Accepted Manuscript

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PII: S0016-5085(17)30158-0
DOI: 10.1053/j.gastro.2017.01.056
Reference: YGAST 60985

To appear in: *Gastroenterology*
Accepted Date: 17 January 2017

Please cite this article as: Thom G, Lean M, "Is there an optimal diet for weight management and metabolic health?", *Gastroenterology* (2017), doi: 10.1053/j.gastro.2017.01.056.

Invited 2017 14th Issue: Obesity

"Is there an optimal diet for weight management and metabolic health?"

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Competing interests

ML and GT have received funding from Cambridge Weight Plan and Counterweight Ltd for conference attendance and other departmental research, outside the submitted work. ML also acts as a consultant to Counterweight Ltd.

Abstract

Individuals can lose body weight and improve health status on a wide range of energy (calorie) restricted dietary interventions. In this paper, we have reviewed the effectiveness of the most commonly utilized diets, including low-fat, low-carbohydrate and Mediterranean approaches in addition to commercial slimming programmes, meal replacements and newly-popularized intermittent fasting diets. We also consider the role of artificial sweeteners in weight management. Low-fat diets tend to improve LDL-cholesterol most, whilst lower-carbohydrate diets may preferentially improve triglycerides and HDL-cholesterol, however differences between diets are marginal. Weight loss improves almost all obesity related co-morbidities and metabolic markers, regardless of the macronutrient composition of the diet, but individuals do vary in preferences and ability to adhere to different diets. Optimizing adherence is the most important factor for weight loss success, and this is enhanced by regular professional contact and supportive behavioral change programs. Maintaining weight losses in the long-term remains the biggest challenge, and is undermined by an 'obesogenic' environment and biological adaptations that accompany weight loss.

Key words: obesity, diet, weight-loss, type 2 diabetes, sweeteners

Introduction

Few areas of nutritional science have divided opinion as much as the controversies around the optimal diet for successful weight management and good health. Obesity rates are at an all-time high, with over two thirds of adults classified as overweight (BMI>25 kg/m^2) or obese (BMI>30 kg/m^2) in most of the Western world. The epidemic of obesity is considered the biggest global public health problem of this generation. It is well established that obesity shortens life span and carries a heavy secondary chronic disease burden. It is an important risk factor for several major causes of preventable death and pathology, including type 2 diabetes (T2DM), hypertension, cardiovascular disease, arthritis, several cancers, non-alcoholic fatty liver disease, sleep apnea, gallbladder disease and depression, as well as a host of troublesome and expensive symptoms, including breathlessness, oedema and indigestion. Obesity is thus responsible for most of the total costs to be met by healthcare providers or insurers. Clinically important consequences of obesity can be considerably improved with as little as 5-10% body weight loss, which is achievable by many methods, but this rarely satisfies the wishes of

patients (1). Remission of conditions such as sleep apnea and T2DM typically require 15-20kg weight loss (2, 3), which is also more acceptable to people living with obesity.

Debates regarding the optimal diet have ensued between scholars, which at times has descended to statements of belief more akin to religions than to scientific arguments based on evidence. Are carbohydrates inherently fattening? Does excess saturated fat lead to heart disease? Will fasting help you live longer? What about gluten? At the time of writing, an internet search using the term “diet for weight loss” returns nearly 51 million results and a similar search on Amazon yields more than 31 thousand books on the topic. This proliferation of dietary (mis)information is driven primarily by a multi-billion dollar fad-diet industry, and commercial diet providers. The US weight loss market was said to be worth $60 billion in 2014 (4). Few options are evidence based, and this volume of competing unregulated information highlights how easily individuals seeking to lose weight could be misled. Mark Twain once said “be careful of reading health books, you may die of a misprint”. Even scientists, inadvertently or otherwise, can end up promoting dietary practices that lack a solid evidence base.

Broadly speaking, body weight status depends on a complex inter-play between three powerful forces – the environment in which we live, our genes, and our behaviors, obligatory or chosen in relation to eating and exercise. Genetics cannot be changed, but epigenetics can. Although modifying the food environment would be most effective in terms of prevention, it is unlikely to occur soon, therefore dietary intervention remains the cornerstone of management. Much is known about strategies for weight loss, but much is still to be learned about optimal approach for weight loss maintenance. This paper reviews the key evidence-based dietary interventions for weight loss and maintenance with reference to macronutrient composition, and impact on metabolic health. Pharmaceutical and surgical interventions are not discussed here, but both still ultimately depend on improving diet.

Calorie restriction for weight loss

Assuming that most people cannot maintain physical activity outputs of athletes, overweight and obese people must consume more calories than thinner people to avoid weight loss, and weight loss can (realistically) only be achieved with reduced energy consumption. The properties of the three main macronutrients - carbohydrates, protein and fat are listed in table 1 (5). Whether a diet is targeted towards reducing fat or carbohydrate,

or increasing protein, for weight loss to occur an energy deficit must be established. This 'energy in / energy out' model of obesity hinges on the first law of thermodynamics, that energy can neither be created or destroyed. Therefore all calories entering the body must be oxidized as fuel or stored as adipose tissue. Weight gain occurs when energy intake exceeds energy expenditure, and energy balance and weight stability is achieved when these two factors are matched over time. In theory, energy restriction sounds simple, however, there are complex and tightly regulated processes with interacting environmental and (epi-)genetic factors, and secondary homeostatic endocrine (6) and behavioral responses which oppose weight loss. Consequently, maintenance of lost weight and achieving a state of energy balance, following a period of deliberate energy restriction presents a formidable challenge.

