The effects of hypocaloric, high-protein diets on cardiovascular risk factors and weight loss in metabolically healthy obese adults: a systematic review

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Abstract

Background: 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. Method: 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 Clinicaltrials.gov was also searched in order to identify unpublished or on-going studies.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 (WHO, 2020). The obese state is correlated with established risk factors for cardiovascular disease such as an unhealthy lipid profile , which include elevated triacylglycerols, total cholesterol, and low-density lipoprotein cholesterol levels as well as a decreased high-density lipoprotein 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 . 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 rather than cardiovascular disease risk as a result of the co-morbidities associated with obesity, 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 . Furthermore, weight loss is associated with a decrease in the aforementioned lipid levels (Van Gaal, Mertens and Ballaux, 2005) and therefore obese participants may experience more balanced lipid profiles when undergoing weight

reduction, as through dietary energy deficits (Strasser, Spreitzer and Haber, 2007). 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 (LaPorte and Stunkard, 1990). A clinical trial noted that hypocaloric, high-protein diets significantly lower food cravings, and improve mood in obese participants (J., E. and G., 2018). This finding concurred with the observations of several studies which suggested that hypocaloric, high-protein diets enhance weight loss and increase dietary compliance as result of increased satiety and decreased hunger (Halton and Hu, 2004; Wycherley *et al.* , 2012; Leidy *et al.* , 2015). Adding to these findings', studies involving hypocaloric, high-protein diets also concluded improved lipid profiles (Layman *et al.* , 2003; Layman and Baum, 2004). This systematic review therefore hopes to explore the effects that hypocaloric, high-protein diets have 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. The eligibility criteria of the study participants involved obese subjects (BMI [?] 30), adults (18-69 years of age), metabolically healthy participants (no co-morbid diseases such as diabetes or insulin resistance), non-smokers. The diet intervention eligibility criteria were based on hypocaloric (at least Basal Metabolic Rate (BMR)-250 kcal/day), high-protein diets (at least 25% of diet comes from proteins). 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 diet macronutrient composed 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.

Study Selection

Two reviewers will screen all the titles and/or abstracts independently and if a disagreement is reached on whether a study should be included in the full-text eligibility assessment; appropriate discussion between the two reviewers will follow, and if disagreement persists then a third independent reviewer will be invited to reach a consensus. The eligibility of each full-text study to be included in the systematic review according to the aforementioned characteristics will be assessed independently by the two reviewers and any disagreement will be solved by the independent third reviewer to reach consensus. All the required information for this systematic review was found in the studies. 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 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 will independently extract 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 will be extracted: age and mean

BMI, gender, baseline and final measures of; mean LDL-C, HDL-C, TAG, and TC. Each reviewer will independently use the Cochrane risk of bias tool 2.0 (Higgins PT Julian, Savović Jelena , Page J Matthew, Elbers G Roy, 2020) to evaluate the degree of bias in each study and a third reviewer will be invited to reach a consensus in cases of disagreement in the risk of bias of a study. Risk of bias will be 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 (123M, 260F) 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 (Abete *et al.* , 2009; D.A. *et al.* , 2015). 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 (Johnstone *et al.* , 2011). Significant mean BMI changes were present therefore in three studies (Abete *et al.* , 2009; D.A. *et al.* , 2015; Johnstone*et al.* , 2011), 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 (Abete*et al.* , 2009; D.A. *et al.* , 2015; Petrisko *et al.* , 2020). 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 (Figure 2) noted a high risk of bias in three out of four studies (Abete*et al.* , 2009; D.A. *et al.* , 2015; Petrisko *et al.* , 2020) 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 Johnstone *et al.* 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* . 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 D.A. et al. 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 (Azadbakht *et al.* , 2013; Amini *et al.* , 2016). 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 (Hu, 2005; Layman *et al.* , 2003; Layman and Baum, 2004). 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 (Müller *et al.* , 2003). Mean BMI was significantly decreased ($p<0.05$) in three of four studies (Abete *et al.* , 2009; D.A. *et al.* , 2015; Johnstone *et al.* , 2011) between the high-protein and control diet groups (-2.28 kg/m^2 vs -1.85 kg/m^2respectively) which is in agreement with other studies involving hypocaloric, high-protein diets (Halton and Hu, 2004; Wycherley *et al.* , 2012; Leidy *et al.* , 2015). 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 (Baba*et al.* , 1999; Mikkelsen, Toubro and Astrup, 2000; Wycherley*et al.* , 2012). 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, 2009. Additionally, dietary protein intake increases dietary thermogenesis (Halton and Hu, 2004) and contributes to lessened REE decreases in high-protein diets (Westerterp, 2004; Tentolouris*et al.* , 2008). 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 (Stubbs *et al.* , 1996). 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 (Westerterp-Plantenga *et al.* , 2009) 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* . 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* 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. 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 (Yang and Van Itallie, 1976; Bilsborough and Crowe, 2003). 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 that had complete control over the prescribed diets was the study by Johnstone *et al.* 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.* 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,*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* 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 BMR as adjusted for physical exercise, dietary studies should calculate BMR via indirect calorimetry as recommend by other studies (Abete, Parra and Martinez, 2009; Lam and Ravussin, 2017). 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 (Shimokata and Kuzuya, 1993). 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.

Author Contributions:

Study design, data gathering and interpretation of results: all authors

Drafting: ML

Critically revise: MH, KMA

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