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Reversal of Obesity: The Quest For the Optimum Dietary Regimen

Rachel Nicoll[1*]

1. Department of Public Health and Clinical Medicine, Umeå University and Heart Centre, Umeå, Sweden

Abstract

A new approach to weight loss and weight loss maintenance is urgently needed, with the global epidemic of obesity leading to ever higher levels of chronic disease. This new approach should be cheap and simple, it should maintain essential nutrients and not deplete lean mass, should have minimal adverse effects and be carried out safely at home without support from the healthcare profession. This review looked at the forms of caloric restriction (CR) investigated in randomised controlled trials (RCTs) and found that supervised continuous and intermittent CR was more effective than other forms of weight loss over periods from 12 weeks to 2 years and could improve cardiovascular and diabetes risk factors. CR was equally as effective as bariatric surgery, suggesting that it is the post-surgery caloric restriction that has the impact on weight, rather than the surgery itself. Intermittent CR, including alternate day fasting (ADF), was as effective as continuous CR but may show improved compliance and higher lean mass. Unsupervised weight loss maintenance presents a greater problem, since in most weight loss regimens all the weight lost is ultimately regained. Although both continuous and intermittent CR can be effective, it has been found that ADF and a higher protein intake is more likely to maintain the weight loss. These results hold for all age groups and ethnicities and both genders. These findings suggest that intermittent CR, and particularly ADF, may be a viable form of weight loss and maintenance which fulfils all the criteria above. It is therefore recommended that larger RCTs investigate intermittent CR and ADF as a viable and cost effective form of weight loss and weight loss maintenance.

Corresponding author: Rachel Nicoll, Department of Public Health and Clinical Medicine, Umeå University and Heart Centre, Umeå, Sweden, Email: rachelnicoll25@gmail.com, Phone: 0044-207 585 1443

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Introduction

There is now a global epidemic of obesity [1], which is a critical risk factor for development of insulin resistance [2,3], metabolic syndrome and type 2 diabetes (T2D) [4-7] and its co-morbidities, including cardiovascular disease and cancer [8,9]. In 2014, more than 1.9 billion adults were classified as overweight, of whom 600 million were considered obese; these figures are double those from the 1980s. In the UK alone, figures from 2005 show that over 50% of the population were overweight or obese; this percentage will only have worsened in the intervening years. Obesity incidence is occurring at considerably younger ages [10] and there are now more deaths globally from obesity and diet-related chronic disease than from malnutrition [11]; it was estimated that over 15% of all US deaths result from obesity-related comorbidities [12]. The health costs of morbid obesity (BMI >40kg/ m^2) are estimated at 81% higher than for non-obese adults, with T2D incurring the highest direct cost of all co-morbidities [13].

Reversing obesity, however, is not easy. There can be few people in the developed world who are not familiar with the health benefits of weight loss, and many are desperate to prevent the inevitable health problems to come, with around 40% of women and 20% of men dieting at any given time [14]. Yet obesity seems resistant to both medical intervention and the latest celebrity diets, which can work in the short term but are largely unsustainable for the long term. Other than bariatric surgery, there are currently no generally accepted easy and effective approaches for successful and sustained weight loss [15]. Dietary strategies advocated by most physicians and dieticians, particularly those focusing on reducing fat intake, are associated with only modest weight loss, poor long-term compliance and ultimate weight regain [16-19]. Many different approaches have been trialled, including substitution of one food for another or reducing whole food groups but although all have been initially effective to some extent, in general none has reversed the mechanism that caused the obesity in the first place and none has been sufficiently pleasant that compliance has continued in the long term, even where the medical consequences of non-compliance have been made clear [20]. Furthermore, a systematic review of various weight loss interventions showed that weight loss tended to plateau after as little as six months [21]. Even where some weight loss has been maintained, the biomarkers of glucose, insulin and insulin resistance tend to creep back up to baseline levels through adaptation or non-compliance [17]. One study found that five years after significant weight loss, mean weight was back at pre-intervention levels, with fasting glucose, insulin and insulin resistance even higher in some subjects [22].