Some authors present a simplistic argument that insulin regulates fat accumulation and weight gain, whilst hyperinsulinemia, characteristic of obesity, reduces mobilization of fatty acids by inhibiting hormone sensitive lipase (7, 8). This argument neglects the imperative of energy restriction. Others report a 'metabolic advantage' for low carbohydrate diets (LCD), suggesting that calorie for calorie, restriction of carbohydrate leads to greater fat loss by virtue of increased thermogenesis, in addition to altered metabolism (9). The theory is that to lose body fat, carbohydrate as a primary driver of insulin secretion, must be restricted, so as insulin secretion falls, fatty acids are mobilized and weight loss ensues. Although plausible, this interpretation is overly simplistic. Studies have conclusively demonstrated that in weight management terms caloric restriction below metabolic requirements is fundamental for weight loss.

This principle was validated by numerous inpatient feeding studies, where energy intake was tightly controlled and energy expenditure calculated using gold standard techniques. For instance, data collected over 80 years ago by Keeton and Bone (1935) under metabolic ward conditions in 9 obese subjects demonstrated no increase in energy expenditure on an energy restricted, higher protein diet (90g/day) when compared with a lower protein diet (13g/day), followed in crossover fashion (10). Weight loss was comparable between the diets and commensurate with caloric restriction (~45% below basal requirements). Werner et al (1955) compared an isocaloric, HCD (287g/day) with a LCD (52g/day) in 6 inpatient subjects who each experienced similar results (11). Continuing this theme, Olesen and Quaade reported identical weight losses of 4.1kg when subjects followed LCDs (32% protein/50% fat/18% carbohydrate) and HCDs (32%

protein/18% fat/50% carbohydrate) for 21 days each in a crossover-design study whereby energy intake was held constant at 1000 kcals/day (12). Further evidence was reported by Golay and colleagues (1996) who admitted 43 obese subjects each to receive a 1000 kcal/day diet, but were randomly allocated either to a relatively high (115g/day) or low (37g/day) carbohydrate diet. Weight losses were 7.5kg and 8.9kg respectively, which were not significantly different (13). A slightly higher weight loss with a LCD can be explained entirely by the accompanied glycogen depletion and water loss which occur with marked carbohydrate restriction. The body can store approximately 500g of glycogen (~100g in liver, 400g in muscle), and each gram of glycogen is stored with ~ 3g water. When carbohydrate is severely restricted, glycogen stores are utilized to maintain blood glucose. During the first 1-2 weeks of a low-carbohydrate diet, it is quite possible that an additional 2kg is lost consequent to glycogen and water loss (14, 15). The principle that calorie restriction is the 'sine qua non' for weight loss has also been well documented in detailed metabolic ward studies elsewhere (16-20).

In a more recent study, Hall et al (2015) enrolled 19 participants (mean BMI 35.9) who each undertook an isocaloric (1918kcals/day) restricted carbohydrate (RC) (20.9% protein/50.1% fat/29% carbohydrate) and restricted fat (RF) (21.1% protein/7.7% fat/71.2% carbohydrate) diet for 6 days at a time (21). The RC diet resulted in a 22% reduction in insulin secretion and increased fat oxidation, but reduced energy expenditure and fat loss was observed when compared with the RF diet, which despite no impact on insulin levels and fat oxidation, resulted in 463g body fat loss compared to 245g body fat loss on the RC diet. Although the RC diet used in this study is higher in carbohydrate than most LCDs (i.e. Atkins diet) a subsequent study by the same research group (22) reported similar results using a 4-week ketogenic diet (15% protein, 80% fat, 5% carbohydrate), with insulin secretion again significantly reduced (by 47%) but not associated with greater fat loss. The low-carbohydrate, high protein, Atkins' Diet was once marketed as magic: "the high calorie way to stay thin forever" (23), but these findings demonstrate that when calories are held constant no 'metabolic advantage' for LCD's exists. Repeated meta-analyses have shown convincingly that longer term weight losses and metabolic improvements occur independent of macronutrient composition of the diet, and greater energy restriction, results in greater weight loss regardless of whether restrictions are mainly from protein, carbohydrate or fat (24, 25).

Interpreting findings from dietary studies

Studying weight changes and metabolic outcomes of free-living individuals puts to the test the acceptability of diets under 'real life' circumstances, rather than during inpatient feeding studies where dietary compliance is enforced. The findings of each study must be interpreted in this context. In addition, understanding the key ingredients of a successful intervention is further complicated as most weight loss programmes are multicomponent and aligned with behavioral therapy and recommendations for increasing physical activity. In addition, studies comparing dietary approaches tend to be of relatively short duration i.e. 6-24 months which is not long enough to evaluate long term health effects; confounded by an objective to lose weight (rather than maintain) and tested on free-living individuals which means researchers do not know what people are actually eating. Dietary assessment methods (i.e. food frequency questionnaires, dietary recall) are notoriously unreliable as overweight people tend to under-report dietary intake, either intentionally or otherwise (26-28). This uncertainty means demonstrating a causal relationship between dietary intake and health outcomes is complicated and this continues to limit scientific advancement in nutrition and obesity.

What is known about diet, weight management and longevity?

