Review Article

The Effects of High Protein Intake on Cardiovascular Risk Factors and Weight Loss in Low Caloric Diets in Obese Adults: A Systematic Review

Martin Lauran[1], Ali Moghadas Jafari[2*], Kosar Mohamed Ali[3], Mostafa Hosseini[4*]

[1]GKT School of Medical Education, King's College London, London, UK.
[2]Farhikhtegan Hospital, Azad university of Medical Sciences, Tehran, Iran.
[3]College of Medicine, University of Sulaimani, Sulaimani, Iraq.
[4]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

ABSTRACT

Introduction: This systematic review has been undertaken in order to assess the effects of hypocaloric, high-protein diets on weight loss and cardiovascular risk factors such as serum lipid levels in metabolically healthy obese adults. The primary outcomes measured include changes in pre-and post- diet mean BMI, LDL-C, HDL-C, TAG, and TC levels.

Methods: Four databases including: Embase, MEDLINE (via PubMed), Cochrane and Web of Science were searched with no restrictions on language or publication period. Clinicaltrials.gov was also searched in order to identify unpublished or on-going studies.

Results: Three of four studies included in this systematic review noted a significantly greater loss in pre- and post- diet mean BMI levels in the hypocaloric, high-protein diet group as compared to hypocaloric, non-high protein diets (control). Whilst pre- and post-diet mean LDL-C, HDL-C, TAG, and TC levels did not differ significantly among hypocaloric, high-protein and control diet groups.

Conclusion: Hypocaloric, high-protein diets had an unclear effect on blood-lipid levels as compared to control. Weight loss however was significantly greater in the hypocaloric, high-protein group as compared to other hypocaloric, non-high-protein diet groups.

Introduction

Obesity as defined by a body mass index above 30 kg/m^2 is a global health concern that as of 2016 affects 650 million adults worldwide. The condition is associated with several health consequences, one of which being an increased risk of cardiovascular disease.[1] The obese state is correlated with established risk factors for cardiovascular disease such as dyslipidaemia,[2-4] which include elevated triacylglycerols, total cholesterol, and low-density lipoprotein cholesterol levels as well as a decreased high-density lipoprotein

*.Corresponding Author: a.moghaddasjafari@iautmu.ac.ir

Lauran M et al.   Vol 10 No 1 (2024)

The Effects of High Protein Intake on Cardiovascular Risk Factors ...

cholesterol level. Furthermore, the relationship between cardiovascular disease and obesity was confirmed in a prospective cohort study on 5209 participants known as the Framingham Heart Study which noted that obese participants had an increased age-adjusted relative risk for cardiovascular disease.[2] A multivariable adjusted relative risk (adjusted for age, smoking, hypertension, hypercholesterolemia, and diabetes) in the same study noted that the total cardiovascular disease relative risk was increased for both obese men and women in comparison to men and women with a healthy ranged body mass index (18.5 – 24.9 kg/m^{2}). Therefore, as a means to further explore cardiovascular disease risk as a result of an obese state in the absence of co-morbidities associated with obesity (such as diabetes, insulin resistance), this systematic review hopes to focus on metabolically healthy obese adults which include a subgroup of obese adults who do not exhibit overt cardiometabolic abnormalities such as diabetes, or hypercholesterolemia.[5] Furthermore, weight loss is associated with improving lipid profiles[6] and therefore obese participants may experience more balanced lipid profiles when undergoing weight reduction, as through dietary energy deficits.[7] However, in the context of hypocaloric diets, hunger has been noted as one of the primary issues in obese participants compliance to weight-loss diets.[8] A clinical trial noted that hypocaloric, high-protein diets significantly lower food cravings, and improve mood in obese participants.[9] This finding was consistent with the results of several other studies in this field, which showed that hypocaloric, high-protein diets lead to greater weight loss and increased participants' compliance with the diet as a result of increased satiety and decreased hunger.[10-12] In addition to these findings, the results of studies on hypocaloric, high-protein diets also showed an improvement in lipid profile.[13,14] This systematic review therefore hopes to explore the effects of hypocaloric, high-protein diets on cardiovascular risk factors, specifically serum lipid levels and weight loss in metabolically healthy obese adults, a subgroup of participants which to current knowledge have not been exclusively explored in regards to the effects of this specific diet. As suggested from the aforementioned findings in previous studies it is predicted that hypocaloric, high-protein diets will produce a significant reduction in cardiovascular risk factors and an increased weight loss in comparison to other hypocaloric, non-high-protein diets in metabolically healthy obese adults.

Methods

Inclusion and exclusion criteria

Only randomised controlled trials (RCT) were eligible for this review. Eligibility criteria for study participants included obese (BMI≥30) adults (18-69 years), apparently metabolically healthy participants (without comorbidities such as diabetes or insulin resistance), and non-smokers The diet intervention eligibility criteria were based on hypocaloric, high-protein diets (at least 25% of total energy of the diet). High-protein diets with a sole focus on plant-proteins, intermittent-fasting and studies shorter than 4 weeks were excluded. Finally, the control diets had to be hypocaloric, and less than 25% of dietary macronutrients consisted of protein, if there were no control diets in the RCT, the study would still be included in the

systematic review.

