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Exploring high-protein diets in the context of cardiac rehabilitation

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The review aims to explore the potential benefit and risk of high-protein diets (HPD) regarding the comorbidity of sarcopoenia and CVD in the setting of cardiac rehabilitation (CR). CR is standard care for individuals who have experienced a cardiac event, but the current practice of predominantly aerobic exercise, a lower-fat diet and weight loss poorly addresses the issue of sarcopoenia. HPD, especially when combined with resistance exercise (RE), may be valuable adjuncts to current CR practice and benefit both muscle and cardiovascular health. Meta-analyses and randomised controlled trials of HPD and CVD risk show beneficial but variable effects regarding weight loss, the lipid profile, insulin resistance and lean body mass in those living with or high risk of CVD. Meta-analyses of prospective cohort studies on hard CVD endpoints favour lower- and plant-protein diets over higher animal protein, but the evidence is inconsistent. HPD augment the strength and muscle gaining benefits of RE in older populations, but there are no published data in those living with CVD providing promising opportunities for CR research. HPD raise concern regarding renal and bone health, the microbiome, branched chain amino acids and environmental sustainability and findings suggest that plant-based HPD may confer ecological and overall health advantages compared to animal-based HPD. However, incorporating RE with HPD might alleviate certain health risks. In conclusion, a largely plant-based HPD is deemed favourable for CR when combined with RE, but further research regarding efficacy and safety in CR populations is needed.

Key words: Cardiac rehabilitation: High-protein diets: CVD: Sarcopoenia

The role of cardiac rehabilitation

Living with CVD carries considerable patient and financial burden. Being responsible for 25 % of deaths in the UK, and costing about £19 billion in healthcare and productivity[1–3], and with over 46 000 CVD-related hospital admissions over the last decade[4], further efforts to enhance and save lives are needed. Cardiac rehabilitation (CR) is a standard of care service for those who have had a cardiac event (e.g. myocardial infarction, coronary angioplasty, heart surgery, heart failure (HF) or unstable angina), involving exercise, dietary and lifestyle change, with behaviour change at its core[5]. The combination of which reduces morbidity and CVD mortality[6], improves quality of life (QoL) and reduces National Health Service costs.

In the UK, CR is delivered in four phases: phase-1 is hospital based and phase-2 at home. These two phases

Abbreviations: BCAA, branched chain amino acid; CM, cardiometabolic; CR, cardiac rehabilitation; EI, energy intake; GI, glycaemic index; HF, heart failure; HPD, high-protein diet; LDL-C, LDL-cholesterol; QoL, quality of life; RCT, randomised controlled trial; RE, resistance exercise; RR, relative risk; SPD, standard-protein diet; T2D, type 2 diabetes.

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are discussions with health care professionals about personalised lifestyle changes, returning to work and any concerns regarding a phase-3 exercise-based programme. Phase-3 is usually hospital based, and programmes are supervised by a qualified physical trainer typically delivering 6–8 weeks of aerobic-based exercise; other health care professionals provide additional education on stress, pharmacy and nutrition (dietitian). Phase-4 is delivered at local leisure/community centres by qualified physical trainers when patients are deemed cardiac stable, it provides not only about 12 week free programme but an opportunity for continued paid attendance. This is where behaviour change can be honed, and at least aimed to become habitual and further reduce risk of re-occurring cardiac events. Additionally, the British Association for Cardiovascular Prevention and Rehabilitation recognises that individuals who are at CVD risk, via other non-communicable diseases (e.g. obesity, (pre)diabetes, etc.), would benefit from CR in a preventative manner[5]. Indeed, CVD is often comorbid with the afore-mentioned and other conditions such as sarcopoenia[7], which collectively are implicated in the causal pathway. Therefore, individuals at risk can, theoretically, attend paid phase-4 CR. However, questions arise on the efficacy of this latter stage CR, especially in relation to dietary education and exercise quality as most of the research showing benefits has been conducted in phase-3 CR. Regarding the dietary component, the British Association for Cardiovascular Prevention and Rehabilitation advise a cardioprotective (lower fat) diet based on National Institute for Health and Care Excellence guidelines, with weight management where necessary[5], but recommendations in the UK are inconsistent[8].

High-protein diets (HPD) have gained a surge in popularity in recent years possibly from marketing of various high(er) protein food products[9]. The evidence base for HPD is strong for the athletic community and in older populations, where the goal of increased lean body mass and physical performance is evident[10,11]. Likewise, the effect on weight loss is reasonably convincing, via mechanisms such as enhancing anorexigenic and decreasing orexigenic satiety hormones, increased diet-induced thermogenesis and other mechanisms beyond the scope of this review[12,13]. However, the literature is controversial for cardiometabolic (CM) health and CVD.