From a diet, nutrition and health perspective, maintaining a healthy body weight (usually BMI 18.5-25 kg/m^2) is vital (29, 30). Large-scale epidemiological studies have generally demonstrated that all-cause mortality increases in linear fashion as overweight and obesity increases (30). On average, median survival is reduced by 2-4 years in those maintaining a BMI of 30-35 kg/m^2, and by 8-10 years at a BMI of 40-45 kg/m^2 (29). This reduced life expectancy is largely due to cardiovascular disease and some cancers, and further reduced when type 2 diabetes is present (31). Some studies, notably the now historic Rotterdam Study have found no reduction in life expectancy, possibly because recruitment was of relatively old subjects (32)

Low-fat and low-carbohydrate diets

Dietary management of obesity has traditionally been based upon an energy restricted, portion controlled diet that is low in fat, and relatively high in starchy carbohydrates. This is logical given that gram-for-gram, fat is the most energy-dense macronutrient and is known to have a weak effect on hunger and satiety, whereas carbohydrate is more filling and has the lowest energy density (Table 1). Studies have shown that people eat a consistent weight of food on a daily basis, therefore substituting lower energy dense foods (e.g. vegetables) for higher energy dense foods can significantly reduce energy intake (>350

kcals/day) and promote satiety without vastly altering overall volume of food consumed (33). Nonetheless, the rise in obesity throughout the 1980's and '90's has led some authors to point the finger of blame directly at dietary guidelines and in particular, low-fat, high-carbohydrate diets (34) apparently favouring carbohydrate restriction. Clearly, if energy restricted diets were followed, then rates of obesity would not be a concern. Adherence is a separate issue, but energy intake on a population level remains too high, not through any knowledge deficiency, but due to substantial changes in food pricing, availability and marketing (James, 2008). This has created an 'obesogenic' environment where people are constantly bombarded with opportunities to eat, and specifically high-sugar, high-fat snacks which humans never met during our evolution as a species. In a busy world, with the breakdown of home cooking, we have become reliant on energy dense processed meals and a regular meal pattern has given way to 'grazing' throughout the day on high calorie snack foods leading to 'passive' overconsumption, and consequent increases in obesity.

Low-fat diets (LFDs) have set the standard in weight management. Two landmark studies, The Finnish Diabetes Prevention Study (FDPS) and The Diabetes Prevention Program (DPP) demonstrated that modest weight loss using a LFD and calorie restriction in conjunction with a lifestyle intervention could significantly reduce the incidence of type 2 diabetes (T2DM) in a population with pre-diabetes (36, 37). The DPP enrolled >3000 subjects (mean BMI 34.0 kg/m^2) and randomly assigned them to receive a lifestyle programme, metformin (850mg twice daily) or placebo, with the goals of 7% weight loss and at least 150 minutes of physical activity. 50% of those in the lifestyle arm of the study achieved their weight loss goal at the end of 24 weeks, and progression to T2DM was reduced by 58% in this group as a whole. Subjects were instructed to become "fat detectives" by reducing total fat intake to 25% of calories (based on US Food Guide Pyramid) and assigned an individually tailored fat goal, given in grams of fat, based on their weight and calorie needs. The lifestyle programme consisted of 16 sessions over 24 weeks on an individual basis with a "lifestyle coach", most of whom were Registered Dietitians. Mean weight changes were -5.6kg, -2.1kg and -0.1kg for the lifestyle, metformin and placebo groups respectively. Metformin only reduced incidence of T2DM by 31%, underlining the dominant role that weight management plays in maintaining a non-diabetic state. The FDPS demonstrated similar outcomes, with improvements in weight, glucose, insulin, lipids and blood pressure. Incidence of T2DM was reduced by 58% in the lifestyle intervention group, just as it was in the DPP. Study visits were less frequent in the FDPS,

just seven sessions with a nutritionist over the one-year period. Detailed advice was given on the goals of the programme, which was to lose 5% body weight or more, and to reduce total intake of fat to <30% of total energy consumed and <10% from saturated fat. Given that both interventions were delivered with a wrap-around lifestyle programme, it is difficult to quantify the exact contribution of the diet to weight loss. Subjects may have been highly motivated and adhered with a variety of diets. However, these data do suggest that the LFD approach is acceptable and effective, and demonstrates categorical benefits both in terms of weight management and metabolic outcomes.

Although a LFD has been the mainstay of dietetic advice for decades, LCDs were first popularized as far back as 1863 when William Banting published "*A letter on corpulence addressed to the public*", describing his 46Ib weight loss with a LCD following a lifelong struggle with obesity (38). Systematic reviews and meta-analyses comparing LFDs with LCDs have typically reported better weight loss outcomes at 6 months with LCD's, which may be related to glycogen depletion (22) but this difference disappears at 12 months (24, 39, 40). Hession's review (40) found a relatively high drop-out rate, common in weight-loss trials. Some are unable to undergo the deprivations of energy restriction, regardless of the macronutrient content. The LCD outperformed the LFD by 4kg at 6 months, but by 12 months this margin had shrunk to just over 1kg, suggesting no significant differences. Weight losses ranged between 2-9kg in both groups at 12 months. The LFD groups tended to be structured with an energy deficit of ~500kcal/day. Of the thirteen studies, eleven used a carbohydrate restriction of 20-60g/day in the LCD groups, without implicit instruction to limit energy intake. The low-carbohydrate 'Atkins' diet utilized in these studies encouraged ad-libitum eating on proteins and fats. Marginally improved weight loss outcomes imply greater energy restriction, which leads us to speculate on the exact mechanism since dieters are not advised to restrict calories per se. It likely confers favorable alterations in appetite and satiety, with protein the most satiating of macronutrients (41). Advice to abstain from a whole food group, and specifically, hyper-palatable refined carbohydrate and fat containing foods which stimulate food reward pathways in the hypothalamus and make it near impossible to 'stop at one' will also play a pivotal role in reducing energy intake. There is no standardized definition of a "low-carbohydrate" diet, but < 50g/day has become the convention (42).