The Weight 'set point'

Adult bodies have a weight 'set point', a level about which weight may vary under normal conditions but which represents a stable range, despite variation in energy intake and expenditure. With any deviation from the weight set point, metabolic homeostatic mechanisms such as hunger or satiety ensure the return of the body to its set point range in a negative feedback mechanism. The arcuate nucleus of the hypothalamus integrates various signals from around the body to regulate energy balance through the secretion of gut and adipose tissue hormones, including ghrelin and leptin, and hypothalamic neurotransmitters such as neuropeptide Y, which induce or inhibit feeding. Although partially determined by genetics, nevertheless constant overeating or other factors may force the weight set point upwards, from where it is difficult to lower it because the homeostatic mechanisms will try to maintain the body at its new set point. It is thought that this explains why less weight is lost than expected during caloric deprivation. Continual secretion of the hormones results in insulin, leptin and/or ghrelin resistance, which leads to increased caloric consumption, further raising the set point. Much remains to be learned about this mechanism and it is hypothesised that all diets ultimately fail because no non-surgical mechanism is currently known to lower the set point to its original level. [23-26]

Why Weight Loss Regimens May Succeed or Fail

A few studies have investigated why weight loss programmes succeed or fail and determined that older age (particularly when first overweight), being female, fewer self-implemented weight loss attempts, greater initial weight loss, being unmarried, keeping a diary, positive mental health, frequency of GP visits, more exercise and less sedentary behaviour as well as greater dietary restraint were independent predictors of successful weight loss; studies were divided over the effect, if any, of education and ethnicity [27-30]. LaRose *et al* found a difference in motivation according to age, with successful younger adults being motivated by appearance and social acceptance, whereas older adults were more motivated by health aspects [31].

Furthermore, those weight loss approaches that work in clinical trials often involve supplied food portions and regular meetings with physicians, dieticians and therapists to keep subjects on track; where there appears to be some recidivism there may be 'motivational phone calls'. This is very labour- and therefore cost-intensive for the healthcare profession and is not realistic for the large numbers of patients that need to lose weight and maintain the weight loss. In trials where food is not supplied, or during the weight loss maintenance phase, these weight loss regimens can be complicated and time consuming in terms of calorie counting. In addition, participants in weight loss studies are known for compensatory increases in hunger and may also experience cold, irritability and low energy.

What is Fasting/Caloric Restriction?

Caloric restriction (CR) is a reduction of caloric intake without deprivation of essential nutrients. CR was first noted as a weight loss strategy in the 1980s with the advent of very low calorie diets (VLCDs) comprising fewer than 800 calories per day [32]. These continuous caloric restriction (CCR) diets proved very effective at attaining modest weight loss in the short term by achieving a negative energy balance but they rarely achieved the desired or expected weight loss and were difficult to sustain long term [32]. Furthermore, there was concern that the weight loss might lower resting metabolic rate and cause the depletion of lean mass, possibly affecting bone density or muscle mass; several studies have shown that lower lean mass is associated with reduced resting metabolic rate, which is disadvantageous for weight loss and its maintenance [33]. There is also the risk of nutrient deficiencies, electrolyte abnormalities and binge eating once normal eating is resumed [34]; the phenomenon of dieting resulting in increased weight from baseline is well known. These CCR diets are particularly problematic for patients because firstly they must count calories rigorously, they are usually permanently hungry and the food, being generally depleted of energy, is not satisfying [35,36]; fatigue from lack of energy intake could also be a problem [37]. Furthermore, it was found that metabolic adaptation occurs when caloric intake is greatly reduced, which results in reduced thyroid hormone, catecholamine and leptin concentrations and a slower resting metabolic rate (RMR), causing subjects to be less physically active, which appears to make the body resistant to further weight loss and may cause weight regain [38,39].