The current CR practice of predominantly aerobic exercise[14], a lower-fat diet and weight loss does[15] not adequately address the issue of sarcopoenia and may not be optimum for reducing further cardiac events and improving QoL. Therefore, this review argues that an HPD, especially when accompanied with resistance exercise (RE) has the potential for superiority over current CR practice (but with some caveats). Most of the review focuses on the literature on HPD from a primary and secondary prevention perspective, from relevant clinical trials and observational studies on weight management, CVD endpoint and CM risk factors and discussed in the context of CR. Furthermore, the combination of HPD with RE and areas of concern including, bone and renal health, branched chain amino acids (BCAA) and the microbiome and environmental sustainability will be briefly discussed.

High-protein diets definition

Worldwide dietary recommendations for protein intake are about 0·8 g/kg/d, equivalent to about 10–15 % of energy intake (EI)[16]; in the USA there is a recommendation of 10–35 % EI[17], equivalent to about 0·75–2·5 g/kg/d for an 85 kg male consuming 10 460 kJ. In the UK recommendations are at the lower end of this range at 0·75 g/kg/d, with no range provided[18]. For this review standard-protein diets (SPD) are considered as about 0·8 g/kg/d (10–15 % EI), while an HPD can be defined as >0·8 g/kg/d (>15 % EI) and reaching as high as 2·2 g/kg/d (>30 % EI), the majority of research covered in the current review is HPD ≥18 % EI (about 1·3 g/kg/d); therefore, this value will be used to define an HPD.

High-protein diets, CVD and all-cause mortality

To gain insight into the long-term impact of HPD on hard endpoints such as all-cause and CVD mortality, we must refer to observational evidence as there are no randomised controlled trials (RCT) that have investigated HPD in this context. The four most recent meta-analyses on protein intake provide complementary and conflicting evidence. Qi and Shen[19] investigated twelve prospective cohort studies in a healthy population (*n* 483 615) with a 13 year follow-up and found the relative risk (RR) from highest to lowest total protein intake showed no significant association for all-cause or CVD mortality. Animal protein was also null for all-cause mortality but increased CVD mortality by 11 % (RR = 1·11; 95 % CI 1·01, 1·22). Plant protein reduced all-cause mortality by 8 % (RR = 0·92; 95 % CI 0·88, 0·96) but was borderline significant for CVD mortality (RR = 0·90; 95 % CI 0·80, 1·01). Regarding dose responses, for a 3 % increase in plant and animal protein intake, respectively, there was a corresponding 3 and 5 % reduction in all-cause and CVD mortality with plant protein and a 2 % CVD mortality increase from animal protein.

Chen *et al.*'s[20] meta-analysis also investigated HPD from prospective cohort studies (eleven studies, *n* 350 452 participants) in healthy populations. The results partially disagreed with the afore-mentioned in that comparing the highest with lowest total protein intake resulted in a 5 % increase in all-cause mortality (RR = 1·05; 95 % CI 1·01, 1·10), but a null finding regarding CVD mortality. Animal protein increased CVD mortality by 9 % (RR = 1·09; 95 % CI 1·01, 1·18) but results were null for all-cause mortality. Plant protein for all-cause and CVD mortality showed a 7 and 14 % lower risk (RR = 0·93; 95 % CI 0·87, 0·99; RR = 0·86; 95 % CI 0·73, 1·00, respectively). With respect to dose response, a 5 % increase in total protein, although mainly driven by animal protein, gave a 2 and 5 % increase in all-cause and CVD mortality respectively. Interestingly, geographical differences were observed with subgroup analysis with

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only North American and European studies showing positive associations with animal protein and CVD mortality whereas Japanese studies were null, suggesting the type of animal protein (e.g. red and processed meat in the west and fish in the Far East) plays a significant role. In a similar vein, the inverse associations with plant protein were synonymous with North American and Japanese studies (legumes, whole grains, nuts) but not European (grains).

In contrast to the afore-mentioned, Naghshi *et al.*[21] in a meta-analysis of thirty-one prospective cohort studies in healthy and unhealthy (those with comorbidities) (*n* 715 128) found total protein resulted in a 6 % lower all-cause mortality risk (pooled effect size = 0·94; 95 % CI 0·89, 0·99), with no significant association with CVD mortality. Unlike the Qi's and Chen's meta-analyses, animal protein was not associated with CVD (or all-cause) mortality. However, in concordance with the afore-mentioned plant protein reduced both all-cause and CVD mortality, 8 and 12 % respectively (pooled effect size = 0·92; 95 % CI 0·87, 0·97; and 0·88; 95 % CI 0·80, 0·96). Regarding dose response, for every 3 % increase in total and animal protein intake there was no association with all-cause or CVD mortality. However, plant protein increments of 3 % showed a 5 % reduced risk of all-cause mortality (pooled effect size = 0·95; 95 % CI 0·93, 0·98) but no association with CVD mortality. Subgroup analysis revealed some limitations of the studies used in the meta-analysis, for example inverse relationships with total and animal protein and all-cause and CVD mortality were only found in studies that did not control for energy and macronutrient intake and were followed-up for <15 years. Subgroup analysis for plant protein had little impact, with the inverse relationship and all-cause mortality remaining regardless of studies that controlled for numerous confounding covariables. Sensitivity analysis only affected the plant protein and CVD mortality results, with removal of four studies the results changed from null to marginally inversely significant.