Comparisons of cardiovascular risk factors at 12 months are reasonable given that weight losses were similar. With regards to LDL-cholesterol, there was benefit from a LFD,

weighted mean difference (WMD) 0.37 mmol/l, while LCD diets brought small improvements in HDL-cholesterol, triglycerides, systolic blood pressure and diastolic blood pressure. Similar results have been reported elsewhere (43). Differences between the two groups were small, and beneficial improvements in health were evident in both groups and likely weight loss dependent. It is not clear whether the differences were due to carbohydrate restriction, increased protein intake, lower fat intakes or calorie restriction.

A RCT by Foster et al (2010) reported important findings which could realistically be transferred into clinical practice (44). In a two-year trial, the study utilized an evidence based behavioral lifestyle program (45), which focused on changing attitudes as well as dietary and activity behaviors. Participants met as a group (8-12 people) on a weekly basis for twenty weeks, then on a monthly basis up to two years. The study was conducted by some of the most foremost authors in obesity and compared a LFD (1200-1800kcals) with a LCD (Atkins) in terms of weight loss and metabolic outcomes, in patients with a mean BMI of 36.1 kg/m^2. The study was large, with over 300 participants. Mean weight losses were clinically significant in both groups at year one (11% body weight) and year two (7% body weight) telling us that under the right conditions, and with intensive behavioral treatment, both dietary approaches are equally effective. However, drop-outs were 16%, 26% and 42% at 6, 12 and 24 months.

The near-identical weight loss outcomes achieved at one and two years with both dietary approaches offers an important opportunity to evaluate the contribution made to metabolic change by the varying macronutrient content of the two diets. The striking difference is in HDL-cholesterol which was substantially improved in the LCD group throughout the study. Otherwise, there was little difference between the groups at 2 years, and some of the benefits had regressed, presumably due to weight regain, restoration of energy balance and relaxed dietary adherence. The LCD group experienced significantly greater improvements in triglycerides in the first year of the study, but this was not maintained. Unfavorable changes in LDL-cholesterol were witnessed in the early stages of the LCD, as reported in other studies, but again this was not sustained and may again be related to reduced dietary adherence. Lower saturated fat and omega-3 fatty acids help reduce LDL-cholesterol, which should reduce cardiovascular events (46). Therefore, structuring the diet to emphasize vegetable or lean meat protein sources remains prudent. It appears that both approaches are safe and effective in achieving modest and clinically significant

weight loss. However, sustained adherence generally reduces over time and even with ongoing intervention, a degree of weight regain is common.

Mediterranean Diet

There is no one, singular template for a Mediterranean diet. It is best described as a 'style' of eating, which varies between countries but retains the same core principles (Table 2). A traditional Mediterranean style diet (MSD) is generally considered to be moderate fat, with approximately 35-45% of energy coming from total fat (47), although this does vary and energy restricted approaches may be lower. Fat intake comes primarily from mono (MUFA) and poly-unsaturated fatty acids (PUFA), with small amounts from saturated fat. This pattern of eating has long been associated with a reduced incidence of cardiovascular disease. Epidemiological data coming from the Seven Countries Study (48) was the first study to identify that rates of cardiovascular disease were lower in Mediterranean countries, primarily in poorer, rural locations, giving rise to the hypothesis that the diet provided protective benefits. Further evidence was provided by the Lyon Diet Heart Study. After a first myocardial infarction (MI), 605 patients were randomly assigned to a MSD (<35% fat, <10% saturated fat) enriched with alpha-linolenic acid in the form of an olive oil based margarine provided free of charge to subjects, or to a control group, who were advised by their physician on a typical Western diet as recommended by the American Heart Association (49). Nearly four years later, the intervention group had experienced 65% reduction in coronary heart disease mortality, and 56% reduction in all-cause mortality (50). Importantly for comparison purposes, weight between the two groups remained similar, so cardio-protective benefits were not confounded by changes in body weight.

In an era of effective lipid-lowering drugs, some physicians neglect to offer simple but effective dietary advice, which should be the starting point for patients at cardio-metabolic risk. Importantly, primary prevention of cardiovascular disease has now been demonstrated in patients at high risk of cardiovascular disease. In another large-scale study (n=7447) individuals at high cardiovascular risk (but no established disease) were randomized to a MSD supplemented with olive oil, a MSD supplemented with nuts, or a LFD (51). Follow-up at nearly 5 years showed that in both MSD groups, incidence of MI, stroke and cardiovascular death was reduced by around 30%. The one unanswered

question with both of these primary and secondary prevention studies is the role the MSD plays on its own, independent of additional supplementation.

The health benefits of a Mediterranean style eating pattern have long been established, but little has been documented in a weight loss context, until recently. A systematic review conducted by Mancini et al (2016) included data from 5 RCTs (n=998) and reported that a MSD compared favorably to LFDs, and similar to LCDs (52). Weight losses at 12 months ranged between 4-10kg in the MSD groups. Those following a MSD had no benefit in LDL-cholesterol but greater improvement in triglycerides, and also glycaemic control (in those with T2DM), probably related to increased consumption of mono-unsaturated fats improving insulin sensitivity (53). Given the health benefits and compatibility with weight loss, an energy-restricted MSD appears a good choice for patients at high risk of cardiovascular disease.

