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FEATURE ARTICLE

MODERN FOOD SYSTEMS AND THE RISE OF MEDICALISED WEIGHT LOSS:

THE CARDIOVASCULAR CONSEQUENCES

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ABSTRACT

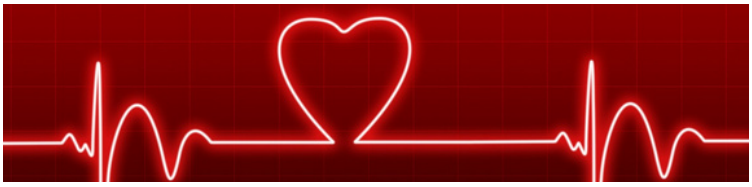
Cardiovascular disease (CVD) remains one of the leading global causes of morbidity and mortality despite advances in medical, nutritional and lifestyle management. Concurrently, ultra-processed food (UPF) consumption has increased, which has been associated with obesity, insulin resistance, dyslipidaemia, hypertension, and cardiovascular events. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown significant reductions in body weight and major adverse cardiovascular events (MACE) in high-risk populations; however, concerns remain regarding their long-term use. This review aimed to evaluate the data surrounding UPF consumption on cardiovascular health and the effect of GLP-1RAs on CVD.

The review highlighted a mismatch between upstream drivers of disease and downstream treatments. Epidemiological evidence reported that the consumption of UPFs was associated with a 50% increased risk of CVD associated mortality and a 12% increased risk of CVD development. Randomised control trials (RCTs) suggested that UPFs may act on the cardiovascular system through gut dysbiosis and impaired cardiovascular function. Cohort studies and RCTs indicated that the displacement of nutrients, with replacement of UPFs, which may benefit the cardiovascular system, such as fibre, polyphenols, and specific micronutrients, may also contribute to CVD risk. However, interpretation should be made with caution as epidemiological studies do not infer causation, and some studies were small and with methodological limitations. The adoption of a minimally processed diet in comparison to an UPF dominated diet may aid weight loss and the improvement of some but not all blood lipid markers associated with cardiovascular risk.

GLP-1RAs were shown in systematic reviews and meta-analyses of RCTs to have clinically meaningful benefits to CVD and reduce the risk of major adverse cardiac events (MACE) by 13% and cardiovascular mortality by 12%. Long-term GLP-1RA use was shown to be associated with side effects such as gastrointestinal (GI) disorders. Nutrient deficiencies were associated with GLP-1RA treatment in observational studies but methodological limitations means that further research is warranted before causation is established. Lean muscle mass reduction was reported in RCTs following GLP-1RA treatment. Weight regain and the reversal of improvements to cardiometabolic risk factors were also reported in RCTs following GLP-1RA treatment cessation.

The Mediterranean diet (MedDiet) was shown in one RCT to be associated with small improvements to systolic blood pressure and endothelial function compared to a typical Western diet, however improvements were likely to be too small to be clinically meaningful. When compared to a low-fat diet, the MedDiet was associated with a 30% decreased risk for cardiovascular events in one large RCT. Despite limitations, the MedDiet and the adoption of minimally processed food diets may provide a nutrition-first upstream solution facilitating lower CVD risk, and may be necessary for individuals who have been medically prescribed GLP-1RA to support nutrient intake. Such diets may also provide a long-term solution to weight loss after GLP-1RA treatment has ceased.

It was concluded that under medical guidance, GLP-1RA therapy may provide CVD benefits but long-term CVD prevention is unlikely to be achieved through pharmacological intervention alone. Greater emphasis on reducing UPF consumption and the adoption of whole-food diets such as the MedDiet may be necessary to address upstream drivers of disease and improve long-term cardiovascular and cardiometabolic outcomes.