The most recent systematic review and meta-analysis of prospective cohort studies (fourteen studies, healthy participants, *n* 656 490) by Mantzouranis *et al.*[22] found no relationship on total protein for cardiovascular death, stroke or a composite endpoint of stroke, non-fatal myocardial infarction and cardiovascular death, but did not investigate differences between animal and plant proteins. Part of the rationale for this study was that previous meta-analyses used a vague definition of high(er) protein diets, where they split the sample population by percentiles and compared highest with lowest protein intakes. Pointing this out as a limitation that even the highest intake may still be within normal range intakes, Mantzouranis *et al.*[22] created an arbitrary cut-off of 18 % EI, equivalent to approximately 1·3–1·4 g/kg/d protein intake, based on previous definitions of HPD falling between 1·2 and 1·6 g/kg/d. The meta-analysis included thirteen studies (*n* 656 490), the HPD group consumed 92·5 g/d of protein daily, and 72·8 g/d in the SPD group – less than the afore-mentioned 1·4 g/kg/d cut-off for average male and female weight of 85 and 72 kg respectively and more like a combined 1·2 g/kg/d although still higher than the global 0·8 g/kg/d. Regarding the lack of subgroup analysis for plant and animal protein, the authors state that it is unrealistic for a solely plant-protein diet to be sustainable due to nutrient availability.

Collectively, the evidence supports that plant protein may have a protective effect, while animal protein could potentially contribute to CVD risk. However, it is essential to acknowledge that the data from these studies are observational and may be subject to limitations such as reliability of diet data collection, residual confounding and are limited regarding the use of percentiles rather than using published high-protein cut-offs. Adjustments for all possible variables were not made, and other factors such as cooking practices and the type of protein consumed, specifically red and processed meat, may play significant roles in these associations. Examining the work of Ibsen *et al.*[23] in the context of type 2 diabetes (T2D), where they demonstrated that replacing red/processed meat with plant-based or alternative protein sources such as chicken and fish led to a lower risk of T2D, raises the importance of investigating the quality of animal protein and the animal:plant protein ratio. Animal proteins are nutrient-dense and constitute a vital part of an omnivorous diet. In addition, most meta-analyses were conducted in healthy populations rather than those living with CVD. Further research is warranted to investigate higher protein intake, its impact on health outcomes in normal healthy populations and those living with or at risk of CVD, to obtain a more conclusive and reliable understanding. For a more complete understanding, we must also consider intervention studies.

High-protein diet and cardiometabolic risk

HPD may be a worthwhile macronutrient to replace SFA and thereby reduce LDL a major causal risk factor for CVD[24]. While evidence on the role of SFA in the aetiology of CVD and CM risk is still under debate[25] the UK and worldwide recommendations limit dietary intake to about 10 % of energy[17,26,27], a consensus built upon over 70 years of research. This has led to a vast amount of research on the most appropriate macronutrient to replace SFA, with evidence showing both PUFA and carbohydrate can reduce cardiovascular events[28] and PUFA, MUFA, wholegrain carbohydrate, and lean animal protein can improve various CVD risk markers including the lipid profile[29]. While replacing SFA with carbohydrate elicits a reduction in LDL-cholesterol (LDL-C) and HDL-cholesterol, the more refined types (e.g. sugar-sweetened beverages) can elevate plasma triglycerides and therefore more whole-grain and other unrefined carbohydrate are recommended[30]. Considering the UK's reduction in sugar recommendations to 5 % EI, HPD could also contribute to their replacement and may mitigate sugar cravings[31]. There are a small number of meta-analyses of RCT over the last decade that have investigated the effects of HPD

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on CM risk markers. For example, Zhao *et al.* and Yu *et al.* focused on T2D with either high-protein low-carbohydrate or high-protein low-fat diets compared to mainly lower protein, higher carbohydrate diets[32,33]. However, Wycherley *et al.* included various CM risk groups[34] and Vogtschmidt *et al.* focused on healthy populations[35]. The consensus of all four meta-analyses was a lowering of plasma triglycerides, but Yu *et al.*[33] also showed HPD superior for LDL-C, total cholesterol and insulin resistance with Vogtschmidt *et al.* agreeing regarding total choleterol but also significantly lowering systolic blood pressure[35]. In the meta-analysis conducted by Zhao *et al.*[32] (duration: 4 weeks to 24 months across eighteen studies, *n* 1099), the authors conducted a subgroup analysis specifically examining CHO intake. Upon contrasting HPD with low-carbohydrate intake against low-protein diets with similarly low-carbohydrate intake (while maintaining a comparable fat ratio), the discernible impact on triglycerdies was negated. This suggests that the observed effect might be due to the lower carbohydrate intake rather than manipulation of protein EI. Regarding the Yu *et al.*'s meta-analysis (12 weeks to 52 months across thirteen studies, *n* 1138), a more stringent set of inclusion criteria was applied with a minimum duration of 12 weeks and a protein EI of ≥25 %, with the intention of enhancing study robustness. Notably, while yielding some of the same studies used by Zhao *et al.*'s meta-analysis, Yu *et al.* did not undertake subgroup analysis with respect to carbohydrate or fat intake, which may have explained the additional reduction of total cholesterol and LDL-C, perhaps being driven by protein replacing saturated fat. Similarly, while Wycherley *et al.*'s[34] meta-analysis of twenty-four studies (*n* 1064) focused on a comparison between HPD and SPD with EI from fat of ≤ 30 % the range of CHO intake across the studies was 25–45 %, with the majority about 40 % EI, again suggesting lower carbohydrate was responsible for the lower triglycerides.