Intermittent energy restriction / fasting diets

Intermittent energy restriction (IER) diets involve alternating periods of partial 'fasting' and 'feeding'. On certain days, eating is severely restricted, this is then followed by days when 'normal' eating resumes. Fasting of one sort or another, has been around for thousands of years, and is often used as a religious practice i.e. Lent, Ramadan. We all 'fast' to some extent; between the last meal of the day and breakfast the following day (~10-12 hours). Conventional dieting relies on the principle of continuous energy restriction (CER) i.e. every day. As a weight loss strategy, intermittent diets have been popularized on the basis that individuals can experience all of these benefits by dieting only two days per week. The energy deficit on 'fast' days is far greater than when applying CER, but this may be more acceptable than having to restrict intake every day. There are many variations (Table 2), the most popular methods are intermittent fasting (IF) and alternate day fasting (ADF) although time restricted feeding (TRF) is also starting to receive more attention in the dietary literature. These approaches don't involve true fasting: IF and ADF tend to restrict intake to 500-600 calories. TRF promotes eating all food within a set window of time i.e. 10am-6pm. This may result in reduced calorie intake, especially in people who usually consume a lot of calories in the evening. IF and ADF can involve taking nutritionally-complete low-energy formula diet products, but more commonly energy intake is restricted by keeping to small portion controlled meals on 2-4 days of the week. On the remaining days, advice is to eat to the point of satiety, but not beyond. Individuals do not appear to engage in compensatory eating on 'non-fast' days (54, 55) and both appear equally

effective for weight loss. The intuitive appeal of IER is that a “feast and famine” pattern of eating may match that of our ‘hunter-gatherer’ ancestors, so we are well adapted for it.

Intermittent energy restriction vs. Continuous energy restriction

Relative to other dietary interventions, research into the effectiveness of IER is in its infancy. The principle for it providing health benefit independent of body weight loss is that regularly inducing a mild stressor such as fasting increases resistance against a number of degenerative age-related problems. Promising findings in animal studies has led to enthusiasm that fasting may extend lifespan, improve health and counteract a wide range of disease processes involved in T2DM, cardiovascular disease, cancer, and neurological disorders such as Alzheimer’s and Parkinson’s (56). However, there are no studies of IER diets in humans which have reported on major health events, focus has instead been on surrogate markers, so it is still uncertain whether the benefits of fasting seen in rodents can translate across to humans (57).

Few long-term studies have evaluated the effectiveness of IER diets. A recent meta-analysis (n=981) conducted by Headland et al (2016) included studies of at least 6-months duration, and a variety of IER protocols (58). They found no difference in weight loss outcomes between the IER and CER interventions. Average drop-out rates were 31%, similar between the groups. Improvements in lipid profiles and glucose homeostasis were also similar. Alhamdan et al, (2016) compared shorter studies of ADF lasting for 8-12 weeks with a very-low-calorie diet (VLCD; <800 kcals/day) lasting 4 weeks, presumably with similar overall energy restriction (59). Pooled weight loss was 4.3kg with ADF and 6.28kg with VLCD although preservation of fat-free mass was more relatively favorable with ADF (0.72kg vs. 2.24kg). This finding has also been reported elsewhere (60). The same author found that IER and CER diets equally effective for weight loss, of ~5-8% body weight across 8-12 weeks with both diets (60). Thus, IER is not superior to CER, but offers an alternative to conventional dieting approaches.

There is a complex relationship governing what and how much we eat, however it is primarily regulated by key hormones interacting between the brain, the gut and our fat cells. A large body of evidence exists to suggest that weight loss leads to adaptive changes in some endocrine factors that have unfavorable effects on appetite and satiety (6) and also reductions in both resting and non-resting energy expenditure (61, 62) greater than what would predicted for the changes in fat mass and fat free mass. This is indicative of compensatory mechanisms opposing reduced body weight and dietary strategies that

support long term weight loss maintenance are clearly needed. It would seem plausible that the unfavourable physiological changes synonymous with energy restriction and weight loss could be offset by intermittently raising energy intake to meet weight maintenance energy requirements, rather than a continuous and ongoing energy restriction. However, a systematic review of clinical trials was unable to find any evidence that IER reduced adaptive responses when compared with CER (63).

Future trials are awaited. Most studies to date have used relatively small samples with short duration follow-up. Longer randomized design trials are needed. Focusing particularly on maintenance of initially lost weight, metabolic health outcomes and overall safety. IER is a novel approach towards energy restriction, and offers an alternative to conventional 'daily dieting' but the optimal intermittent 'fasting' regime for health and acceptability needs to be clarified.

Commercial diets, meal replacements and very-low-calorie-diets

Commercial weight-loss programmes (Table 2) have become increasingly popular and there is now some published evidence documenting their effectiveness. In a UK based RCT comparing outcomes of 4 commercial programmes (Weight Watchers, Rosemary Conley, Atkins diet and Slim-Fast) over a 6-month period, clinically significant weight loss was documented for all diets (64). Of 300 people enrolled into the study, 83 (28%) dropped out, without differences in dropout between the diet groups. In an intention to treat (ITT) analysis, average weight loss was 5.9kg, or 8kg in completers. The spread and range of weight losses for each diet is nicely presented in figure 1, and illustrates the vast differences in dietary adherence and the somewhat misleading nature of only reporting mean weight loss outcomes in weight loss trials. This is an important point to remember. A minority are able to lose >20kg, whilst some actually gain weight using the same diet. This study did not have adequate numbers or power to exclude differences between the diets, which made its purpose and design rather questionable. It was to some extent a stunt, as part of a televised series on dieting, probably intended to find no differences between the diets, which may have influenced participant motivation. Only 15 subjects were filmed, and excluding their data made no difference to the overall statistical outcomes.

Other RCTs have documented that commercial weight management programmes provided better weight loss outcomes and cost effectiveness than the existing primary care based alternatives (65, 66). In these studies, containing patients who were either overweight or had obesity, mean weight losses whilst attending Weight Watchers were

between 4-5kg. 31% lost >5% body weight at one year (66) and were 3-times more likely to achieve this target than those attending NHS based weight management programmes (65). Drop out was between 30-40% in the two studies, and highest in primary care, although the format of commercial interventions was for weekly contact which in itself may have positively impacted on outcome success and facilitated greater engagement. The fact that the intervention has obvious cash-value, and the control group was simply offered more of what they had already tried in primary care, made this a weak study design.