Search Strategy

Four online databases were comprehensively searched, including: Embase, MEDLINE (via PubMed), Web of Science and Cochrane. Additionally, clinicaltrials.gov was searched to account for any possible on-going trials or unpublished data. There were no restrictions to language or publication period in any of these searches. The search strategy varied between different databases, however an example of such a search strategy as used in MEDLINE with medical subject headings (MesH) is presented in Table 1.

Appendix
Table 1. Example Search Strategy - MEDLINE

Concept	Keyword	MesH	MesH + Keyword
Obese Adults #3	Obese OR "Obese Adults"	«Obesity»[Mesh:NoExp]	«Obesity»[Mesh:NoExp] OR Obese OR «Obese Adults»
High-protein diets #2	"Low-carb* diet*" OR "Low carb* diet*"	«Diet, Carbohydrate-Restricted»[Mesh] OR «Diet, High-Protein Low-Carbohydrate»[Mesh]	«Diet, Carbohydrate-Restricted»[Mesh] OR «Diet, High-Protein Low-Carbohydrate»[Mesh] OR «Low-carb* diet*» OR «Low carb* diet*»
Serum lipid levels #1	"Serum lipid*" OR "Serum lipid levels" OR "Lipid profile" OR LDL OR "Low density lipoprotein*" OR "Beta lipoprotein*" OR "Low density lipoprotein cholesterol" OR "Low density lipoprotein cholesterol level*" OR "Total cholesterol" OR "Triglyceride*" OR "Triacylglycerol*" OR "Triacyl glyceride*" OR Fats OR Lipid* OR "Alpha lipoprotein*" OR HDL OR "High density lipoprotein cholesterol level*" OR "High density lipoprotein cholesterol" OR "LDL-C" OR "Non-HDL-C" OR "Apolipoprotein B" OR "Apo-B" OR "Apolipoprotein A1"	«Cholesterol,LDL»[Mesh] OR "Lipoproteins, HDL"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Lipoproteins, LDL"[Mesh]	«Cholesterol, LDL»[Mesh] OR "Lipoproteins, HDL"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Lipoproteins, LDL"[Mesh] OR "Serum lipid*" OR "Serum lipid levels" OR "Lipid profile" OR LDL OR "Low density lipoprotein*" OR "Beta lipoprotein*" OR "Low density lipoprotein cholesterol" OR "Low density lipoprotein cholesterol level*" OR "Total cholesterol" OR "Triglyceride*" OR "Triacylglycerol*" OR "Triacyl glyceride*" OR Fats OR Lipid* OR "Alpha lipoprotein*" OR HDL OR "High density lipoprotein cholesterol level*" OR "High density lipoprotein cholesterol" OR "LDL-C" OR "Non-HDL-C" OR "Apolipoprotein B" OR "Apo-B" OR "Apolipoprotein A1"

#1 AND #2 AND #3

(("Obesity"[Mesh:NoExp] OR Obese OR "Obese Adults") AND ("Diet, Carbohydrate-Restricted"[Mesh] OR "Diet, High-Protein Low-Carbohydrate"[Mesh] OR "Low-carb* diet*" OR "Low carb* diet*")) AND ("Cholesterol, LDL"[Mesh] OR "Lipoproteins, HDL"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Lipoproteins, LDL"[Mesh] OR "Serum lipid*" OR "Serum lipid levels" OR "Lipid profile" OR LDL OR "Low density lipoprotein*" OR "Beta lipoprotein*" OR "Low density lipoprotein cholesterol" OR "Low density lipoprotein cholesterol level*" OR "Total cholesterol" OR "Triglyceride*" OR "Triacylglycerol*" OR "Triacyl glyceride*" OR Fats OR Lipid* OR "Alpha lipoprotein*" OR HDL OR "High density lipoprotein cholesterol level*" OR "High density lipoprotein cholesterol" OR "LDL-C" OR "Non-HDL-C" OR "Apolipoprotein B" OR "Apo-B" OR "Apolipoprotein A1")

MeSH, medical subject headings.