Lowering triglycerides maybe specifically relevant for those living with CVD (attending CR). While the lowering of LDL-C is mainly treated with statin therapy (thereby reducing secondary cardiovascular events)[36] there is a potential residual CVD risk from triglycerides[37]. While the causal role of triglycerides in atherosclerotic CVD is still under debate, due to confounding from other lipids and lipoproteins, there is growing evidence of a causal role for triglyceride-rich lipoproteins such as remnant lipoproteins that can undergo similar uptake by the arterial wall as LDL but with greater atherogenicity per particle[37]. Therefore, a lower carbohydrate diet with higher protein may be effective here with the additional benefit of the high protein keeping saturated fat lower. For example, a macronutrient profile of 30/40/30 for protein, CHO and fat intake may be sufficient to lower triglycerdies and keep saturated fat low enough if carefully designed. Indeed, in the only study in those living with CVD, Evangelista *et al.*[38] compared this ratio of macronutrients *v.* an SPD (15/55/30) showing a significant lowering of triglcyerides, LDL-C and HbA1c after 3 months. While there are no known studies of HPD on remnant lipoproteins, in an open label, pre-post, participant self-designed HPD (30/30/40) study in those living with T2D, Alzahrani *et al.*[39] showed a reduction in traditional lipids including total cholesterol, LDL-C and triglycerides but also more advanced lipoproteins including apolipoprotein B after 36 weeks. By lowering triglycerides and apolipoprotein B these results suggest a reduction in triglyceride-rich lipoproteins.

Beyond the basic lipid profile there is growing consensus that a nuanced analysis of lipids and lipoproteins, including details of lipoprotein subclasses, provides greater insight into age-related diseases including CVD and sarcopoenia[40]. Kratz *et al.*[41] when replacing SFA with either carbohydrate or lean protein, under isoenergetic conditions, showed mixed effects on the different groups of the study. The carbohydrate group (*n* 16), while reducing LDL-C also increased triglycerides and lowered HDL-cholesterol with a shift of LDL to the small and dense, atherogenic phenotype prevalent in obesity and metabolic syndrome[42]. However, the lean protein group (*n* 19) also lowered LDL-C and HDL-cholesterol with no change in trglycerides or LDL subclasses without weight loss; with weight loss the addition of shifting LDL towards the larger, buoyant subclass suggesting a further reduction in CVD risk[42]. This study is of particular interest as it provides evidence that HPD can improve CM risk with or without weight loss. To the authors' knowledge, only one other study[43] on high-protein meals rather than overall diet showed a lower postprandial triglycerides effect of the high-protein meal compared to a high-MUFA meal but the protein meal was less favourable for small, dense-LDL and -HDL. Clearly, further larger powered RCT are needed to investigate the effect of HPD on the intracity of lipoprotein subclasses. Higher relative protein diets in the light of lowercarbohydrate (e.g. Atkins-style) are promising for improving lipoprotein subclasses[44,45] but are not particular high protein in absolute amounts with the effect more likely due to lower carbohydrate and energy restriction.

More recently, Tettamanzi *et al.*[46] demonstrated that their study (*n* 11 on a Mediterranean diet, and *n* 5 on HPD in obese pre-diabetic women) showed the HPD reduced insulin resistance and lowered fluctuations in daily glucose variability. The investigation of microbiome variations associated with the HPD offers partial explanation of the glucose variability, although the study's limited sample size and duration of 21 d warrant further exploration. In contrast, a larger study in overweight/obese adolescents (*n* 126) the prevention of diabetes through lifestyle intervention and population studies in Europe and around the world study showed no effect of an HPD/low glycaemic index (GI) *v.* SPD/medium GI diet but the authors state dietary compliance and retention to the study was a major limitation rendering the study unfeasible[47]. Further evidence on high protein, low GI comes from the largest high-protein dietary intervention (*n* 932) the DiOGenes study (a large Pan European 12 month RCT investigating the most effective diet for weight loss and secondary prevention of weight regain)[48]. The study started with an 8 week, 8 % weight

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reduction phase followed by a weight maintenance phase (26 weeks) that compared SPD *v.* HPD with either low or high GI, resulting in a four-arm intervention *v.* a control diet. While all groups lowered high-sensitivity C-reactive protein (approximately equally) after the weight loss phase, the weight maintenance phase favoured further reductions in the low GI groups and to a lesser extent with the low-protein groups. There were no differences between diets in any lipids or blood pressure between groups after the maintenance phase.