Commercial programmes were previously non-evidence-based so not valued alongside medical weight management interventions, but there is a role for such approaches. In a recent systematic review undertaken by Vakil et al, 2016 (67), head-to-head comparisons were made between a number of commercial weight management programmes including Weight Watchers, Jenny Craig, Nutrisystem, Atkins and Slim-Fast and the authors concluded that there was little evidence to endorse one approach over the other. There were no significant differences in mean weight change, waist circumference or blood pressure readings.

A valuable addition to the literature on commercial diets was the large-scale network meta-analysis conducted by Johnston et al (2014). It examined data from 48 RCTs (n=7286), looking at LFDs, LCDs and 'moderate macronutrients' (70). Median weight was 94.1kg and BMI 33.7 kg/m^2. Diets were as follows: Ornish and Rosemary Conley (LFDs); Atkins, South Beach and Zone (LCDs); Biggest Loser, Jenny Craig (both incorporate meal replacements), Nutrisystem (meal delivery service), Volumetrics, and Weight Watchers were all described as moderate macronutrients. Weight losses were highest at 6 and 12 months with LFDs and LCDs, but differences between all approaches were small and considerable benefit was evident with all diets. At 12 months, when compared to not a 'no diet' control group, weight losses ranged between 5.7kg-7.27kg, and underlines again that there is little difference in weight loss outcomes between diets that typically aim to reduce intake gently.

Meal replacements offer a more structured approach towards portion control and have been used in high profile clinical trials, including Look AHEAD (68) - the largest ever lifestyle study which enrolled >5000 individuals with T2DM to evaluate the impact of intentional weight loss on cardio-vascular morbidity and mortality. Subjects were randomly assigned to a control arm, or intensive lifestyle intervention (ILI). In the ILI group,

recommendations during months 0-4 were to replace two meals and one snack with shakes and a meal bar. From months 5-12, participants were advised to replace one meal and one snack per day with a meal replacement and dietary recommendations were structured around low-fat principles. Meal replacements were provided free of charge. Mean weight loss was greater in the intervention group than standard care (8.6% vs. 0.7% body weight) at the end of year 1. The study was halted at year 8, at which point 50% of individuals were maintaining a >5% weight loss, and 27% had lost >10% body weight. Although there was no difference between the groups in terms of cardiovascular outcomes, this was potentially due to the improved level of care T2DM patients receive from a cardio-protective perspective, and the fact that with a mean duration of T2DM of 8years, many already had at least subclinical vascular disease. Nonetheless, the ILI did experience improvements in sleep apnea, depression, mobility and urinary incontinence. In the first-year participants were seen either in a group, or individually 3-4 times per month as part of a comprehensive behavioral lifestyle programme. Although hunger may be a problem for some, meal replacements tend to outperform calorie controlled diet plans as there is less margin for error and reduced decision making required. A simplistic approach often works best, especially in people who lack cooking skills. A meta-analysis (69) reported similar outcomes from seven studies, with mean weight losses of 8.6 and 6.7kg (9.6% and 7.5% body weight) at 6 and 12 months respectively (Figure 2).

Diets using modest energy restrictions, as discussed extensively in this paper, yield modest weight loss outcomes in the region of 5-10% of total body weight. This will prevent progression to conditions such as T2DM as evidenced by the DPP study and improve many markers of metabolic health, but is less likely to reverse disease once established. However, patients themselves are dissatisfied with 5-10% weight loss. The conventional teaching was that slow, and steady weight reduction is more likely to be maintained in the long term. However, there is now strong evidence that the opposite is true (71, 72). Data from Look AHEAD show that rapid early weight loss is the strongest predictor of long-term success (71). Indeed, high quality evidence from meta-analyses clearly demonstrates that very-low-calorie-diets (VLCDs; 450-800 kcals), with larger energy deficits (1000-2000 kcals) than standard diets achieve superior weight loss and more importantly, maintenance in comparison to all other dietary interventions (Figure 2). Data taken from 11 studies showed marked weight reduction at 6-12 months (69) with mean losses of 17.9kg (16%) and 10.9kg (10%) respectively. Meaningful weight losses are still evident as far out as 5 years (73). The problem has been a failure to incorporate, or even define, appropriate

weight maintenance programmes following the initial weight loss phase. Importantly, that appears to be changing, with weight losses achieved with formula diet programmes now better maintained in the long term, with published data with a structured maintenance programme documenting >10% weight loss for four years (74). Several components of effective maintenance programmes have now been identified, including continuing professional contact, increased physical activity, ongoing use of meal replacements, use of anti-obesity medications and optional 'rescue plans' incorporating short periods back on the formula diet in the event of weight regain.

There is also good evidence now emerging that a micronutrient replete Total Diet Replacement (TDR) programme provide similar mean weight loss outcomes to VLCDs but at a higher energy prescription e.g. 800-1000 kcals/day. All conventional foods are still withdrawn and replaced by a liquid formula diet, but adherence is better, preservation of lean body mass is more favorable, known side effects are less pronounced and nutritional status can be improved (74, 75). A study conducted within routine NHS primary care, in 91 adults with BMI >40 kg/m^2 found that an 810 kcal/day TDR resulted in a mean loss of about 17kg in 12 weeks (76). In sharp contrast to routine care outcomes, at 12 months, on an ITT analysis 30(33%) of the 91 patients, 40% of those with known weights, remained >15kg below baseline following a structured food reintroduction and a long-term weight maintenance programme. There was 33% drop-out over that period, comparable with other weight management studies. These findings are important given that resolution of co-morbidities such as T2DM, the biggest concern with regards to increasing obesity, and the increasing numbers of patients with BMI >40, require maintained weight losses of this magnitude, justifying more aggressive approaches than conventional dietary methods within routine healthcare.