A strategy which may address some of these issues is intermittent caloric restriction (ICR), where the limited intake generally lasts for any period ≥20 hours but is time limited, following which the individual may eat *ad libitum* for a day or two, after which ICR resumes. Most of the studies comparing CCR with ICR attempt to determine whether it is safe and equally effective. For some, this type of regimen may be easier to follow than CCR and its duration may be short enough to make compliance more successful and to overcome the problems of metabolic adaption [40]. Furthermore, ICR may carry additional benefits over and above those found in CCR, such as improved retention of lean body mass and less risk of malnutrition. As with CCR, there have been concerns that ICR would result in disordered eating patterns and over-consumption on non-fasting days, although short term studies have found no evidence of this [41,42].

A popular approach in recent trials is alternate day fasting (ADF), a variant of ICR, where calories are severely restricted (ranging from zero calories per day to <800 calories/day or 25% of energy requirements) for 24 hours, but the following day the individual may eat *ad libitum*. Although many rodent studies consistently show that it has beneficial effects on weight, glycaemic control and metabolism, there are, as yet, few RCTs that investigate the efficacy of ADF. Yet many researchers consider that it may hold the key to patient compliance, since one is only fasting for today and tomorrow one can eat as much as is wanted, returning a greater element of control to the individual [43,44].

Other Advantages of Fasting/Caloric Restriction

Fasting and caloric restriction promote longevity and delay or slow progression of numerous age-related diseases in most laboratory animal studies [45-49]. The same result has been seen in human observational studies of long-lived populations, such as those in Okinawa, Japan [50] and in studies of individuals who have been practising caloric restriction for some years [51,52]. Even a reduction of 5% of body weight is associated with a marked decrease in incidence and progression of age-related conditions such as hypertension, cardiovascular disease, dementia and cancer [53-55]. In animal studies CCR and ICR appear equally effective in preventing mammary tumours [56,57], delaying a prostate cancer diagnosis [58], protecting against cardiovascular disease (CVD) [59], increasing resistance to neuronal damage [60] and consequent cognitive impairment [61] and increasing lifespan [62,63]. In humans, there are few randomised controlled trials (RCTs) of ICR but early results suggest it is as effective as CCR for overall health benefits [64]. Some have hypothesised that ICR may be even more effective at disease prevention than CCR due to increased cellular stress resistance and through brief energy restriction upregulating beneficial antioxidant enzymes, proteins and other protective molecules [65].

Fat Mass as a Predictor of Obesity-related Pathology

Obesity is a manifestation of the increased storage of fatty acids as triglycerides in adipose tissue, particularly within the abdominal cavity. Obesity may be assessed by measuring weight but also by considering adiposity (fat mass), whether through BMI, waist circumference or some other measure. It has been shown that development of adiposity and the distribution of body fat may be a more accurate predictor of obesity-related pathology than weight gain. There are two types of adipose tissue: white adipose tissue (WAT), which stores energy, and brown adipose tissue (BAT), which generates body heat. WAT develops in size through increased storage of the fatty acids in triglycerides. This may occur either as an increase in the number of adipocytes or an increase in the size of adipocytes, although weight loss is believed to reduce the size of adipocytes, rather than their number [66]. The extent of visceral adipose tissue may be estimated from the extent of abdominal adipose tissue, with which it is strongly correlated. Both may be assessed by waist circumference measurement; a high waist circumference (the 'apple' shape) is a known risk factor for T2D and CVD, particularly in females, whereas a higher hip and thigh circumference (the 'pear' shape) is associated with a lower risk. A high waist circumference is also associated with elevated plasma triglycerides, as higher visceral lipid metabolism delivers high concentrations of non-esterified free fatty acids into the portal circulation. For this reason, many consider that the goal of treatment should be to reduce waist circumference rather than weight alone, especially in patients with T2D. [67-69]