THE BURDEN OF CARDIOVASCULAR DISEASE

INTRODUCTION

In 2019 global burden of CVD was more than 523 million individuals worldwide, with prevalence expected to increase by 90% over the coming decades (1,2). Although risk factors such as hypertension, dyslipidaemia, obesity, smoking, and type 2 diabetes (T2D) have been long recognised for CVD, growing evidence suggests that changes within modern food environments may act as upstream contributors to CVD (3).

Modern dietary patterns have shifted towards increased consumption of UPFs, which now contribute a substantial proportion of energy intake in many countries including the UK, which reported that between 2008-2016 UPFs accounted for 54.3% of energy intake amongst adults (4). Mechanistic evidence suggests that associations with CVD may extend beyond poor nutrient composition, with marketing and UPF ingredients contributing to hyper-palatability, disruption of the gut microbiota, inflammation, and endothelial dysfunction (5–8). In addition to these intrinsic properties, displacement of nutrient-dense foods containing fibre, polyphenols, vitamins, minerals, and other bioactives with cardioprotective effects may be contributing to CVD risk. Suboptimal diet has been shown to be responsible for 4.06 million ischaemic heart disease (IHD) deaths in 2023 (95% uncertainty interval: 0.74-6.22), with low intakes of nuts, seeds, low whole-grains, low fruits and high sodium all shown to be primary contributors (9).

With increasing CVD and obesity, management strategies have become more medicalised. Statins, antihypertensives, and more recently GLP-1RAs are used to reduce cardiometabolic risk. GLP-1RAs have demonstrated clinically meaningful reductions in body weight and cardiovascular events in high-risk populations (10–12). However, concerns have been highlighted regarding long-term sustainability, weight regain, nutrient adequacy, side effects, and whether GLP-1RA administration is only targeting the downstream consequences of modern food environments rather than addressing underlying causes of disease.

With growing rates of CVD despite medicalisation there may be a disconnect between upstream causes not being addressed and a shift towards treating downstream symptoms. This narrative review therefore aimed to evaluate current evidence on the effects of UPF consumption on cardiovascular health, whilst evaluating the efficacy of GLP-1RAs in CVD and their long-term administration.

UPFS AND CARDIOMETABOLIC DISEASE

UPFS AND DIETARY PREVALENCE

Foods purchased in the supermarket have undergone processing to get them to the shop floor. The NOVA food-processing spectrum is the most widely used classification system, which categorises foods depending on the nature and extent of processing they have undergone (13). The scale ranges from minimally processed foods, which have been cleaned, ground, dried or cooled, to the ultra-processed, which have been extensively modified through chemical processing (14).

The ultra-processed category contains foods, which are recognised as so-called “junk foods”, but also contain foods marketed as healthy, such as protein bars, flavoured and low-fat yoghurts, and mass-produced wholegrain breads. These foods are hyperpalatable, convenient, and highly profitable (13). Common additives in UPFs include colours, flavour enhancers, preservatives, and emulsifiers, which are rarely used in home cooked foods. Food additives in particular have been associated with negative disruption of the gut microbiota and the development of chronic diseases (15,16).

The consumption of UPFs is increasing and becoming a large part of the diet at a young age. In the UK, UPFs have been shown in one systematic review to consistently account for around half of total dietary intake between 2008-2016, with an estimated 51-57% of overall energy intake across adults and children (4). This systematic review of 55 papers spanning 32 countries on the sociodemographic determinants behind UPF consumption also reported that higher UPF intakes were associated with younger people, urbanisation, and being unmarried, single, or divorced (4). Sociodemographic status, education, and income all showed varying associations with UPFs depending on the country.