The evidence on the impact of HPD on CM risk is clearly mixed. The effects on the lipid profile favours HPD with lower carbohydrate intake for improvement of plasma triglycerides, which seems to be the most consistent result. While this is probably driven by the lower carbohydrate percentage of the diet, HPD can replace saturated fat. The lowering of LDL-C that would be expected to follow this, however, is inconsistent. Other CM risk markers including glycaemic control and inflammation are limited by the number of studies. Overall, there is a high degree of heterogeneity in study designs including proportions of macronutrients, comparison diets, populations studied, duration, sample size and the type of CM risk markers measured. Furthermore, contemporary nutrition research focuses on dietary patterns with more emphasis on the quality of foods within the diet. To date, studies on HPD have not largely stipulated the quality of food and it is possible to have a similar macronutrient profile but with varying quality of food. Further research on HPD that focus on the dietary pattern including the type and quality of protein-rich food, as well as the quality of CHO and fats are needed to fully understand the effects. Regarding the study population, there is a need for more RCT on the secondary prevention of CVD in the setting of CR.

High-protein diets, body composition and sarcopoenia

Overweight and obesity are global problems that increase with age and are implicated in several non-communicable diseases, such as T2D and CVD amongst others. They also exacerbate risk of falls in older populations, render activities of daily life difficult and contribute to a poor QoL[49–51]. The afore-mentioned resonates with patients living with CVD[52], and why weight management is a key component of CR. One of the reasons HPD are popular is their potential for weight loss and maintenance, and their implication to CR programmes may provide an effective strategy for those living with CVD. A recent meta-analysis/systematic review regarding HPD and weight loss/maintenance shows superiority for weight loss compared to an SPD, with a relatively small but significant mean difference of 1·6 kg[53]. Although modest, for every 1 kg of weight loss there is a reduction of 16 % risk of T2D[54], but greater weight loss of 5–10 % might be necessary for various CVD risk markers and >10 % is predicted for mortality[55]. Therefore, an HPD in CR where weight loss is needed could be a useful contributor in combination with other weight loss or body composition strategies. The study also highlighted studies that grouped participants by phenotype and genotype, with prediabetics losing significantly more weight than normoglycaemic populations, and perhaps more importantly regaining less weight compared to an SPD. Given the frequent comorbidity of dysglycaemia with CVD, an HPD could be especially pertinent for individuals attending CR. Regarding genotype, the transcription factor activator protein-2 β is recognised as an obesity contributing factor[56], that seems to play a role in weight loss/maintenance success. Those with the AA (non-obesity) genotype regained body weight with an SPD but lost further weight on an HPD. However, carrying a G allele resulted in regained weight regardless of diet. This approach is important and should be further investigated in those living with CVD to gain insight into the responsiveness of an HPD, that maybe used to personalise future CR. A limitation of this meta-analysis was a lack of evidence regarding body composition, and the majority of included studies substituted carbohydrate for protein.

HPD are often promoted for the ability to preserve lean mass during energy restriction. This is especially important in older populations, where not only obesity and CVD prevalence peaks in the fifth and sixth decade but sarcopoenia or sarcopoenic obesity is also widespread[57]. Indeed, sarcopoenia is often comorbid with CVD, pre- and T2D and a common feature in CR clinics[58] and why indiscriminate weight loss may be suboptimal to reduce secondary CVD events and QoL. In this context, weight loss and maintenance strategies should be designed to preserve lean body mass. A recent network meta-analysis investigated various nutrition (including energy restriction, HPD, 5:2 diet) exercise (aerobic, resistance and combined) and combinations of nutrition and exercise RCT on body composition and anthropometric outcomes in a retirement age population[59]. The most effective interventions for the combined outcomes were energy restriction and an HPD; resistance or mixed exercise alone or energy restriction, HPD and exercise combined. This paints a favourable picture for an HPD during energy restriction for an age group at risk of CVD, which may be translated to CR. The exercise component is of particular importance as previous meta-analyses that focused only on an HPD have been inconsistent regarding body mass/composition, with Zhao *et al.*[32] showing no effect on T2D but an older study by Wycherley *et al.*[34] improved both outcomes in mixed CVD risk populations, including a study in HF.

The study on HF by Evangelista *et al.*[60] was the only available RCT in those living with CVD (overweight and obesity) at the time of Wycherley's meta-analysis. This was a 12 week pilot study with *n* 5 on HPD and SPD respectively, against a conventional diet control (*n* 4). The HPD resulted in nearly 10 kg loss in body weight (while preserving lean body mass) *v.* 5·5 kg with the SPD and a 1·5 kg weight gain with the conventional diet ($P < 0{\cdot}001$). Evangelista *et al.*[38] published a larger study in 2021 in those living with HF comorbid with T2D; the HPD (*n* 33; SPD *n* 43) resulted in a less profound weight loss than the pilot study of 3·6 and 3·0 kg

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for HPD and SPD respectively with no significant difference between diets. Unfortunately, the study did not measure lean body mass. These studies are the only known (to the authors' knowledge) HPD RCT on those living with CVD. With HF being only one category of CVD, and as most CR deals with CHD[61], this highlights the importance of further research in other categories of CVD (CR).