The role of non-nutritive sweeteners in weight management

The food industry developed sweeteners to allow us to have our metaphorical cake and eat it. Humans have over the last 2-3 generations developed a preference for very sweet tasting food and drinks and in response to demand to help people to reduce sugar intake, sweeteners came into the food supply to maintain palatability but without adding additional calories (77). To reduce energy density and energy consumption, it seems logical to substitute sugar-sweetened-beverages (SSBs) with low or zero calorie drinks. However, their role in helping people to manage their weight effectively is controversial and has been widely debated. Indeed, there is evidence that artificially sweetened beverages (ASBs) are associated with weight gain in the same way as sugar (78).

While reverse causality is playing a part, there is a plausible argument, supported by animal evidence that artificial sweeteners are so much sweeter than sugar, that their consumption disrupts appetite regulation, leading to increased cravings for sweet foods and eating more calories, rather than less. There have also been sensationalist claims linking sweeteners to cancer, and other worrying health conditions, but the evidence does not support this and their safety has been reviewed extensively and approved by regulatory bodies (79).

Some support for their role in successful weight management comes from the National Weight Control Registry (http://nwcr.ws/default.htm), a self-selected group (>10,000) of weight loss masters who must have lost a minimum of 13.6kg (30Ibs) and kept it off for at least one year, although most have lost more than double this amount and maintained it for over 5 years. Their habits have been studied extensively, and although this is only one associated finding, few (10%) regularly drink SSBs, however >50% report regular consumption of ASBs as a way to control energy intake (80).

In a recent meta-analysis, Rogers et al (2016) concluded that, although there was uncertainty in the evidence, on balance ASBs, taken in place of sugar, had small beneficial effects on energy intake and body weight (81). If patients cannot do without their carbonated soft drinks, and are wondering whether it is safe and helpful to swap SSBs for low calorie, artificially sweetened alternatives, then the answer certainly seems to be yes. Having said that the differences in weight are much less than would be expected from the reduction in calories from cutting out sugar. It does appear possible that the normalization of very sweet drinks, at a level of sweetness far beyond what humans ever met during evolution may have altered palates to encourage consumption of the highly sweetened, high-fat, high-calorie snacks that commercial marketing has made ubiquitously available and even ‘expected’, between meals. People who do not consume sweetened carbonated beverages find the level of sweetness in these snack-foods unpleasant. It seems that global shifts in food culture has played a large part in increasing consumption of sweet, high-fat snacks leading to weight gain, just as occurs when experimental animals are given sweetened drinks and foods (79). This hypothesis needs prospective research.

Conclusion

Human beings prefer things to be simple, and therefore there is a desire to pinpoint the one best diet that solves everything. Unfortunately, things are rarely that straightforward. There is no optimal macronutrient distribution for weight management, no “one size fits all” strategy that will suit everyone. We are told the era of personalized nutrition is drawing closer, and there may at some point be a time when we can make recommendations based on genotype, however if this does materialize, that will not detract from the challenges of achieving dietary adherence. We have highlighted a number of evidence based methods to achieve clinically significant weight loss, but there appears to be little weight loss advantage or difference in metabolic health outcomes between dietary approaches and improvements in health are relative to degree of weight loss. Caloric restriction is the fundamental premise of every successful weight loss strategy, whether that is achieved by lowering fat, carbohydrate, fasting or using meal replacements. Everything is relative, and the best diet ultimately, is the one you can stick to long enough to achieve the weight loss goals that you desire. Given the seriousness of the increasing rates of obesity, it seems wise that we do not limit our options and take an individualized approach. Studies predominantly present outcomes as averages, but this hides the fact that in every study, there is a minority who achieve an excellent response, so no strategy that we have profiled should be ruled out. Although over and underfeeding studies have demonstrated variable responses to the same energy prescription, the principle reason underpinning the success or failure of a dietary attempt will always be compliance. The key to improving this is not just the choice of diet, a whole host of factors influence the process of change. Practitioners must ask themselves not what the best diet is, but how they may optimize patient adherence to the plan. Healthcare staff seeing patients for weight management advice should possess advanced communication skills. Working collaboratively with the patient to agree together on the best way forward (rather than telling them what to do) will go a long way to achieving the best weight loss outcome.

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Tables and Figures

Table 1: Characteristics of the main macronutrients fat, protein and carbohydrate. Alcohol (7kcal/g) is inappropriate as a contributor to a weight-management diet. Reprinted with permission (5)

Characteristics of macronutrients			
	Fat	**Protein**	**Carbohydrate**
Ability to bring eating to an end	Low	High	Intermediate
Ability to suppress hunger	Low	High	High
Contribution to daily energy intake	High	Low	High

Characteristics of macronutrients			
Energy density	High	Low	Low
Storage capacity in the body	High	None	Low
Metabolic pathway to transfer excess intake to another compartment	No	Yes	Yes
Autoregulation (ability to stimulate own oxidation on intake)	Poor	Good	Good
Calories per gram	**9**	**4**	**3.75**