UPFs AND CVD

Epidemiological studies have indicated that the consumption of UPFs is associated with an increased risk for the development of CVD. One umbrella review of 45 epidemiological meta-analyses has reported direct associations between higher UPF consumption and a 50% higher risk for CVD related mortality (risk ratio 1.50, 95% confidence interval (CI) 1.37 to 1.63), a 12% higher risk for T2D (dose-response risk ratio 1.12, CI: 1.11 to 1.13), and increased risk for obesity (odds ratio 1.55, CI: 1.36 to 1.77) (17). Similarly, in the landmark prospective NutriNet-Santé cohort study of 105,159 individuals, which assessed the usual consumption of 3300 food items classified according to the NOVA scale, it was found that higher UPF intake was associated with a 12% increased risk of CVD (hazard ratio (HR) 1.12 (95% CI: 1.05 to 1.20); P= <0.001), an increased coronary heart disease risk (HR 1.13; CI: 1.02 to 1.24; P=0.02), and increased cerebrovascular disease risk (HR 1.11; CI:1.01 to 1.21; P=0.02) (18).

In addition to being associated with CVD development, UPF consumption has been associated with an increased risk of death due to CVD. In the multicentre prospective cohort analysis of over 428,000 individuals known as the European Prospective Investigation into Cancer and Nutrition (EPIC) study, UPF intake was positively associated with all-cause mortality (HRs per 1-SD: 1.04; 95% CI: 1.02 to 1.05) and mortality from ischaemic heart disease (IHD) (HR:1.10; 95% CI: 1.06 to 1.15) (19). This prospective cohort analysis also identified that replacing processed and UPFs with unprocessed/minimally processed foods was associated with a 6% lower mortality risk. Additionally, a meta-analysis of 10 studies highlighted that a 31% increased likelihood of death due to CVD was associated with the consumption of UPFs s (20).

MECHANISTIC LINKS BETWEEN UPF CONSUMPTION AND CVD

INTRINSIC FACTORS

Recent mechanistic research has shown that food processing may independently contribute to CVD risk. Additives commonly found in UPFs, particularly emulsifiers, may contribute to gut dysbiosis and intestinal permeability, however conclusions should be conservative as research has only been carried out in small numbers of individuals. Gut dysbiosis and impaired intestinal barrier integrity have both been associated with chronic low-grade inflammation, which may be a predictor for future cardiovascular events (21–23). One small randomised control trial (RCT) of 16 individuals given an emulsifier free diet or one containing the synthetic emulsifier commonly found in UPFs, carboxymethylcellulose (CMC), has shown that compared to control, CMC consumption for 14 days (15g/day) was associated with altered gut microbiota composition (P=0.002) (16). Reduced microbial richness, which may be an indicator of disease, was also observed in the CMC group as well as reductions in the beneficial bacterial taxa Faecalibacterium prausnitzii and Ruminococcus species, which have physiological roles in gut barrier integrity, short-chain fatty acid production, and anti-inflammatory activity (7).

Consumption of CMC was also associated with altered faecal metabolomes indicating disrupted metabolic activity of the gut (P=0.001). Upon resampling one month after CMC cessation, changes in metabolic activity of the gut microbiome had resolved, suggesting possible transient effects experienced only whilst CMC is in the diet.

In contrast, other research has reported significant effects on intestinal barrier integrity as well as alteration in lipid metabolism, which may further contribute to the development of UPF consumption associated with CVD. In one 2-week RCT of 60 healthy individuals, impaired intestinal function has been reported following a diet containing emulsifiers (Polysorbate-80, CMC, and Carrageenan) compared to an emulsifier free diet (EFD) (P=0.04) (8). Reduced total cholesterol (P=0.00006) and low-density lipoprotein cholesterol (LDL-c) (P=0.002) and minimal but significant weight loss (0.3 kg; P=0.02) was reported following an EFD diet which could have further CVD implications. However, high-density lipoprotein cholesterol (HDL-c) was also shown to decrease (P=0.002), although no changes were seen in metabolic health markers. An EFD diet was followed by all participants with the delivery of the emulsifiers in a chocolate muffin eaten three times per day, which was replaced with a placebo muffin in the control group. Results should be interpreted with caution as dietary adherence was not formally assessed throughout the trial and could account for the observations.

