi F, Khamseh ME. Role of Residual Inflammation as a Risk Factor Across Cardiovascular-Kidney-Metabolic (CKM) Syndrome: Unpacking the Burden in People with Type 2 Diabetes. Diabetes Therapy. 2025;16(7):1341-65.
15. Sánchez-Rosales AI, Guadarrama-López AL, Gaona-Valle LS, Martínez-Carrillo BE, Valdés-Ramos R. The Effect of Dietary Patterns on Inflammatory Biomarkers in Adults with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022;14(21):4577.

16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009;339.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
18. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology. 2005;5(1):13.
19. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John wiley & sons; 2021.
20. Chandler J, Cumpston M, Li T, Page MJ, Welch V. Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley. 2019;4(1002):14651858.
21. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
22. Borenstein M, Rothstein H, Cohen J. Comprehensive meta-analysis: A computer program for research synthesis. Englewood, NJ: Biostat. 1999.
23. Brinkworth GD, Noakes M, Parker B, Foster P, Clifton PM. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: one-year follow-up of a randomised trial. Diabetologia. 2004;47(10):1677-86.
24. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. A very low-carbohydrate, low–saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes care. 2014;37(11):2909-18.
25. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102(4):780-90.
26. Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metab. 2018;20(4):858-71.
27. Watson N, Dyer K, Buckley J, Brinkworth G, Coates A, Parfitt G, et al. Effects of Low-Fat Diets Differing in Protein and Carbohydrate Content on Cardiometabolic Risk Factors during Weight Loss and Weight Maintenance in Obese Adults with Type 2 Diabetes. Nutrients. 2016;8(5).
28. Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. Diabetes Care. 2010;33(5):969-76.
29. Rock CL, Flatt SW, Pakiz B, Taylor KS, Leone AF, Brelje K, et al. Weight loss, glycemic control, and cardiovascular disease risk factors in response to differential diet composition in a weight loss program in type 2 diabetes: a randomized controlled trial. Diabetes Care. 2014;37(6):1573-80.
30. Attaye I, Lassen PB, Adriouch S, Steinbach E, Patiño-Navarrete R, Davids M, et al. Protein supplementation changes gut microbial diversity and derived metabolites in subjects with type 2 diabetes. iScience. 2023;26(8):107471.
31. Fathy SA, Meligi AE, AlWakil SS, Ahmed MB, Ahmed GR. Comparison of different diet plans on patients with type 2 diabetes. The Egyptian Journal of Internal Medicine. 2024;36(1):53.

32. Kempf K, Röhling M, Banzer W, Braumann KM, Halle M, McCarthy D, et al. High-Protein, Low-Glycaemic Meal Replacement Decreases Fasting Insulin and Inflammation Markers-A 12-Month Subanalysis of the ACOORH Trial. Nutrients. 2021;13(5).
33. Badrooj N, Jayedi A, Shab-Bidar S. Comparative effects of different macronutrient compositions for type 2 diabetes management: a systematic review and network meta-analysis of randomized trials. Journal of Health, Population and Nutrition. 2025;44(1):108.
34. Yu X, Liu X, Li H. Nutrient metabolism and complications of type 2 diabetes mellitus: implications for rehabilitation and precision care. Frontiers in Nutrition. 2025;12:1699259.
35. Dandona P, Ghanim H, Chaudhuri A, Dhindsa S, Kim SS. Macronutrient intake induces oxidative and inflammatory stress: potential relevance to atherosclerosis and insulin resistance. Experimental & molecular medicine. 2010;42(4):245-53.
36. Jafaripour S, Sedighi S, Jokar MH, Aghaei M, Moradzadeh M. Inflammation, diet, and type 2 diabetes: a mini-review. Journal of Immunoassay and Immunochemistry. 2020;41(4):768-77.
37. Ma X, Rohani P, Sohouli MH. The effect of high-protein vs. low-protein diets on CRP, IL-6, TNF-α, and liver enzymes in adult participants: a systematic review and meta-analysis. Food & Function. 2026.
38. Khodarahmi M, Seyedhosseini-Ghaheh H, Askari G. Effect of Low-Carbohydrate Diets on C-Reactive Protein Level in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Food Science & Nutrition. 2025;13(7):e70566.
39. Mousavi SM, Djafarian K, Mojtahed A, Varkaneh HK, Shab-Bidar S. The effect of zinc supplementation on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. European journal of pharmacology. 2018;834:10-6.
40. Sucher S, Markova M, Hornemann S, Pivovarova O, Rudovich N, Thomann R, et al. Comparison of the effects of diets high in animal or plant protein on metabolic and cardiovascular markers in type 2 diabetes: a randomized clinical trial. Diabetes, Obesity and Metabolism. 2017;19(7):944-52.
41. Ma X, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, et al. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. International Journal of Biological Sciences. 2021;17(8):2050.
42. Aragno M, Mastrocola R. Dietary sugars and endogenous formation of advanced glycation endproducts: emerging mechanisms of disease. Nutrients. 2017;9(4):385.
43. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018;10(11):1564.
44. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Molecular aspects of medicine. 2009;30(1-2):1-12.
45. McNeal CJ, Meininger CJ, Reddy D, Wilborn CD, Wu G. Safety and effectiveness of arginine in adults. The Journal of nutrition. 2016;146(12):2587S-93S.
46. Klop B, Elte JWF, Castro Cabezas M. Dyslipidemia in obesity: mechanisms and potential targets. Nutrients. 2013;5(4):1218-40.
47. Dmytriv TR, Storey KB, Lushchak VI. Intestinal barrier permeability: the influence of gut microbiota, nutrition, and exercise. Frontiers in Physiology. 2024;15:1380713.