Study Selection

Two reviewers (ML, KA) have screened all the titles and/or abstracts independently and where a disagreement arose on whether or not a study should have been included in the full-text eligibility assessment; appropriate discussion between the two reviewers had followed, and if disagreement persisted then a third independent reviewer (TR) was invited to reach a consensus. The eligibility of each full-text study to be included in the systematic review according to the aforementioned characteristics was assessed independently by the two reviewers and any disagreement was then solved by the independent third reviewer to reach a consensus. All the required information for this systematic review was found in the studies chosen. A summary of the selection process according to PRISMA guidelines for systematic reviews is presented in Figure 1. Initially the search retrieved 984 studies, from which 242 duplicates were removed resulting in 742 studies. From the remaining abstracts and/or titles 706 records were excluded according
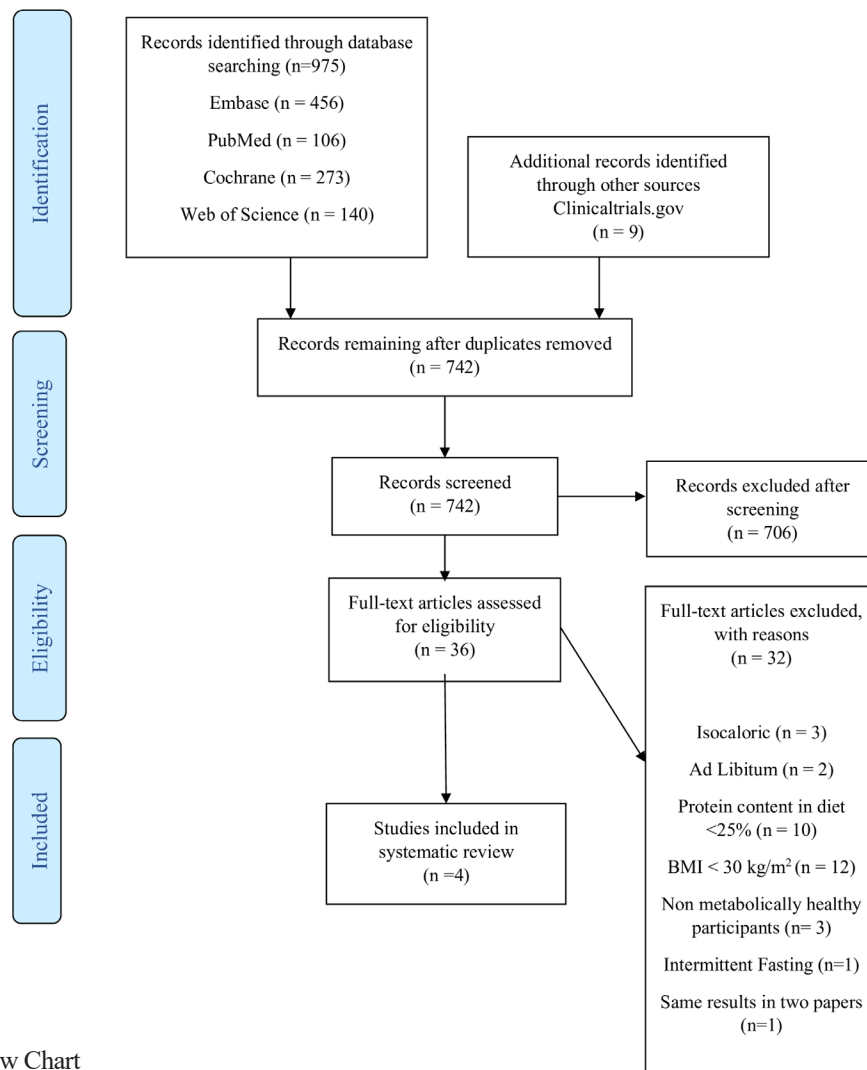

Figure 1. PRISMA FLow Chart

to eligibility criteria, a further 32 from the 36 full-text reviews were excluded based on not matching inclusion/exclusion criteria. Four studies remained at the end of the selection process.

Data Extraction

The two reviewers (ML, KA) have extracted the following data onto an excel spreadsheet, in terms of study characteristics: number of individuals randomized to each diet, length of study, diet composition, and retention rates. In terms of population characteristics, the following have been extracted: age and mean BMI (Body Mass Index), gender, baseline and final measures of; mean LDL-C (Low Density Lipoprotein Cholesterol), HDL-C (High Density Lipoprotein Cholesterol), TAG (Triacylglycerols), and TC (Total Cholesterol). Each reviewer has independently used the Cochrane risk of bias tool 2.0[15] to evaluate the degree of bias in each study and a third reviewer (TR) was invited to reach a consensus in cases of disagreement in the risk of bias of a study between the two principal reviewers. Risk of bias has been judged as "low-risk of bias, some concerns, or high-risk of bias" and evaluated according to the following domains: bias from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.

Results

In total 383 obese adults (123 Males, 260 Females) aged 36.0 to 55.0 years old (Table 3) assigned to eight hypocaloric diets (five high-protein, and three non-high-protein diets) were included across the studies. The initial mean BMI and primary outcomes measured are listed in table 2, they include changes in pre- and post- diet mean BMI, LDL-C, HDL-C, TAG, and TC levels. Studies were 4 weeks to 9 months in length. Retention rates ranged from 88.9%-100%. All studies reported statistical powers as compared to baseline values as well as between diet groups, all p-values are stated in table 2. Mean BMI change was significant from -21.3% to -60.9% of a greater decrease in the high-protein diet group as compared to the control diet groups in the two out of three studies which had both a control and high protein diet group.[16, 17] In one study both diet groups were high in protein and significant mean BMI changes were present in both diet groups as compared to baseline.[18] Significant mean BMI changes were present therefore in three studies,[16-18] the high-protein group and control diets had a mean BMI change of -2.28 kg/m^2 vs -1.85 kg/m^2 respectively. There were no significant changes in mean LDL-C, HDL-C, TAG, and TC levels among diet groups in the three studies which had both a control and high protein diet group.[16, 17, 19] The one study where participants withdrew was before randomization, and therefore whether or not an intention-to-treat analysis would have been applied to that or any of the other studies with 100% retention rates was unknown.