Impaired endothelial function and altered cardiovascular responses have also been shown after the consumption of UPFs. It was shown in one RCT of 14 healthy males that even after a single UPF meal, myocardial blood flow and myocardial flow reserve were increased (1.62 vs. 1.22 mL/min/g, P = 0.015, and 2.43 vs. 1.88, P = 0.012, respectively) (5). This highlights the potential for UPFs to acutely alter cardiovascular function, which if sustained could result in endothelial injury in individuals with existing coronary arterial plaques (24).

UPFs are engineered to maximise consumer appeal with attractive packaging and advertising. Increased levels of sugar and salt makes UPFs hyperpalatable, which could promote excessive energy intake leading to the development of obesity, one of the risk factors associated with CVD. One observational study of 215 University students who were shown 64 pictures of UPFs reported that the pictures prompted a desire to eat the foods because of the

rewarding properties associated with their sugar, fat, and salt content (25). One RCT of 42 individuals with obesity given a breakfast of one of two test meals matched for energy density, macronutrients, sodium, and fibre, but differing in NOVA classification has shown that when individuals were given the UPF meal, rate of food intake increased, with less chewing and bites (07:52 ± 3:00 vs. 11:07 ± 03:16 min; P<0.01), and a greater capacity to eat (39.68 ± 22.69 vs. 23.95 ± 18.92 mm; P<0.02) compared to the non-UPF meal (6).

DISPLACEMENT THEORY AND THE IMPORTANCE OF NUTRIENTS

The detrimental effects of UPF components may not be the only contributors to CVD risk. In addition, UPFs are low in fibre and micronutrient density, and high in total fat, sugar, and salt posing the question as to whether adverse health outcomes may also be due to the displacement of more nutrient dense foods, which may have protective benefits to the cardiovascular system. This “displacement theory” proposes that reductions in fibre, polyphenols, and micronutrients found in whole foods due to the addition of UPFs may promote inflammatory and metabolic mechanisms increasing CVD risk.

The reduced risk of CVD with nutrient dense foods has been attributed to the component parts they contain. Nutrients such as fibre, which is found exclusively in plant-foods, wholegrains, and cereals has been shown to be inversely associated with risk for CVD (risk ratio (RR) 0.91 per 7 g/day; 95% CI: 0.88 to 0.94) and coronary heart disease (RR:0.91; CI: 0.87 to 0.94) in a previous meta-analysis of 22 cohort studies (26). Fibre has been reported to act through improvements to glycaemic control, heart rate, and non-HDL-c (27–29).

Polyphenols are naturally occurring plant-based antioxidants and have been shown in one systematic review and meta-analysis of 16 studies to be associated with significantly improved systolic (mean difference (MD) −1.01, 95% CI: −2.04; 0.02, P = 0.005) and diastolic blood pressure (mean difference −1.32 mmHg, 95% CI: −2.37, −0.27 mmHg; P = 0.001), HDL-c (MD 2.68 mg/dL, 95% CI: 2.43, 2.92 mg/dL, P < 0.001), LDL-c (MD −4.39 mg/dL, 95%CI: −7.66, −1.11 mg/dL, P = 0.009), and endothelial function (MD 0.89%, 95% CI: 0.40, 1.38%, P < 0.001), all of which may reduce CVD risk (30).

Supplementation of selenium and coenzyme Q10, which are naturally found in fruits, vegetables, nuts, and seeds has been shown in one RCT to decrease CVD mortality through modulation of thyroid function, thyroid-stimulating hormone (TSH) (< median: n = 34 out of 103 vs. > median: n = 47 out of 100; P = 0.042) and thyroxine (T4) (> median: n = 47 out of 101 vs < median: n = 33 out of 102, P = 0.039) (31). Reductions in oxidative stress implicated in CVD mortality have also been observed following supplementation with selenium and coenzyme Q10, further supporting the potential cardioprotective role of nutrients derived from whole foods (32).