48. Park J-E, Park H-Y, Kim Y-S, Park M. The role of diet, additives, and antibiotics in metabolic endotoxemia and chronic diseases. Metabolites. 2024;14(12):704.
49. Ross FC, Patangia D, Grimaud G, Lavelle A, Dempsey EM, Ross RP, et al. The interplay between diet and the gut microbiome: implications for health and disease. Nature Reviews Microbiology. 2024;22(11):671-86.
50. Sohouli MH, Mirmiran P, Seraj SS, Kutbi E, Alkahmous HAM, Almuqayyid F, et al. Impact of low-protein diet on cardiovascular risk factors and kidney function in diabetic nephropathy: a systematic review and meta-analysis of randomized-controlled trials. Diabetes Research and Clinical Practice. 2022;191:110068.

Table1. Demographic Characteristics of the included studies

First author (country; year)	RCT design	Target population	Sex	Mean Age (year)	Mean BMI (kg/m^2)	Sample size (Intervention /Control)	Duration (weeks)	Intervention		Outcomes
								Intervention group	Control group	
Brinkworth (Australia,2004)	Parallel	Type 2 Diabetes Mellitus	F/M	60.9	33.6	38(19/19)	64	HP diet (40% carb, 30% pro, and 30% fat)	LP diet (55% carb, 15% pro, and 30% fat)	CRP
Thomas Wycherley (Australia,2010)	Parallel	Type 2 Diabetes Mellitus	F/M	50.8	35.4	28(12/16)	16	HP diet (43% carb, 33% pro, and 22%fat)	CON diet (53% carb, 19% pro, and 26% fat)	CRP
Cheryl Rock (USA,2014)	Parallel	Type 2 Diabetes Mellitus	F/M	57.3	36.2	135(68/67)	48	LC diet (45% carb, 25% pro, and 30% fat)	LF diet (60% carb, 20% pro, and 20% fat)	CRP
Cheryl Rock (USA,2014)	Parallel	Type 2 Diabetes Mellitus	F/M	57.3	36.2	136(68/68)	48	LC diet (45% carb, 25% pro, and 30% fat)	UC diet (55% carb, 15% pro, and 30% fat)	CRP
Jeannie Tay (Australia,2014)	Parallel	Type 2 Diabetes Mellitus	F/M	58	34.4	93(46/47)	24	LC diet (14% carb, 28% pro, and 58% fat)	HC diet (53% carb, 17% pro, and 30% fat)	CRP
Jeannie Tay (Australia,2015)	Parallel	Type 2 Diabetes Mellitus	F/M	58	34.2	112(56/56)	52	LC diet (14% carb, 28% pro, and 58% fat)	HC diet (53% carb, 17% pro, and 30% fat)	CRP
Nerylee Watson (Australia,2016)	Parallel	Type 2 Diabetes Mellitus	F/M	55	34.3	61(32/29)	12	HP diet (34% carb, 29% pro, and 31% fat) + weight loss	HC diet (48% carb, 21% pro, and 24% fat) + weight loss	CRP
Nerylee Watson (Australia,2016	Parallel	Type 2 Diabetes Mellitus	F/M	55	34.3	60(31/29)	12	HP diet (34% carb, 29% pro, and 31% fat) + weight maintance	HC diet (48% carb, 21% pro, and 24% fat) + weight maintance	CRP
Jeannie Tay (Australia,2018)	Parallel	Type 2 Diabetes Mellitus	F/M	58	34.6	113(56/57)	104	LC diet (14% carb, 28% pro, and 58% fat)	HC diet (53% carb, 17% pro, and 30% fat)	CRP
Kerstin Kempf (Germany,2010)	Parallel	Type 2 Diabetes Mellitus	F/M	51	27-35	446(301/145)	52	HP, low glycemic meal replacement	control	CRP
Ilias Attaye (Amsterdam,2023)	Parallel	Type 2 Diabetes Mellitus	F/M	58.2	30.7	151(78/73)	12	HP diet (30% pro)	LP diet (10% pro)	CRP
Shaimaa A. Fathy (Egypt,2024)	Cohort	Type 2 Diabetes Mellitus	F/M	53.1	33.43	54 (27/27)	12	HP diet (40% carb, 30% pro, and 30% fat)	HF diet (10% carb, 25% pro, and 65% fat)	CRP