The risk of bias assessment noted a high risk of bias in three out of four studies[16, 17, 19] The high risks of bias in the "deviations from the intended interventions" domain in these three studies was due to a likely lack of compliance to diets as participants may have eaten more than the prescribed diet as subjects were not resident at a dietary unit. The study by

Lauran M et al.

Vol 10 No 1 (2024)

The Effects of High Protein Intake on Cardiovascular Risk Factors ...

Table 2. Reported cardiovascular risk factors and weight loss in high-protein and control diet groups

Author, Year, Country	Number of participants; M/F	Length of study	Initial Mean BMI ± SD (kg/m²)	Diet (calories/day, protein %)	(Original participants) Retention rate (%)	ΔMean BMI (kg/m²)	ΔMean LDL-C (mg/dl)	ΔMean HDL-C (mg/dl)	ΔMean TAG (mg/dl)	ΔMean TC (mg/dl)	Conclusion from each study
de Luis et al., 2015, Spain	331; 85M, 246F	9 months	35.4 ± 5.3	HP-HC (1050, 34%)	100	-2.60*	-4.30*	+1.80 NS	-14.0*	-5.60*	Mean BMI decreased significantly in both diet groups when compared to baseline, however the decrease in mean BMI was significantly higher in the HP-HC diet group than the SP-HC diet group (p<0.05). The HP-HC diet group showed a significant decrease in mean TAG whilst the SP-HC diet group did not when compared to baseline values. No significant differences were detected among basal and post-treatment values of mean HDL-C in both diet groups. No significant differences were detected between the diet groups in mean TC and mean LDL-C level decreases, which had significant decreases in both diet groups as compared to baseline.
			35.4 ± 5.3	SP-HC (1093, 20%)	100	-2.10*	-5.00*	-1.30 NS	-6.40 NS	-6.50*	
Johnstone et al., 2011, UK	(18ᵃ) 16ᵇ; 16M, 0F	4 weeks	35.8 ± 5.5	HP-LC (1907, 30%)	88.9	-2.16*	-6.57 (p<0.009)	+8.51 (p<0.001)	-51.4 (p<0.001)	-10.8 (p<0.022)	The HP-LC diet group lost significantly more mean body weight compared to the HP-MC diet group, as demarcated by the HP-LC diet group's ΔMean BMI compared to the HP-MC diet group's Δmean BMI (p<0.001). Both diet groups had significant decreases in mean LDL-C, TC, and TAG as compared to baseline, however the HP-MC diet group produced a significantly greater decrease in mean TC (p<0.05) and mean LDL-C (p<0.05) as compared to the HP-LC diet group. There were no significant differences between the diet groups in mean TAG levels. Mean HDL-C was increased significantly in both diet groups compared to baseline values, and mean HDL-C in the HP-LC diet group increased significantly more as compared to mean HDL-C increases in the HP-MC diet group (p<0.05).
			35.8 ± 5.5	HP-MC (1986, 30%)	88.9	-1.37*	-7.73 (p<0.009)	+4.24 (p<0.001)	-35.4 (p<0.001)	-22.0 (p<0.022)	
Petrisko et al., 2020, USA	17ᵇ; 3M, 14F	4 weeks	33.2 ± 2.9	VLCA (1900, 30%)	100	-	-14.5 NS	-3.90 NS	-31.2 NS	-28.5*	Mean weight loss from baseline was significant for both the LF (-2.8 kg) and VLCA (-3.3 kg) diet group however there were no significant differences in mean weight loss between the diet groups. Both diet groups had significantly decreased levels of mean TC from baseline however no significant difference in mean TC levels were found between the diet groups. There were no significant differences in mean HDL-C, or mean TAG values from baseline values in both diet groups. Mean LDL-C was decreased significantly from baseline in the LF diet group however not in the VLCA diet group.
			33.2 ± 2.9	LF (1900, 18%)	100	-	-4.00*	-4.60 NS	-6.10 NS	-9.60*	
Abete et al., 2009, Spain	19; 19M, 0F	8 weeks	34 ± 2.0	HP (18.7 kcal/kg, 30%)	100	-3.00*	-9.30 NS	-5.60*	-4.50 NS	-15.9 NS	Mean BMI was significantly reduced in both diet groups and reduced significantly more in in the HP-diet group (p=0.001) as compared to the C-diet group. Decreases in mean LDL-C, TAG, and TC in both diet groups were not significant as compared to baseline nor between diet groups. However, decreases in mean HDL-C were significant in the HP diet group and insignificant in the C-diet group as compared to baseline, however differences between the two diet groups in mean HDL-C was insignificant.
			34 ± 2.0	C-diet (17.5 kcal/kg, 15%)	100	-1.60*	-8.30 NS	-3.70 NS	-3.00 NS	-12.6 NS	

BMI, Body mass index HP-HC, High-protein, hypocaloric; SP-HC, Standard-protein, hypocaloric; HP-LC, High-protein, low-carbohydrate; HP-MC, High-protein, moderate carbohydrate; VLCA, Very low-carbohydrate; LF, Low-fat; C-diet, *Control diet*; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; TAG, Triacylglycerol; TC, Total cholesterol; NS, Not significant as compared to baseline values;
(Δ) Change between pre- and post-diet values
*p<0.05 in each value compared to baseline, ᵃ'Two participants from the original eighteen withdrew before randomization due to personal reason, ᵇcrossover RCT's where all the participants participate in each diet at separate times (randomly allocated orders), (-) values unable to be obtained
See table 3 for a complete nutritional composition of diets

Lauran M et al.   Vol 10 No 1 (2024)

The Effects of High Protein Intake on Cardiovascular Risk Factors ...