Zinc, which is found in both animal and plant-based foods has been shown in one systematic review and meta-analysis of 27 studies that when supplemented at low-doses (LD) (<25 mg/day), and for long durations (LDu) results in improvements to several CVD risk factors compared to placebo including fasting blood glucose (LD MD:-19.69; 95% CI: -33.64, -5.75, P=0.006, LDu MD: -18.18, 95% CI: -27.74, -8.61, P= 0.0002), triglycerides (LD MD: -19.65, 95% CI: -27.83, -11.47, P= <0.00001 and LDu MD -25.68, 95% CI: -47.83, -3.54), total cholesterol (LD MD: -11.05, 95% CI : -17.49, -4.60, P= 0.0008 and LDu MD: -12.88, 95% CI: -23.89, -1.86, P=0.02), and LDL-c (LD MD: -11.14, 95% CI: -21.61, -0.67, P= 0.04 and LDu MD: -8.49, 95% CI: -15.82, -1.16; P=0.02) (33).

The intrinsic properties of UPFs may directly contribute to inflammation, metabolic dysfunction, and gut dysbiosis and their addition to the diet, displacing more nutrient dense foods, may act synergistically to increase the risk for CVD. It is important that practitioners consider not only the reduction of UPF intake, but also the adoption of a whole-food dietary pattern such as the MD, rich in fibre and polyphenols, to help prevent CVD.

MEDICAL MANAGEMENT OF CVD

The Global Burden of Disease study put CVD prevalence in 2019 at 523 million (1). This is projected to increase to 1.14 billion in 2050 (2). In addition to biological and genetic factors driving CVD risk, socioeconomic, psychological, and commercial factors may be involved. Adherence to nutrient dense foods can be challenging with the food environment being dominated by inexpensive, highly palatable UPFs which may contribute to the development of CVD risk factors and comorbidities (34). Perceived time and money to cook healthy food may also factor into the challenges surrounding healthy diets and drive food choices towards convenient UPFs (35). As a result medical management of CVD through statins, antihypertensives, anti-inflammatories and more recently GLP-1RAs, has become common practice (36).

GLP-1RAS, TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

GLP-1RAs should only be initiated under guidance from a doctor or qualified medical professional. They mimic the endogenous incretin hormone glucagon-like peptide-1, which may act to regulate appetite, insulin secretion, satiety, and delayed gastric emptying resulting in weight loss (37).

Increased usage of GLP-1RAs for cardiovascular health may have resulted from early cardiovascular outcome trials demonstrating modest but significant reductions in MACE, which includes cardiovascular death, stroke, or myocardial infarction (MI), in individuals with T2D.

One systematic review and meta-analysis of seven RCTs with 56,006 participants with T2D has shown that compared to placebo, GLP-1RA administration led to a low-moderate 12% relative risk reduction (RRR) of MACE (HR 0.88; 95% CI: 0.82, 0.94; P<0.001) (10). The number needed to treat (NNT) was relatively high at 75, however given the severity of the outcome prevented, this could be considered clinically significant.

When assessing the components of MACE, GLP-1RA use led to a reduction in risk from cardiovascular causes (HR 0.88; 95% CI: 0.81, 0.96; P=0.001), fatal- or non-fatal stroke (HR 0.84; 95% CI 0.76, 0.93; P<0.001), and fatal or non-fatal MI (HR 0.91; 95% CI 0.84, 1.00; P=0.043).

More recently a systematic review and meta-analysis of 13 RCTs in 65,878 individuals with T2D has shown that compared to placebo, GLP-1RA use led to a reduced risk of MACE of 13% (OR: 0.87; 95% CI: 0.81–0.94; P < 0.01; I2 = 37%), and cardiovascular mortality of 12% (OR: 0.88; 95% CI: 0.80–0.96; P < 0.01; I2 = 14%) (12). The odds of stroke, in particular ischaemic stroke were also reduced (OR: 0.74; 95%CI:0.61-0.91; P<0.01; I2=0%).