Regarding HPD with lower carbohydrate content, Clifton *et al.*[62] presented evidence from a wide range of low carbohydrate, HPD studies with ≥12 months follow-up (*n* 34). The evidence shows a consistent reduction in body weight, with no effect on lean body mass suggesting most of the weight loss was from fat mass. The greater the difference (≥5 % protein energy) between diets, or the higher the absolute amount of protein, the more profound the result with respect to fat mass reduction. In contrast, a meta-analysis of 12 month studies of HPD with low fat showed no difference in body weight or fat mass[63]. The meta-analysis by Clifton *et al.*[62] used a broad definition of low carbohydrate, HPD and it is not clear on whether the higher protein or the lower carbohydrate was the 'driving' factor for weight management benefits. In a novel 12 month weight loss and maintenance study, Soenen *et al.*[64] showed that raising dietary protein is much more relevant than lowering CHO with respect to weight and fat loss. The design of this study compared four isoenergetic diets: HPD low carbohydrate; HPD lower fat; SPD low carbohydrate and SPD lower fat. The results revealed that both HPD induced superior effects with respect to weight and fat mass reduction compared to normal protein (low carbohydrate or low fat). The benefits of HPD show that after a minimum of 12 months post-intervention there remains a small, but significant reduction in body weight and fat mass suggesting that the success of the intervention encouraged the participants to remain on the HPD. Compliance at post-intervention was indicated and that while the high-protein groups appear to be more compliant post-intervention compared to the SPD, compliance was still an issue. Further evidence regarding compliance can be drawn from the DiOGenes project[65]. The results showed an HPD with a drop-out rate of 26 % compared to 61 % in the low-protein group. Other benefits were a slower rate of mean weight regain (3·8 *v.* 5·8 kg) and fat mass (3·4 *v.* 1·8 kg). The authors speculate the HPD may be easier to comply with due to a more palatable diet.

Further supportive evidence, for weight maintenance, was found by Ankarfeldt *et al.*[66] who matched large data sets from an observational study (Danish Diet, Cancer and Health study) and the DiOGenes project. The Danish Diet, Cancer and Health shows a positive association with body weight gain and dietary protein whereas the DiOGenes study[65] found HPD reduce body weight and aid in weight maintenance as described earlier. Therefore, Ankarfeldt *et al.*[66] matched and re-analysed data from both studies and found similar results to Clifton *et al.*[62] in that HPD *v.* SPD resulted in greater weight maintenance. Additional findings from this study showed the obese or abdominally obese participants are even more likely to benefit from an HPD with respect to weight maintenance, which may benefit CR post weight loss.

As mentioned, sarcopoenia and sarcopoenic obesity, characterised by low physical strength and muscle mass[67] with added adipose (especially visceral) for sarcopoenic obesity are comorbid with CVD[7,68]. This is particularly prevalent in older populations and a predominant feature in CR[69,70]. There are numerous mechanisms implicated in the aetiology of sarcopoenia, including inflammation, oxidative stress, dyslipidaemia and endothelial dysfunction amongst others that are beyond the scope of this review. The author refers the reader to other comprehensive reviews for further details[7,68]. The most effective treatment for sarcopoenia is exercise[71]. While aerobic style exercise offers reduction of CVD risk from other mechanisms (e.g. peak oxygen consumption), the benefit to physical strength and muscle mass is inferior to RE and a concurrent approach may be best for CR[72]. Beyond its contributions to strength and lean mass, RE offers a multitude of substantial benefits, particularly in the context of CR. Engaging in RE results in a notable reduction in overall mortality and specifically CVD mortality, enhances insulin sensitivity and improves the lipid profile and other components of metabolic health. Beyond the physiological benefits it also enhances the ability to engage with activities of daily living and QoL[72].

It becomes evident that there is a compelling rationale for the integration of RE alongside an HPD for those living with comorbid CVD and sarcopoenia. While there is no direct evidence in this population for this combined approach, we can draw from other supportive evidence. Meta-analyses of HPD or high-protein supplementation combined with RE in older populations show an HPD augments the existing benefit of RE of increasing both lean body mass and strength[11,59,73]. While the advantage of RE over current CR has not been established for functional capacity[71,74] this may be due to the lack of nutritional consideration especially regarding adequate protein intake. Multimodal interventions including concurrent exercise training and appropriate nutrition are hypothesised to be the most effective. The current author is leading a study investigating an HPD Mediterranean-style diet, the protein Mediterranean-style diet and resistance exercise in cardiac rehabilitation patients with sarcopoenic obesity study[75,76], which is currently in the pilot phase. The results from this study are anticipated to offer a deeper understanding of a multimodal intervention of an HPD Mediterranean-style diet pattern with RE, and its potential impact on sarcopoenia and CM risk in those attending CR.