Johnstone et al.[18] had complete control over dietary input as participants were resident at a Human Nutrition Unit over the course of the study, nonetheless some concerns arose in this study as participants left the unit to attend their workplace, again indicating possible calorie intake outside of the prescribed diet. However ethical concerns arise in the nature of such dietary studies when complete surveillance of participants is present, and therefore a dietary control design as presented in the study by Johnstone et al.[18] has attempted to decrease bias in terms of dietary control to it's best abilities whilst remaining within ethical guidelines of such studies, as such the relevance of the bias score in this domain is lessened in this study. All the studies had not stated available pre-specified planned outcome analyses (as seen in registered studies on ISRCTN or an equivalent register of randomized control trials) and therefore leading all of the studies to having some concerns in the "selection of the reported result" domain. Finally the study by de Luis et al[17] had stated that subjects were allocated "alternatively" to diets, which arises concern in whether or not the subjects assigned to the diets were randomly allocated.

Discussion

Mean BMI was significantly decreased ($p<0.05$) in the hypocaloric, high-protein diet groups as compared to the control diets groups, in contrast, no significant changes ($p>0.05$) were found in mean LDL-C, HDL-C, TAG, and TC levels among diet groups. This finding suggests that hypocaloric, high-protein diets have an unclear effect on blood lipid levels as compared to other non-high-protein hypocaloric diets. In agreement with our findings, previous studies have noted that blood lipid levels were only improved within high-protein and control diet groups individually however no significant changes were found in lipid levels between diet groups.[20, 21] This is in contrast to the stated hypothesis as well as other studies' findings that suggest that higher-protein diets improve blood lipids, including decreasing LDL-C, TAG, TC and increasing HDL-C levels.[13, 14, 22] An indication for a meta-analysis of these studies is therefore justified to uncover possible combined significant changes of blood-lipid levels between diets. The results within these studies are also speculated to be confounded by dietary composition which was limited in information, for example if a diets was richer in saturated fatty acids it would likely raise lipid levels, an opposing effect to diets richer in unsaturated fatty acids.[23]

Mean BMI was significantly decreased ($p<0.05$) in three of four studies[16-18] between the high-protein and control diet groups (-2.28 kg/m^2 vs -1.85 kg/m^2 respectively) which is in agreement with other studies involving hypocaloric, high-protein diets.[10-12] A plausible explanation to the increased weight loss is that hypocaloric, high-protein diets lessen decreases in REE as compared to other energy restricted diets.[11, 24, 25] This lessened decrease in REE in high-protein diets may be explained by an increase in mitochondrial oxidation pathways specific to dietary protein intake as theorized by Abete, Parra and Martinez.[26] Additionally, dietary protein intake increases dietary thermogenesis[10] and contributes to lessened REE decreases in high-protein diets.[27, 28] The increased weight loss in the high-protein diets may also be due to these diets being more satiating than non-high-protein diets as suggested in previous studies.[29]

The Effects of High Protein Intake on Cardiovascular Risk Factors ...

Table 3. Complete stated and experimental compositions of the diets used in the studies

Author, Year, Country	Type of diet	Average Age ± SD (years)	Stated Average Calories (kcal/day)	Actual[a] Average Calorie Intake (kcal/day)	Protein (%)	Actual[a] Average Protein Intake (%)	Carbohy-drates (%)	Actual[a] Average Carbo-hydrate Intake (%)	Fat (%)	Actual[a] Average Fat Intake (%)
de Luis et al., 2015, Spain	HP-HC	50.1±13.2	1050	1101.8	34	35.9	33	34.1	33	33.0
	SP-HC		1093	1193.8	20	18.8	53	52.3	27	28.9
Johnstone et al., 2011, UK	HP-LC	55.0±14.0	1984	1907	30	28.8	4	4.68	66	67.4
	HP-MC		1984	1986	30	28.0	35	36.5	35	37.3
Petrisko et al., 2020, USA	VLCA	43.2±13.3	1900	1621.5	30	25.8	10	19.1	60	61.6
	LF		1900	1717.5	18	17.1	61	53.2	21	29.3
Abete et al., 2009, Spain	HP	36.0±6.0	18.7 kcal/kg	-	30	30.7	40	43.2	30	28.5
	C-diet		17.5 kcal/kg	-	15	17.5	55	55.9	30	30.1

SD, Standard deviation; HP-HC, High-protein, hypocaloric; SP-HC, Standard-protein, hypocaloric; HP-LC, High-protein, low-carbohydrate; HP-MC, High-protein, moderate carbohydrate; VLCA, Very low-carbohydrate; LF, Low-fat; C-diet, named "Control diet"; HP, High-protein.
(-) values unable to be obtained
[a]Actual calories, protein, carbohydrate and fat intake measured by two- or three-day food logs

This finding agrees with the decrease in caloric intake between actual and stated caloric intake values in high-protein diet groups compared to control diet groups (Table 3). Indicating voluntarily limited intake of food in the high-protein diet groups as compared to control. Qualitative questionnaires in the context of satiety are therefore warranted to explore appetite control in these diets.