GLP-1RAs and secondary prevention of CVD

While initial cardiovascular outcome trials of GLP-1RAs focused primarily on individuals with T2D, more recent research has expanded into populations with overweight or obesity or at elevated cardiovascular risk. In one RCT known as the SELECT trial, including 17,604 individuals who had pre-existing CVD and a body mass index of 27 kg/m2 or higher, it was shown that the administration of the GLP-1RA (2.4mg), Isemaglutide, led to a 20% reduction in a composite of death from cardiovascular causes, nonfatal MI, or non-fatal stroke, compared to placebo (HR, 0.80; 95% CI:l 0.72 to 0.90; P<0.001) (11). Death from cardiovascular causes occurred in 569 individuals (6.5%) in the semaglutide and 701 (8.0%) in the placebo groups.

INTEGRATED PREVENTION MODEL

NUTRITION-FIRST CVD PREVENTION

A joint advisory group from the American College of Lifestyle Medicine, the American Society for Nutrition and the Obesity Medication Association concluded that to support GLP-1RA therapy, nutritional priorities need to be addressed by practitioners (38). Preventing nutrient deficiencies and preserving bone and muscle mass through diet and exercise should be prioritised. However, what these strategies fail to recognise is the mismatch between upstream causation of CVD, driven by high UPF consumption, and downstream treatment, which may contribute to nutrient deficiencies, muscle loss, and support the need for lifelong therapy. Additionally, concerns remain over side effects with long-term use of GLP-1RAs. The SELECT trial showed that adverse events leading to discontinuation of the trial occurred in significantly more individuals in the GLP-1RA (semaglutide) group than placebo (1461; 16% vs 718; 8.2% P<0.001) (11). Gastrointestinal (880 vs 172, P<0.001) and gall-bladder disorders (246 vs 203, P=0.04) were most commonly reported.

Muscle loss resulting from rapid weight loss may also occur during GLP-1RA treatment and may need to be addressed through dietary and lifestyle changes such as increased dietary protein and strength training. One systematic review and meta-analysis of 38 trials involving 1735 individuals with and without T2D showed that individuals given GLP-1RAs had significantly reduced fat mass (T2D:-3.18 kg, 95% CI: -4.09, -2.28, P < 0.0001 and non T2D: -6.02 kg, 95% CI: -7.53, -4.50, P < 0.0001) (39). This was accompanied by significantly reduced mean muscle mass in individuals without T2D (-1.41 kg, 95% CI: -2.12, -0.71, P = 0.0001), however this was not significant amongst those with T2D.

GLP-1RAs act to decrease nutrient intake and although weight loss may be seen, it should not be assumed that optimal nutritional status is being achieved. Nutrition deficiencies have been reported in one observational trial of 461,382 adults newly prescribed GLP-1RAs (40). Nutrition deficiencies or deficiency complications were

seen in 22.4% of individuals after taking GLP-1RAs for 12 months. Vitamin D deficiency was the most prevalent deficiency at 13.6% after 12 months. A smaller percentage of individuals reported thiamine deficiency (0.1%) and other B vitamin deficiency (2.6%). In a smaller subset (n=9010) comparing individuals taking metformin only and those on GLP-1RAs and metformin, it was shown that there was a significantly higher number of individuals on GLP-1RAs with a vitamin D deficiency (GLP1RA: 489 vs control: 259; P= <0.01) and thiamine deficiency (GLP-1RA: 7 vs control: 5; P=<0.01), although the actual numbers of individuals was incredibly low for thiamine deficiency and may not be a cause for concern.

There are some limitations to this as participants did not undergo routine vitamin testing and diagnosis was based upon health insurance claims data. Individuals may have had existing deficiencies before GLP-1RA initiation or other deficiencies may not have been detected if they weren't tested for. Despite limitations in the research, practitioners should recognise that some individuals may be at increased risk of nutritional compromise as food intakes fall substantially during treatment. Dietary assessment and nutritional monitoring may be of benefit to individuals at an increased risk of inadequate nutrient intake and nutrition related diseases such as sarcopaenia. In addition, more research is warranted on the effects of GLP-1RAs on nutrient levels.