The Relationship between Adipose Tissue and Insulin Resistance

But adipose tissue is not just a passive reservoir for storage of energy. All WAT acts as an endocrine organ, secreting hormones, pro-inflammatory adipokines and cytokines, such as oestrogen, leptin, adiponectin, retinol-binding protein-4 (RBP4) and tumour necrosis factor-α (TNF- α), which promote development of insulin resistance by interrupting insulin signalling and metabolism and can lead to cardiovascular disease (CVD). Visceral adipose tissue, the adipose tissue surrounding the organs, has higher endocrine and metabolic activity relative to subcutaneous adipose tissue, and is associated with higher cardiometabolic risk and incidence of insulin resistance. Higher subcutaneous relative to visceral adipose tissue is associated with a lower risk of obesity-related conditions. [67-69]

The relationship between obesity and insulin resistance has long been recognised, with studies showing a significant and broadly linear relationship between degree of insulin resistance and BMI in all ethnicities, including among the elderly. Insulin resistance correlated better with BMI relative to weight or other measures of adiposity. The only possible exception is among patients who are morbidly obese (BMI >40 kg/m^2), suggesting that the relationship holds for all those with a BMI of 20-40 kg/m^2. There is also a strong association between insulin resistance and visceral (abdominal) adiposity, which is stronger than with total adiposity. [34,70,71] Insulin resistance is found in virtually all T2D patients and in many of those who are obese but not diagnosed diabetic, since it occurs early in the condition [72]. Nevertheless, there are ethnic differences in the incidence of insulin resistance, which occurs less frequently in African Americans compared to Caucasians or Hispanics [73]. Weight loss invariably leads to reduced insulin resistance, no matter how it occurs [71].

Meal Timing

The human genotype has evolved over hundreds of thousands of years, when food sources were scarce and there were inevitably long time gaps between meals. Furthermore, intermittent fasting and increased interval between meals have been used in various religions and for health benefit for millennia [74]. Consequently we have developed genes adapted to this way of life, with increased storage of fat following a meal, which is slowly released to provide energy during periods with no food; there is no suggestion that our prehistoric ancestors were obese. Yet it is the general belief that to maintain a healthy weight, food should be taken in three meals per day, with snacks in between if hungry; in fact many doctors and dieticians recommend small, frequent meals (grazing) as the answer to weight loss on the basis that it increases satiety and reduces hunger. Yet this is counter-intuitive and there is concern that the practice may lead to over-consumption; furthermore, the continual stimulation of insulin secretion by constant eating, which generates a sustained level of blood glucose, could lead to or perpetuate insulin resistance.

There are a number of studies investigating the efficacy of small, frequent meals for weight loss but these are mostly observational and cross-sectional and the results are mixed. Furthermore, prospective studies which have compared the effects of 1-2 meals per day versus 3-5 meals per day have all been short term so the long term impact is unknown. Despite this, the American Dietetic Association recommends that 'total caloric intake should be spread throughout the day, with the consumption of 4-5 meals'.[12,75] However, since increased meal frequency appears in general to lead to a positive energy balance, this seems unlikely to benefit weight or fat mass, although usually there is no reduction in lean mass. The obverse of grazing is time restricted feeding (TRF), where food intake is *ad libitum* but is restricted to narrow windows of time (normally 4-13 hours in the day). This has also been explored in rodents and proved to reduce body weight and counteract a high fat diet [76].

Bariatric Surgery

Bariatric surgery, normally Roux-en-Y gastric bypass (RYGB), has had an astonishing success in reducing weight and reversing T2D almost immediately following surgery but the mechanisms are uncertain. There has been controversy over whether the success is due to the surgery *per se* or to the calorically restricted post-surgery diet, or some combination of the two; furthermore, the reversal of T2D and normalisation of glucose metabolism and insulin sensitivity may itself be due to the weight and/or fat loss, with lowered release of adipokines.

Objective of this Review Article

A new approach to weight reduction is urgently needed, one in which weight loss is relatively rapid, cheap, simple to carry out, provides the essential nutritional requirements, has minimal adverse effects, can be carried out safely at home without any support or intervention from the health care profession and can be continued indefinitely without risk. Some of the recent clinical trials looking at intermittent caloric restriction, and particularly alternate day fasting, may point the way towards just such as approach. This article investigates RCTs comparing CR to other weight loss programmes and ICR versus CCR, the types of CCR or ICR diet, the addition of oral supplements, optimal meal timing, CR versus bariatric surgery, CCR versus ICR in unsupervised weight loss maintenance and the special case of ADF in order to determine what time of regimen is optimal for weight loss and weight loss maintenance. Recommendations will then be made for future studies.