On the other hand, increased gluconeogenesis as a result of the lower-carbohydrate composition[30] in high-protein as compared to control diet groups of all studies (Table 3) may have increased weight loss through additional energy expenditure as theorized in the study by Johnstone et al.[18] This study produced a significantly greater weight loss in the low-carbohydrate high-protein (LC-HP) diet group compared to the moderate-carbohydrate, high-protein diet group (MC-HP) (Table 3, Table 2). In disagreement to this explanation however, the high-protein low-carbohydrate diet group in the study by Petrisko et al[19] did not produce a statistically significant mean weight loss as compared to the control diet. This may be because actual dietary carbohydrate values (19.1%) (Table 3) were higher than stated dietary carbohydrate values (10%), therefore possibly decreasing gluconeogenesis, and hence less energy expenditure. Another possibility for the increased weight loss between diet groups is due to increased mean total body water (TBW) losses in lower-carbohydrate diet groups compared to the higher-carbohydrate diet groups as theorized in the study by Johnstone et al.[18] Even though in this study TBW loss was not significant between diets (Table 4), there was a significantly greater loss in mean free-fat mass (FFM) in the LC-HP diet group as compared to the MC-HP diet group. The increased mean FFM loss may reflect greater mobilisation of hepatic glycogen stores as a result of the low-carbohydrate content in the diet, causing an associated water loss as suggested in previous studies.[31, 32] Therefore, weight loss may have been centred around the carbohydrate rather than the high-protein composition of the diets, hence reducing the clarity of effects of hypocaloric, high-protein diets on weight loss. Reflecting on bias in the studies, the only study

Table 4. Additional reporting's in high-protein and control diet groups

Author, Year, Country	Type of diet	Average ΔFM (kg)	Δ FM P value between diet groups	Average ΔFFM (kg)	Δ FFM P value between diet group	Average ΔTBW (kg)	Δ TBW P value between diet groups
de Luis et al., 2015, Spain	HP-HC	-5.1* (p<0.05)	<0.05 S	-	-	-	-
	SP-HC	-3.4* (p<0.05)		-		-	
Johnstone et al., 2011, UK	HP-LC	-4.03* (p<0.05)	=0.733 NS	-2.72* (p<0.05)	=0.042 S	-2.55* (p<0.05)	0.075 NS
	HP-MC	-3.71* (p<0.05)		-0.61* (p<0.05)		-0.29* (p<0.05)	
Petrisko et al., 2020, USA	VLCA	-1.77* (p<0.05)	NS	-	-	-1%#	NS
	LF	-2.21* (p<0.05)		-		+1%#	
Abete et al., 2009, Spain	HP	-5.8* (p<0.05)	=0.079 NS	-	-	-	-
	C-diet	-3.5* (p<0.05)		-		-	

HP-HC, High-protein, hypocaloric; SP-HC, Standard-protein, hypocaloric; HP-LC, High-protein, low-carbohydrate; HP-MC, High-protein, moderate carbohydrate; VLCA, Very low-carbohydrate; LF, Low-fat; C-diet, "Control diet"; HP, High-protein; FM, Fat mass; FFM, Fat free mass; TBW, Total body water.
(*) Significant as compared to baseline
(#) Not significant as compared to baseline
(NS) Not significant between diets
(S) Significant between diets
(-) Values unable to be obtained

that had complete control over the prescribed diets was the study by Johnstone et al.[18] The other studies' protocols involved either providing dietary recipes to follow or food on an outpatient basis, therefore not having as much dietary input control as in the study by Johnstone et al.[18] Additionally three-day self-reported food logs to measure compliance were done towards the end of all studies. In the study by de Luis et al,[17] participants had a 100% retention rate whilst being on a supposed 1193.8 daily caloric restriction for 9 months. The food log was self-reported as being more or less within dietary guidelines of the study, however the actual mean weight loss was around -8.4 to -5.0 kg after 9 months. This weight loss is relatively low considering that participants had a calculated average BMR of 1747 kcal/day (Harris-Benedict Equation), which proposes a weight loss of at least -21.3 kg if the 9 month

diet plan was adhered to (-553.2 kcal deficit/day). The lesser-than-expected weight loss may indicate participants falsly self-reporting dietary intakes and not completely adhering to the prescribed diets.

In most studies, participants received a fixed caloric intake based on averages in weight, height, age, and sex of all participants, hence caloric deficits were not individualized, leading to possible confounding bias in primary outcome measures. The study by Abete et al[16] was the only study to measure BMR adjusted for physical exercise in individual participants via indirect calorimetry and provided diets with adjusted caloric requirements to individuals based on these BMR values. Other studies estimated average physical exercise via activity logs, which predisposes the same biases as with food logs. Therefore in order to accurately estimate individual participants

Lauran M et al.   Vol 10 No 1 (2024)

The Effects of High Protein Intake on Cardiovascular Risk Factors ...