Weight regain following GLP-1RA cessation has been reported, which may partly reflect continued poor diet and failure to implement sustainable long-term maintenance strategies including adherence to healthier dietary and lifestyle patterns during and after treatment (41-43). Without these, a large proportion of the lost weight could be regained. This metabolic rebound has been shown in one systematic review of 18 RCTs with 3771 participants following discontinuation of GLP-1RAs (41). Post-discontinuation follow-up of at least 12 weeks was characterised by a body weight regain of 5.63 kg (95% CI: 3.52–7.73; P <0.0001) and an increase in waist circumference (3.81 cm; 95% CI: 2.15–5.47; P <0.0001), BMI (2.34 kg/m2 ; 95% CI: 1.21–3.46; P <0.0001), systolic blood pressure (4.15 mmHg; 95% CI: 1.87–6.44; P <0.0001), and fasting plasma glucose (0.45 mmol/L, 95% CI: 0.32–0.59 P<0.0001).

The SURMOUNT-4 study, which was a RCT of 783 individuals given the GLP-1RA tirzepatide for 36-weeks and then placebo or tirzepatide continuation for 52 weeks, showed that although GLP-1RA led to weight loss (MD, −19.4%; 95% CI: −21.2%to −17.7%; P< 0.001), switching to placebo led to weight regain, with many of the initial improvements to cardiometabolic risk factors, such as waist circumference, fasting glucose, lipid levels, insulin levels, and blood pressure, observed with GLP-1RA treatment, being reversed (42). Only continuation of treatment ensured weight maintenance or further reductions (mean percentage weight change −6.7% with tirzepatide vs 14.8% with placebo; difference, −21.4%; 95% CI: −22.9% to −20.0%; P< .001). Similar outcomes were seen in the Step 1 Trial extension with two thirds of weight lost, regained and a reversal of cardiometabolic benefits seen during treatment (43).

DIET AND CARDIOVASCULAR DISEASE

Historically, low-fat diets were recommended for CVD prevention based on the Seven Countries Study, which reported associations between saturated fat intake, serum cholesterol, and coronary heart disease risk (44). However, more recently dietary quality has been shown to be important for some cardiovascular disease risk markers. Weight loss, LDL-c levels, blood pressure, and endothelial function have all been shown to be negatively impacted when minimally processed food (MPF) is replaced with UPF (45, 46).

In one crossover RCT of 55 adults with overweight and obesity it was shown that a minimally processed food (MPF) diet for 8-weeks with a 4-week washout and then an UPF diet resulted in weight loss with both diets but MPF diet resulted in significantly greater percentage weight change compared to UPF diet (Δ%WC, −1.01; 95% CI, −1.87, −0.14, P = 0.024) (46). Clinical markers of cardiovascular disease showed mixed outcomes with changes in triglycerides being significantly superior with UPF diet compared to MPF diet (−0.25

mmol l−1(s.e., 0.08);P = 0.004), whereas improvements to LDL-c being greater with MPF (0.25 mmol l−1 (s.e., 0.10); P = 0.016). No differences were seen between the two diets in heart rate and blood pressure.

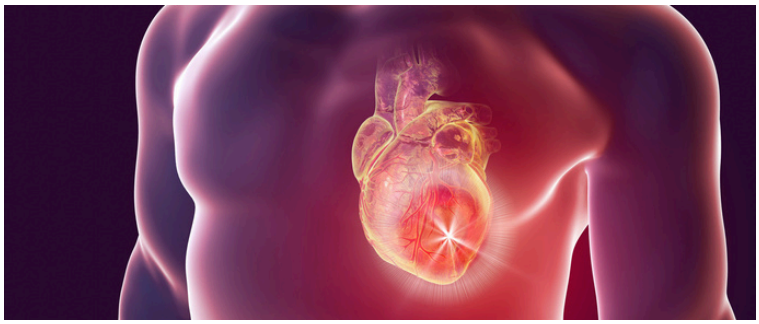
Nutrient dense diets, such as the MedDiet, may be the gold standard diet for managing CVD risk. The landmark Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) study, which was a multicentre, RCT of 7447 of nearly 5 years, reported that individuals at high risk of CVD had an approximate 30% decrease in risk for the development of cardiovascular events following a MedDiet containing 30g of nuts (HR: 0.72; 95% CI, 0.54 to 0.95) or 4 tablespoons of olive oil (HR 0.69; 95% CI, 0.53 to 0.91) compared to a reduced-fat diet (47).