Pubmed was searched for 'fasting' (ignoring studies relating to fasting blood measurements), 'caloric restriction' and 'calorie restriction'. Studies were not included in this literature review unless there was an element of food abstention or caloric/energy restriction and the study lasted for longer than 1 week; studies of religious fasting were excluded. The studies were then categorised into those investigating some form of CR vs no CR, CCR vs ICR, types of diet, optimal meal timing, the efficacy of food supplements, CR vs bariatric surgery and weight loss maintenance. Only RCTs are included in the tables and detailed analysis but other studies are discussed if they provide additional clarification. Results are not mentioned unless there is a statistically significant difference between groups.

Analysis of RCTs and other studies

RCTs of Caloric Restriction (CR) Versus no CR

Ten RCTs (Table 1) looked at the efficacy of caloric restriction versus no caloric restriction or other forms of therapy for reduction in weight, BMI and fat mass over time periods ranging from 12 weeks up to 2 years. Shai *et al* [77], one of the 2 year studies, investigated overweight or obese middle aged adults with T2D or coronary heart disease, who were randomised to a CR low fat diet, a CR Mediterranean diet or a low carbohydrate diet; those randomised to the CR Mediterranean diet or the low carbohydrate diet lost significantly more weight than the CR low fat diet. Another, Brehm *et al* [78], a 6 month trial which randomised obese females to an *ad libitum* very low carbohydrate diet or a CR low fat diet, found that those on the low carbohydrate diet lost significantly more weight than those calorically restricted.

The remaining eight studies all found that CR was significantly more effective than the alternatives.

Table 1: RCTs of caloric restriction studies versus no caloric restriction

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets	Length of study	Outcome for weight and BMI
Ruggenenti *et al*, 2016 [82]	74	18-60	M Caucasian	Overweight or obese + T2D	25% CR or standard	6 months	25% CR
Fontana *et al*, 2016 [81]	218	20-50;	Caucasian	Normal- or overweight	25% CR or standard	2 years	25% CR
Ravussin *et al*, 2015 [80]	218	21-50	F Caucasian	Normal- or overweight	25% CR or control	2 years	25% CR
Choi *et al*, 2013 [79]	76	Mean 56	F Asian	Overweight with T2D	30% CR or control	12 weeks	30% CR
Varady *et al*, 2013 [83]	30	35-65	-	Normal or overweight	400-600 cal/day ADF or control	12 weeks	ADF (i.e. CR)
Tapsell *et al*, 2010 [169]	122	>18	-	Overweight or obese	Low fat ± PUFA; ER ± PUFAs	3 months	ER
Shai *et al*, 2008 [77]	322	40-65	M	Overweight or obese with T2D or CHD	Low fat CR, Mediterranean CR, low carb	2 years	Low carb or Med CR
Brehm *et al*, 2003 [78]	53	>18	F	Obese	Low carb or CR low fat	6 months	Low carb
Harvey-Berino *et al*, 1999 [170]	80	25-45	F	Obese	CR or low fat	24 weeks	CR
Williams *et al*, 1998 [107]	54	30-70	-	Obese with T2D	Therapy or VLCD	20 weeks	VLCD

Key: T2D = Type 2 diabetes; CHD = coronary heart disease; CR = caloric restriction; PUFAs = polyunsaturated fatty acids; Carb = carbohydrate; VLCD = very low calorie diet; BMI = body mass index; ADF = alternate day fasting;