Figure 2. Risk of Bias

BMR as adjusted for physical exercise, dietary studies should calculate BMR via indirect calorimetry as recommend by other studies.[26, 33] Providing individualized diets through indirect calorimetry may have also solved the confounding bias present in all studies with a wide age range of participants (Table 3), the wide age range is deemed a confounding bias as BMR decreases linearly with age.[34] Furthermore, all participants had voluntarily signed up to be in all these studies, which meant that these were obese adults who were motivated enough to start dieting, which may prove less external validity of studies as obese adults in the general population may not be as motivated to diet and therefore possibily have different retention rates to the obese participants in these studies. Finally, the internal validity of the studies presented in this systematic review is low as a result of non-individualized caloric intakes, high risk of biases within studies (Figure 2), different dietary compositions and other aforementioned confounders. Studies with

larger sample sizes and different study designs such as longitudinal studies are warranted to increase external validity, as well as studies with a particular focus on other cardiovascular risk factors such as hypertension and asking for complete dietary nutrient composition in these studies would provide a more complete outlook on the effects that hypocaloric, high-protein diets have on cardiometabolic health.

Conclusion

Collectively this study is unable to comment on the effects of hypocaloric, high-protein diets on blood lipid levels in obese adults, further exploration of the literature of these diets are therefore required. In contrast, weight loss was significantly greater in the hypocaloric, high-protein diet groups as compared to non-high-protein, hypocaloric diets. Further experimental studies however to investigate the reasons behind the greater weight loss relating to hypocaloric, high-protein diets

in comparison to other hypocaloric diets are strongly recommended.

Acknowledgements

Conflict of interest

None.

Declaration

The preliminary version of this paper as a Pre-Print has been appeared in AUTHORIA (2022-06-01; DOI: 10.22541/au.162694045.55171124/v1;
URL: https://doi.org/10.22541/au.162694045.55171124/v1)

References

1.   World Health Organization. Obesity and overweight [WHO]. World Health Organization. World Health Organization; 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

2.   Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and Obesity as Determinants of Cardiovascular Risk. Archives of Internal Medicine [Journal]. 2002 Sep 9;162(16):1867. Available from: https://pubmed.ncbi.nlm.nih.gov/12196085/.

3.   Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis. 1996 Jul;124:S1–9.

4.   Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a Cardiovascular Risk Factor. The American Journal of Cardiology [Journal]. 1998 Feb 26;81(4, Supplement 1):7B12B. Available from: https://www.sciencedirect.com/science/article/pii/S0002914998000319?via%3Dihub.

5.   Blüher M. Metabolically Healthy Obesity. Endocrine Reviews [Journal]. 2020 Mar 4;41(3):405–20. Available from: https://academic.oup.com/edrv/article/41/3/bnaa004/5780090.

6.   Van Gaal LF, Mertens IL, Ballaux D. What is the relationship between risk factor reduction and degree of weight loss? European Heart Journal Supplements. 2005 Nov 1;7(suppl_L):L21–6.

7.   Strasser B, Spreitzer A, Haber P. Fat Loss Depends on Energy Deficit Only, Independently of the Method for Weight Loss. Annals of Nutrition and Metabolism [Journal]. 2007;51(5):428–32. Available from: https://www.karger.com/Article/Abstract/111162.

8.   LaPorte DJ, Stunkard AJ. Predicting attrition and adherence to a very low calorie diet: a prospective investigation of the eating inventory. International journal of obesity [Journal]. 1990 Mar;14(3):197–206. Available from: https://pubmed.ncbi.nlm.nih.gov/2341226/.

9.   Bowen J, Brindal E, James-Martin G, Noakes M. Randomized Trial of a High Protein, Partial Meal Replacement Program with or

without Alternate Day Fasting: Similar Effects on Weight Loss, Retention Status, Nutritional, Metabolic, and Behavioral Outcomes. Nutrients. 2018 Aug 23;10(9):1145.

10.   Halton TL, Hu FB. The Effects of High Protein Diets on Thermogenesis, Satiety and Weight Loss: A Critical Review. Journal of the American College of Nutrition. 2004 Oct;23(5):373–85.

11.   Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. The American Journal of Clinical Nutrition. 2012 Oct 24;96(6):1281–98.

12.   Hj L, Pm C, A A, Tp W, Ms WP, Nd LM, et al. The Role of Protein in Weight Loss and Maintenance [Journal]. The American journal of clinical nutrition. 2015. Available from: https://pubmed.ncbi.nlm.nih.gov/25926512/.

13.   Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, et al. A Reduced Ratio of Dietary Carbohydrate to Protein Improves Body Composition and Blood Lipid Profiles during Weight Loss in Adult Women. The Journal of Nutrition. 2003 Feb 1;133(2):411–7.

14.   Layman DK, Baum JI. Dietary Protein Impact on Glycemic Control during Weight Loss. The Journal of Nutrition. 2004 Apr;134(4):968S973S.