The weight of evidence suggests HPD *v.* SPD with energy restriction are superior for weight loss/maintenance and preserving lean body mass, with the latter improved with the addition of exercise. Individuals with a higher CVD risk profile (overweight and obesity and/or impaired glucose metabolism) show a higher magnitude of response regarding weight and fat loss. The combination of preserving lean body mass while losing fat mass is especially important to those living with

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CVD as sarcopoenia and/or sarcopoenic obesity is prevalent. While the evidence regarding HPD is relevant to CR, it is currently premature to suggest their incorporation into CR programmes. Further research is necessary to fully understand the implications of HPD in the secondary prevention of CVD, with robust evidence base focused not only on weight loss and body composition, but long-term maintenance, compliance, the importance of personalised responses with the consideration of pheno- and genotyping, and its combined effect with exercise and lifestyle change programmes.

High-protein diet and areas of concern

The afore-mentioned shows that HPD may benefit those living with CVD, but there may be potential risks related to bone and renal health, the microbiome, saturated fat intake and the role of BCAA. Furthermore, the potential for any environmental harm should be considered.

There is a common belief that HPD are detrimental to bone health, based on the hypothesis that a higher acidic load from animal protein would cause mobilisation of calcium carbonate from bone tissue to act as a buffer and eventually lead to osteoporosis[77]. However, in healthy individuals, protein intake variations do not significantly impact blood pH and serum bicarbonate levels[77]. Furthermore, recent systematic reviews/meta-analyses and the European Society for Clinical and Economical Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation support a protein intake beyond SPD in older populations as long as dietary calcium is met[78–80]. Regarding renal health, there are concerns that excess dietary protein may induce an initial increase in glomerular filtration rate followed by a detrimental decline that could lead to kidney damage or impaired function[81]. This is particularly relevant for those living with CVD and comorbid with pre-existing renal disease, where an HPD should be avoided, and recommendations are often lower than SPD[82]. Regarding causality there is no strong evidence that HPD can cause kidney damage. However, Ko *et al.* suggest those living with T2D and CVD are at higher risk of renal damage with an animal (mainly red and processed meat) based HPD, but plant-based protein maybe beneficial[81]. For individuals without renal disease, an HPD of up to 1·5 g/kg/d might generally be appropriate. However, individuals at risk of renal disease, such as those living with CVD, may need to exercise with caution[83]. Notably, it is worth considering that the combination of concurrent exercise training (resistance plus aerobic) has been shown to enhance renal function in chronic kidney disease[84]. Therefore, combining exercise with a predominantly plant-based HPD (e.g. 1·3–1·5 g/kg/d) is hypothesised to yield beneficial or at least neutral effects on renal function within the context of CR.

Dietary proteins, after digestion, are absorbed in the small intestine but a small undigested component and peptides/amino acids are fermented by the microbiome in the large intestine. In turn, various byproducts are produced that may impact CVD risk, including hydrogen sulphide, indoles, butyrate, *p*-cresol sulphate, trimethylamine *N*-oxide, amongst others[85]. There is limited evidence from RCT regarding HPD, with some studies showing detrimental associations with red and processed meat with microbiome diversity and potentially harmful molecules, with the absence of dietary fibre potentially underpinning this mechanism[46,85–88]. For example, Russell *et al.*[88] found potential drawbacks of an HPD with low CHO/fibre with fewer beneficial bacteria and reduced butyrate and antioxidant phenol levels. However, HPD with high-fibre and plant-based HPD may exhibit beneficial effects. For example, Dong *et al.*[89] showed in obese participants, a hypoenergetic HPD compared to an SPD elicited differential effects on the microbiome but both diets were beneficial regarding specific bacterium linked to improved insulin resistance. The HPD was a mix of animal and plant proteins, with additional supplementation with a pea protein product. When HPD are coupled with exercise, concerns are largely alleviated, as the inclusion of physical activity may counteract any potential negative impact on the microbiome[85] but evidence is lacking in those living with CVD. With relevance to CR and comorbid sarcopoenia, the combination of exercise, an HPD (high in fibre) with a combination of animal- and plant-based proteins, tailored to the individual, is a potential solution. While this agrees with others regarding older obese populations[90], large-scale RCT are needed in those living with CVD to determine the amount and type of protein and the impact of exercise before making any specific recommendations. There may be some trade-offs with this approach, i.e. superior effect on sarcopoenia but suboptimal for the microbiome.

HPD of animal sources are often labelled as higher in saturated fat with concerns regarding LDL-C and CVD. By opting for lean protein sources, such as poultry, fish and plant-based proteins, it is possible to achieve the desired protein intake without significantly increasing saturated fat intake. For example, when incorporating lean red meat into a Mediterranean-style diet both LDL-C and apolipoprotein B were reduced compared to a standard Mediterranean-style diet[91], and a low-fat HPD either animal- (high in meat and dairy) or plant-based (rich in legumes) reduced hepatic fat and improved insulin resistance independent of weight loss with no significant difference between diets[92].