Table 2: Popular diets at a glance

Popular dietary approaches for weight management			
Type/ examples	**General dietary principles**	**Foods eaten / avoided**	**Other comments**
Low-fat diet: based on Eatwell guide, MyPlate, DASH, Volumetrics	Carbohydrate - 50-60% Protein - 15% Fat - 25-35% Saturated fat <10% - Balanced diet, typically 500-1000 kcals/day below metabolic requirements - Advice can be tailored & structured into a food exchange eating plan	- Limit foods high in saturated fat, trans fats, sugars, salt e.g. highly processed foods - Emphases on choosing low energy dense foods such as starchy carbohydrates, (especially high-fibre wholegrain varieties) and fruit & vegetables. - Energy density should be reduced by opting for lean proteins & low-fat dairy products whilst keeping foods high in fat and sugar (chocolate, biscuits, crisps, oils, spreads) to smallest part of diet.	- Generally considered most appropriate diet for achieving & maintaining good health - Recommended by government and major health organizations such as United States Department of Agriculture, Public Health England, American Heart Association, British Heart Foundation, American Diabetes Association, Diabetes UK - Slower rate of weight loss may dishearten some dieters

Popular dietary approaches for weight management			
Commercial diets e.g. Weight Watchers (WW)	- Energy restricted diet to achieve 0.5-1.0kg/week weight loss - Recommendations mirror those for low-fat diets (above)	- In WW individuals guided toward healthy, low energy choices by points based system - A daily points allowance is calculated for each individual - Points values are assigned to all foods which is calculated in relation to nutrient and energy density - Most fruit and vegetables "free" - High fibre carbohydrates, lean proteins, legumes, all have low points values	- Commercial diets shown to be at least as effective as primary care led programmes - Weight Watchers is market leader & most extensively researched - Weekly group support meetings held within local communities, usually led by successful slimmer - Web-based support also available
Low-carbohydrate diet e.g. Atkins	- Intake of calories, protein and fat not limited per se - Carbohydrate allowance varies but popular approaches recommend 20-60g per day during weight loss	- Focus on eating high protein foods such as meat, fish, poultry, eggs, cheese, nuts - Choose low-carbohydrate vegetables e.g. salad greens, brocolli, asparagus. - Limit fruit intake, opt for berries, melon, grapefruit - Liberal use of fats such as butter, mayonnaise, oils - Starchy carbohydrate foods should be avoided e.g. bread, rice, pasta, potatoes, oats - Dairy foods also strictly limited - No place for refined carbohydrate containing foods such as biscuits, chocolate, desserts	- Concerns over increased saturated fat intake but diet is safe & effective up to 12 months (at least) - Risk of nutritional deficiency without supplementation. - Restricted nature of diet may limit long term implementation - Beneficial impact on appetite due to ketosis & satiating effects of higher protein intake - Simple to follow with a clear structure of what foods are permitted & restricted - No suggestion to count calories may appeal to dieters
Mediterranean style diet	- Moderate fat diet, rich in mono & poly unsaturated fat (MUFA & PUFA), & low in saturated fat	- There is no single dietary pattern as subtle differences exists between countries but emphasis is mainly on plant based foods including fruit, vegetables, wholegrains, legumes, & nuts - Olive oil main source of fat - Lean fish, seafood & poultry recommended in moderate amounts with red meat to be limited - Moderate consumption of wine with meals, if preferred	- Reasonable evidence base demonstrating protection against coronary heart disease, & improvement in cardiovascular risk factors - Comparable weight loss outcomes when compared to low-fat & low-carbohydrate diets
Intermittent energy restriction (IER) diets e.g. intermittent fasting (IF), alternate day fasting (ADF), & time restricted feeding (TRF)	- IF: 2 days per week eat 500 kcal/day (women) or 600 kcal/day (men) & eat healthily 5 days per week - ADF: 3-4 days/week eat 500-600 kcals/day & on other days eat healthily - TRF: food consumption restricted to certain hours of the day i.e. 4-8 hour windows of time	- Low energy density foods on 'fasting' days - Follow general healthy eating principles on other days of the week i.e. low fat diet, maintaining energy balance	- Novel approach towards achieving calorie restriction - IER approaches may be easier and more acceptable to dieters than continuous daily energy restriction - Helps dieters learn to deal with feelings of hunger, an important skill in achieving and maintaining weight loss

Popular dietary approaches for weight management			
Meal replacements e.g. Slimfast, Cambridge Diet, Optifast	- Partial meal replacement diet (PMRD): 1200-1400 kcal diet. Meal replacements tend to provide 2/3's of vitamin and mineral requirements. - Total Diet Replacement (TDR): ~ 800 kcal nutritionally replete diet, typically supplemented with fibre - Very-low-calorie diets (VLCD): >450-<800 kcal/day	- PMRD: 1200-1400 kcal diet which replaces 2 meals per day (usually breakfast and lunch) with a shake or bar (~200-250 kcals each) and have a healthy balanced meal based on low-fat principles (~600 kcals). 2 low-calorie snacks (~100 kcal) may also be taken between meals (ideally fruit) - TDR: All meals replaced with shakes, soups or meal bars, typically for a time-limited period e.g. 12 weeks - VLCD: similar to TDR but provide fewer calories	- Offer simple and structured approach to reducing energy intake - TDR & VLCD's facilitate larger energy deficits than conventional approaches - Greater rate of weight loss may facilitate adherence and retention - Potential to achieve 15-20kg weight loss in compliant individuals, greater than conventional weight reduction diets - Reduces day-to-day decision making around food choice and may help break problematic eating behaviours - VLCD's should only be done under medical supervision

Figure 1: Weight loss outcomes at 6 months for participants who completed the BBC diet trials study. Reprinted with permission (64)

Figure 2: Average weight loss of subjects completing a minimum 1-year weight-management intervention based on review of 80 studies (n=26,455; 18,199 completers [69%]). Reprinted with permission (data from sibutramine has been removed) (69)