15.   Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions [Website]. Cochrane Training. 2023. Available from: https://training.cochrane.org/handbook/current.

16.   Abete I, Parra D, De Morentin BM, Alfredo Martínez J. Effects of two energy-restricted diets differing in the carbohydrate/protein ratio on weight loss and oxidative changes of obese men. International Journal of Food Sciences and Nutrition. 2009 Jan;60(sup3):1–13.

17.   de Luis DA, Izaola O, Aller R, de la Fuente B, Bachiller R, Romero E. Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipocytokine levels and insulin resistance in obese patients along 9months. Journal of Diabetes and its Complications. 2015 Sep;29(7):950–4.

18.   Johnstone AM, Lobley GE, Horgan GW, Bremner DM, Fyfe CL, Morrice PC, et al. Effects of a high-protein, low-carbohydrate v. high-protein, moderate-carbohydrate weight-loss diet on antioxidant status, endothelial markers and plasma indices of the cardiometabolic profile. British Journal of Nutrition. 2011 Apr 27;106(2):282–91.

19.   Petrisko M, Kloss R, Bradley P, Birrenkott E, Spindler A, Clayton ZS, et al. Biochemical, Anthropometric, and Physiological Responses to Carbohydrate-Restricted Diets Versus a Low-Fat Diet in Obese Adults: A Randomized Crossover Trial. Journal of Medicinal Food. 2020 Mar 1;23(3):206–14.

20.   Azadbakht L, Izadi V, Surkan PJ, Esmaillzadeh A. Effect of a High Protein Weight Loss Diet on Weight, High-Sensitivity

C-Reactive Protein, and Cardiovascular Risk among Overweight and Obese Women: A Parallel Clinical Trial. International Journal of Endocrinology. 2013;2013:1–8.

21.   Ghiasvand R, Amini P, Maghsoudi Z, Feizi A, Askari G. Effects of high protein and balanced diets on lipid profiles and inflammation biomarkers in obese and overweight women at aerobic clubs: A randomized clinical trial. International Journal of Preventive Medicine. 2016;7(1):110.

22.   Hu FB. Protein, body weight, and cardiovascular health. The American Journal of Clinical Nutrition. 2005 Jul 1;82(1):242S247S.

23.   Müller H, Lindman AS, Brantsæter AL, Pedersen JI. The Serum LDL/HDL Cholesterol Ratio Is Influenced More Favorably by Exchanging Saturated with Unsaturated Fat Than by Reducing Saturated Fat in the Diet of Women. The Journal of Nutrition. 2003 Jan 1;133(1):78–83.

24.   Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity [Journal]. 1999 [cited 2020 Jan 28];23(11):1202–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10578211.

25.   Mikkelsen PB, Toubro S, Astrup A. Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate.

The American Journal of Clinical Nutrition. 2000 Nov 1;72(5):1135–41.

26.   Abete I, Parra D, Martinez JA. Legume-, Fish-, or High-Protein-Based Hypocaloric Diets: Effects on Weight Loss and Mitochondrial Oxidation in Obese Men. Journal of Medicinal Food. 2009 Feb;12(1):100–8.

27.   Westerterp KR. Diet induced thermogenesis. Nutrition & Metabolism [Journal]. 2004;1(1):5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC524030/.

28.   Tentolouris N, Pavlatos S, Kokkinos A, Perrea D, Pagoni S, Katsilambros N. Diet-induced thermogenesis and substrate oxidation are not different between lean and obese women after two different isocaloric meals, one rich in protein and one rich in fat. Metabolism. 2008 Mar;57(3):313–20.

29.   Stubbs RJ, van Wyk MC, Johnstone AM, Harbron CG. Breakfasts high in protein, fat or carbohydrate: effect on within-day appetite and energy balance. European Journal of Clinical Nutrition [Journal]. 1996 Jul 1;50(7):409–17. Available from: https://pubmed.ncbi.nlm.nih.gov/8862476/.

30.   Westerterp-Plantenga MS, Nieuwenhuizen A, Tomé D, Soenen S, Westerterp KR. Dietary Protein, Weight Loss, and Weight Maintenance. Annual Review of Nutrition. 2009 Aug;29(1):21–41.

31.   Yang MU, Itallie TBV. Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to

starvation and low-calorie ketogenic and nonketogenic diets. The Journal of Clinical Investigation [Journal]. 1976 Sep 1;58(3):722–30. Available from: https://www.jci.org/articles/view/108519.

32.   Bilsborough SA, Crowe TC. Low-carbohydrate diets: what are the potential short- and long-term health implications? Asia Pacific Journal of Clinical Nutrition [Journal]. 2003;12(4):396–404. Available from: https://pubmed.ncbi.nlm.nih.gov/14672862/.

33.   Lam YY, Ravussin E. Indirect calorimetry: an indispensable tool to understand and predict obesity. European journal of clinical nutrition [Journal]. 2017;71(3):318–22. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27848941.

34.   H S, F K. [Aging, Basal Metabolic Rate, and Nutrition] [Journal]. Nihon Ronen Igakkai zasshi. Japanese journal of geriatrics. 1993. Available from: https://pubmed.ncbi.nlm.nih.gov/8361073/.