These included studies of overweight Asian females with T2D, calorically restricted by 30% for 12 weeks [79], normal or overweight Caucasians, calorically restricted by 25% for 2 years [80,81], overweight or obese male Caucasians with T2D, calorically restricted by 25% for 6 months [82], normal or overweight subjects given 400-600 kcals/day ADF for 12 weeks [83]. The two exceptions [77,78] merely point up the fact that low carbohydrate diets have consistently proved to be more successful than low fat diets for weight loss, while adding CR does not improve the ability of a low fat diet to achieve weight loss. These two studies also suggest that it is not caloric restriction, *per se*, that causes the weight loss but that CR and low carbohydrate diets both help to trigger the mechanism of weight loss. Choi *et al* [79] also investigated the effect of CR on types of fat in Asian females and found significant reductions in total fat mass, body fat percentage and abdominal, visceral and subcutaneous fat. Although several of these studies showed lean body mass decreasing with body weight [79-81], Brehm *et al* found that this did not affect bone mineral content [78].

Other benefits were seen with several, but not all, of the successful CR diets: significant reduction in blood pressure, heart rate, fasting glucose, HbA1c, insulin resistance, total and LDL cholesterol, leptin, liver enzymes and inflammatory markers, with significant increase in HDL cholesterol and LDL particle size (indicating a less harmful form of LDL) [79-83]. Triglyceride levels tended only to fall with low carbohydrate diets or ADF [77,83], rather than CCR. The effect of CR on resting metabolic rate (RMR) and total daily energy expenditure was inconclusive [80,82].

Summary of results: Caloric restriction is more effective for weight and fat loss than other weight loss regimen. One drawback to CR is that lean mass may also reduce.

Continuous caloric restriction (CCR) versus intermittent caloric restriction (ICR)

Of the seven studies shown in Table 2, most show no difference between CCR and ICR, indicating that both would be of equal efficacy in promoting weight and fat loss. Two studies showed a greater reduction of BMI or body fat with ICR [84,85], while Arguin *et al* found increased loss of lean body mass with ICR compared to CCR [86]. The small study by Catenacci *et al* [87] employed a zero calorie ADF regimen versus CCR over 8 weeks and found that resting metabolic rate, absolute weight loss and change in fat and lean mass

Table 2: RCTs of continuous versus intermittent caloric restriction

Authors	No. of sub-jects	Age	Main gender/ ethnici-ty	Condition	Diets	Length of study	Short-term out-come for weight/ BMI
Catenacci *et al*, 2016 [87]	26	18-55	-	Obese	Zero calorie ADF vs CCR	8 weeks	No differ-ence
Davoodi *et al*, 2014 [84]	74	26-50	Iranian	Overweight or obese	CCR or CSD*	6 weeks	Weight: no difference BMI: CSD
Keogh *et al*, 2014 [171]	65	≥18	F	Over-weight/ obese; some with T2D	CCR vs ICR: (1 week on; 1 week off)	8 weeks	No differ-ence
Harvie *et al*, 2013 [85]	115	20-69	F Cauca-sian FH breast cancer	Overweight or obese	Low carb 25% ICR; 25% CCR or 15% ICR	3 months	Body fat: ICR groups; Weight: no difference.
Arguin *et al*, 2012 [86]	25	Mean 60.5	F	Obese	5 week ICR or 15 week CCR + 5 week stabilisation	5 or 15 weeks	No differ-ence
Harvie *et al*, 2011 [65]	107	Pre-menopau-sal	F Cauca-sian	Overweight or obese	25% CCR Med or 75% ICR (2 days) + Med (5 days)	6 months	No differ-ence
Ash *et al*, 2003 [42]	51	<70	M	Overweight or obese	1400-1700 cal/day: ICR liquid 4/7 days PPM or SSM	12 weeks	No differ-ence

Key: T2D = Type 2 diabetes; CR = caloric restriction; CCR = continuous caloric restriction; ICR = intermittent caloric restriction; Carb = carbohydrate; VLCD = very low calorie diet; BMI = body mass index; PPM = pre-portioned meals; SSM = self-selected meals following dietary advice; Med = Mediterranean; ADF = alternate day fasting