Subsequently the CORDIOPREV study, which enrolled 1002 individuals showed further reductions in risk for secondary cardiovascular events following the adoption of the MedDiet compared to a low-fat diet (crude rate per 1000 person-years: 28·1 [95% CI 27·9–28·3] in the MedDiet group vs 37·7 [37·5–37·9] in the low-fat group, log-rank P=0·039) (48). In one 6 month RCT study of 85 Australian adults (MedLey Study) consuming either a MedDiet or asked to continue their habitual diet, which was characterised by lower vegetable, fruit, fish, but undisclosed UPF content showed that MedDiet was associated with significant decrease in SBP (−1.1 mm Hg; 95% CI: −2.0, −0.1 mm Hg; P = 0.03) and increased flow mediated dilation (FMD) (1.3%; 95% CI: 0.2%, 2.4%; P=0.026) (45).

Adopting a nutrient dense diet, low in UPFs may improve some risk factors involved in the development of CVD, acting as a preventative measure. GLP-1RA's may be of benefit to individuals at high risk of CVD, and integration with sustainable dietary and lifestyle modifications and long-term maintenance strategies may prevent progression towards a "yo-yo" pattern of weight loss, weight regain, and CVD risk.

IN SUMMARY

CONCLUSION



CVD prevalence continues to rise suggesting that current medicalisation may be more effective at treating the downstream consequences rather than upstream causes. UPF consumption may represent an important route into CVD through several mechanisms including gut dysbiosis, endothelial dysfunction, metabolic disruptions, and displacement of nutrient dense foods, which may be protective against CVD. Conversely the growing use of GLP-1RAs indicates an increased reliance on the medicalised route out of CVD. Whilst GLP-1RAs have shown that they may reduce body weight and cardiovascular events, concerns remain over long-term suitability with side effects, nutrient deficiencies, muscle loss, and weight regain following treatment cessation.

PRACTITIONER RECOMMENDATIONS

CVD prevention should be considered an integrated strategy combining lifestyle changes and where appropriate, pharmacological therapies. For cardiovascular health, practitioners should prioritise improvements to dietary quality through avoidance of UPFs and focusing on vegetables, fruits, legumes, wholegrains, nuts, seeds, and extra virgin olive oil. Although much of the evidence on UPFs in CVD is observational, whole-food dietary patterns such as the MedDiet consistently demonstrate cardiovascular benefits over other dietary patterns.

When clinically indicated and prescribed by a medical professional, GLP-1RAs may aid body weight reductions and decrease the risk of MACE in high-risk populations such as those with obesity and T2D but individual responses may vary. Nutritional assessment should be considered following reports of reduced food intake, possible lean muscle mass loss during rapid

weight reduction, and emerging observational evidence suggesting possible nutrient deficiencies. It should be noted that current evidence remains limited, and direct causal links between GLP-1RA use and nutrient deficiencies have not been determined. Long-term cardiovascular risk reduction is likely to depend on sustainable dietary and behaviour changes given emerging clinical evidence on weight regain and reversal of cardiometabolic benefits following GLP-1RA treatment cessation. Adequate protein intake, resistance exercise, and dietary monitoring may help preserve lean mass and support nutritional status during weight loss.

AUTHOR CONTRIBUTIONS

CS conceived of the review, wrote the initial draft and is responsible for content. JR peer-reviewed and provided editing of content. JR and CG provided final editing. All authors reviewed and accepted the final manuscript.

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