From an ecological perspective, HPD and high-meat diets have been projected to negatively impact upon environmental, land use and agricultural input metrics[93] but the issue is complex as animal protein is nutrient-dense and certain regions may benefit from an increase[94]. Coupled with world population growth and climate change, there is a higher demand for protein-rich food, creating a nutritional and ecological challenge. Various innovations are suggested in the literature to meet this challenge, including the consumption of edible insects[95], an increase in plant-based and other non-animal proteins such as microbial proteins[96,97] and more efficient animal and milk farming[98]. Fermentation technology such as

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cultured meat and fungal-based egg and whey protein are under development[99,100], but the technology is in its infancy and cultured meat is questionable regarding safety, acceptability and environmental sustainability[101].

The role of BCAA in CM disease has gained considerable interest. Elevated levels of BCAA activate mammalian target of rapamycin signalling in macrophages, promoting inflammation and contributing to atherosclerotic plaque development[102], and are implicated in insulin resistance and the pathogenesis of diabetes[103]. Dietary patterns with high-animal and low plant-based proteins are associated with higher plasma BCAA[104] while exercise also plays a role in BCAA metabolism linked to greater strength, increased muscle protein synthesis with neutral or improved insulin sensitivity[105–107]. It is important to note that the mechanisms between BCAA, mammalian target of rapamycin signalling and cardiovascular risk is complex and not fully understood and beyond the scope of the current review; the author suggests the following for further reading[102,106]. Exercise may mitigate risks, but further research is needed to fully understand the impact of BCAA on macrophage mammalian target of rapamycin signalling and their role in CM health. Based on the current available evidence, once again, a plant-based HPD combined with exercise is likely to be more favourable in a CR population.

Overall, while areas of concern regarding HPD exist careful consideration regarding dietary design to include a largely plant-based HPD in combination with concurrent exercise seems to be the most prudent approach. However, certain areas need further research, and the key may lie with a balance that optimises health benefits while considering potential 'trade-offs', ultimately leading to a sustainable approach to dietary choices.

Conclusions

Regarding observational prospective cohort studies, the potential of plant protein in mitigating the risk of all-cause and CVD is evident. While the evidence for animal protein remains less definitive, notably influenced by variables such as red and processed meat consumption, and the potential influence of confounding factors such as cooking practices must be acknowledged. In the context of RCT, the implementation of HPD (lower in CHO) emerges as a promising strategy for reducing TG levels, although outcomes related to LDL-C and other CM risk markers remain inconclusive. Further evidence on CM risk markers is needed but also investigating advanced lipoproteins such as apolipoprotein B, lipoprotein subclasses, TG-rich lipoproteins amongst others is warranted in a CR population who are subject to residual CVD risk. There is a considerable lack of HPD RCT data in secondary CVD prevention and a CR setting is an obvious place to conduct this type of research.

The combination of an HPD with RE yields a 2-fold benefit: it improves body composition (reduces adipose tissue and increases lean mass), and increases physical strength, which is particularly advantageous in addressing comorbid sarcopoenia accompanying CVD. This symbiotic relationship extends to greater independence with improved ability to perform activities of daily living and a higher QoL, providing obvious benefit to a CR population. While HPD present a risk in the context of renal health for individuals with kidney disease, there is no convincing evidence of a causal relationship in those without or even at risk of renal disease but caution regarding animal proteins seems to be prudent here. The long-held belief of a negative effect on bone health seems to be unfounded with observational evidence suggesting the opposite.

With respect to the gut microbiome evidence on HPD is scarce with a degree of uncertainty. While animal protein maybe detrimental a lack of fibre cannot be ruled out, and therefore including plant-based proteins may be necessary. Whether this is optimum for the microbiome remains to be seen but weighing up a 'trade off' for other health benefits (e.g. body composition) may be needed. Similarly, plant-based proteins offer greater alignment with environmentally responsible dietary choices but it is important to recognise that animal protein is nutrient-dense and an omnivorous diet can still be healthy with careful design. The future path towards sustainable dietary practices may involve technological innovations in farming, fermentation techniques, the incorporation of alternative sources such as insects and microbial based protein and the greater utilisation of plant-based proteins such as legumes. Regarding CR where obesity, overweight and sarcopoenia are prevalent a modernisation of current practice to incorporate HPD with concurrent resistance and aerobic exercise is hypothesised to be effective for cardiovascular and skeletomuscular health. Caution regarding comorbid renal disease should be taken and a careful design of the HPD to include lean sources of animal protein and a high proportion of plant-based proteins to satisfy health and environmental concerns should be considered. However, further research is needed in this population regarding the amount of protein, its proportion from plant/animal and the remainder of the diet. While it is tempting to suggest macronutrient percentages, modern nutrition focuses on dietary patterns and the quality of food and there are many potentials for high-protein dietary patterns that need investigating, how they can be personalised, and how they align with an effective exercise programme for promoting reduced risk of secondary cardiovascular events and improving skeletomuscular health.

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Conflict of Interest

The author has received two grant applications from the Liverpool Clinical Commissioning group for research on high-protein diets in cardiac rehabilitation.

Authorship

I. G. D. conceptualised, wrote and edited the manuscript.

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