*CSD (Calorie shifting diet): CSD comprised 11 days of eating only at 4 CR set meals per day, with 4-hourly intervals between meals, followed by 3 days of self-selected meals, repeated 3 times to total 42 days. The principle behind the CSD was to change intake from high to low calories and back again to keep the resting metabolic rate (RMR) at higher levels. CSD is therefore a variation on ICR, but the advantage of CSD is that subjects could still eat 4 meals per day.

did not differ between groups, but there was a significantly greater decrease in fasting glucose with zero calorie ADF compared to CCR. Although there was no difference in degree of weight loss between groups, nevertheless Harvie *et al* [85] analysed those achieving ≥5% weight loss over the 3 months of the study and found that this was 65% in the 25% ICR group, 58% in the 25% CCR group and 40% in the 15% ICR group, suggesting that the greater the caloric restriction the better, regardless of whether it is CCR or ICR. Fasting insulin and insulin resistance declined to a significantly greater extent in the 25% ICR group compared to the CCR group, with no difference relative to the 15% ICR group. Compliance was significantly better in the ICR group vs CCR and intermittent restriction did not lead to disordered eating and overconsumption on non-restricted days. The earlier study by the same team also found that compliance among the ICR group vs the CCR group was increased [65], with a similarly improved result for insulin and insulin resistance but the ICR group had a higher frequency of headaches, lack of energy and problems fitting the diet into their daily routine. Two of the studies showed a greater reduction in fasting glucose, total cholesterol and triglycerides with ICR vs CCR [84,86]. Ash *et al* [42] found that subjects who attained normal glycaemia had significantly greater weight loss than subjects whose HbA1c level remained >6%; they calculated that a 1% reduction in HbA1c was associated with a 6.5% weight reduction.

Summary of Results: Both CCR and ICR are generally similarly effective for weight and fat loss although a few studies showed greater efficacy with ICR and greater improvement in blood glucose, insulin, insulin resistance and lipids. Compliance was improved with ICR vs CCR.

Caloric restriction: Types of Diet

Table 3 shows the 12 studies looking at various dietary permutations of a caloric restriction regimen: 8 investigating CCR and 4 studying ICR. The 2 studies of ICR comparing low and high fat showed no difference between the groups [88,89] and similarly with CCR, Brinkworth *et al* [90] and Kirk *et al* [91] found no difference between a high fat, low carbohydrate diet and a low fat, high carbohydrate diet for weight, fat mass, fat-free mass or intra-abdominal fat and time to achieve 7% weight loss was the same. Nevertheless, Pascale *et al* [92] found that the addition of low fat to CR enhanced weight loss overall but when analysed into those with T2D and those without but with a family history of the condition, it appeared that the fat restriction only assisted weight loss in those with T2D and made no difference in those without. To support this conclusion, the study by Brinkworth *et al* [90] and the 2 studies of ICR [88,89] which showed not difference, all compared high and low fat diets in subjects without T2D. In addition, Das *et al* [35] found that in young, overweight adults there was no difference in weight, percentage fat loss, fat-free mass or resting metabolic rate between 30% CR with a low glycaemic or a high glycaemic load.

Three studies investigated whether a semi-liquid diet was more effective than solid food. Metzner *et al* [67] investigated overweight or obese females randomised to 1200 kcal/day solid food or isocaloric meal replacements for two meals, and found similar reduction in weight, BMI, waist circumference, fat mass and lean mass in both groups but there were a significantly greater number of subjects in the meal replacement group who lost >5% of baseline weight. Curiously, females with waist circumference ≤88 cm lost significantly more weight in the meal replacement group but there was no significant difference in weight change in females with waist circumference >88 cm. Wadden *et al* [93] found that a continuous liquid 420 kcal/day programme was significantly more helpful for weight loss than continuous 1,200 kcal/day of solid food after 1 year, while Kroeger *et al* [94] and Klempel *et al* [95], using the same subject group, gave an intermittent partially liquid diet (total calories 880-1080 per day) versus an isocaloric solid food diet for 8 weeks and