Abbreviation: BMI, Body mass index; CRP, C-reactive protein; LC, Low carbohydrate; HC, High carbohydrate; LF, Low fat; HP, High protein; UC, Usual care; LP, Low protein

Table 2. GRADE profile regarding the effect of high protein diet on C-Reactive Protein

	Corrected effect size		Begg's rank correlation test			Egger's linear regression test					Fail-safe N test
	WMD	**95% CI**	**Kendall's Tau**	**z-value**	**p-value**	**Intercept**	**95% CI**	**t-value**	**df**	**p-value**	**n**
C-Reactive Protein	-0.039	-0.071, -0.007	-0.015	0.06	0.94	0.04	-0.7,0.79	0.13	10	0.89	0

Table 5. Publication bias for C-Reactive Protein

Quality assessment						**Quality of evidence**
Outcomes	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	
C-Reactive Protein	No serious limitation	No serious limitation	No serious limitation	No serious limitation	No serious limitation	**High** ⊕⊕⊕⊕

Table 4. Results of subgroup analysis of the included trials regarding the effects of high protein diet on C-Reactive Protein.

	Number of comparisons	WMD	CI 95%	P value	I^2 (%)	P-Heterogeneity
C-Reactive Protein (mg\l)						
Age (years)						
≤ 55	4	-0.040	-0.072, -0.008	0.015	0	0.622
> 50	8	0.049	-0.382, 0.479	0.824	30.01	0.188
Duration (weeks)						
≤ 24	6	0.064	-0.434, 0.561	0.802	7.21	0.37
> 24	6	-0.040	-0.072, -0.008	0.015	21.61	0.27
BMI (kg\m^2)						
≤ 35	9	-0.039	-0.071, -0.007	0.017	0	0.641
> 35	3	-0.257	-1.041, 0.528	0.521	64.18	0.061
Sample Size						
≤ 60	5	-0.107	-0.837, 0.622	0.773	0	0.751
> 60	7	-0.039	-0.072, -0.007	0.017	39.89	0.125
Baseline of C-Reactive Protein (mg\l)						
≤ 3.5	6	0.246	-0.327, 0.819	0.4	49.16	0.08
> 3.5	5	-0.040	-0.073, -0.008	0.014	0	0.89

WMD; weighted mean difference, CI; confidence interval, BMI; body mass index

Table 3. Quality assessment of the studies included using the Cochrane Collaboration tool investigating the effect of high protein diet on C-Reactive protein.

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete Outcome data	Selective outcome reporting	Other potential threats to validity	General risk of bias
Brinkworth et al. 2004	L	U	U	U	L	U	L	**Low**
Thomas Wycherley et al. 2010	L	U	U	U	L	L	L	**Low**
Jeannie Tay et al. 2014	L	L	H	L	L	L	L	**Low**
Cheryl Rock et al. 2014	L	U	U	U	L	U	L	**Low**
Jeannie Tay et al. 2015	L	L	H	L	L	L	L	**Low**
Nerylee Watson et al. 2016	L	U	U	U	L	L	L	**Low**
Jeannie Tay et al. 2018	L	L	H	L	H	L	L	**Moderate**
Kerstin Kempf et al., 2021	L	U	U	L	L	L	L	**Low**
Ilias Attaye et.al. 2023	L	U	H	U	L	L	L	**Low**
Shaimaa A. Fathy et al., 2024	L	U	H	U	L	L	L	**Low**

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear risk of bias