Table 3 : RCTs of caloric restriction: types of diet

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets	Length of study	Short-term outcome for weight/ BMI
Brinkworth *et al*, 2009 [90]	107	18-65	F	Obese + ≥1 Met RF	CER low carb high fat or high carb low fat	1 year	No difference
Kirk *et al*, 2009 [91]	22	Mean age 44	F	Obese + IR	CCR (-1000 kcal/day) + high carb vs low carb	11 weeks	No difference
Das *et al*, 2007 [35]	34	24-42	-	Overweight	30% CR high GL vs 30% CR low GL	24 weeks	No difference
Pascale *et al*, 1995 [92]	90	Mean 45	F	Obese with T2D or FH	CR or CR + low fat	16 weeks	CR + low fat
Metzner *et al*, 2011 [67]	87	18-60	F	Overweight or obese	CR 1200 kcal/day ± liquid meal replacement	12 weeks	Meal replacement
Wadden *et al*, 1994 [93]	49	Mean 39	F	Obese	Continuous LCD or VLCD liquid for 16 weeks, then LCD	1 year	VLCD
Wing *et al*, 1994 [96]	93	30-70	F	Obese + T2D	Continuous 1000 or 400 calories/day	12 weeks	400 calories/ day
Foster *et al*, 1992 [97]	76	Mean 40.5	F	Obese	Continuous 800, 650 or 420 calories/day	6 months	No difference
Varady *et al*, 2015 [88]	29	25-65	F	Obese	25% ADF high fat vs low fat	8 weeks	No difference
Klempel *et al*, 2013 [89]	35	25-65	F	Obese	ADF high fat vs low fat	8 weeks	No difference
Harvie *et al*, 2013 [85]	115	20-69	F Caucasian	Overweight or obese	ICR with 25% energy + carb restriction vs 15% energy restriction	3 months	No difference
Kroeger *et al*, 2012 [94]; Klempel *et al*, 2012 [95]	54	35-65	F	Obese	ICR liquid vs ICR food	8 weeks	Weight: ICR liquid; BMI/ fat: no difference

Key: T2D = Type 2 diabetes; CR = caloric restriction; ER = energy restriction; Carb = carbohydrate; VLCD = very low calorie diet; FH = family history; BMI = body mass index; ADF = Alternate day fasting, a form of intermittent caloric restriction (ICR); Met RF = metabolic syndrome risk factor; GL = glycaemic load; IR = insulin resistance

showed that the liquid diet group had a greater decrease in weight and waist circumference compared to the solid food group but a similar reduction in BMI, fat mass and visceral fat; lean mass and abdominal subcutaneous fat were unchanged in both ICR groups. The remaining studies all investigated whether lower caloric intake was more effective than higher. Wing *et al* [96] studied subjects with T2D and found that those on a continuous diet of 400 calories/day lost significantly more weight than those on 1000 calories per day, although Foster *et al* [97] studied three different levels of continuous caloric restriction and Harvie *et al* [85] investigated 2 caloric levels plus carbohydrate restriction in non-diabetics and neither study found any difference between the groups.

Those studies that investigated cardiovascular or diabetes markers mostly found little difference between groups, although Brinkworth *et al* [90] found that total, LDL and HDL cholesterol increased and triglycerides decreased to a greater extent with the low carbohydrate, high fat diet compared to the high carbohydrate, low fat diet. Similarly, Harvie *et al* [85] showed that greater caloric plus carbohydrate restriction resulted in greater reductions in serum insulin and HOMA-IR, while Kirk *et al* [91] found no difference in the change in fasting glucose, c-peptide, leptin, adiponectin between a low carbohydrate, high fat diet compared to a high carbohydrate, low fat diet, although fasting insulin and HOMA-IR were significantly decreased with the low carbohydrate, high fat diet and plasma 3-hydroxybutyrate was increased 10-fold. Pascale *et al* [92] found no difference among diabetics if a fat restriction was added to the caloric restriction but among non-diabetics there was a greater decrease in total cholesterol in the low fat group.

Studies of ICR semi-liquid diet versus isocaloric ICR solid food generally found that fasting glucose, insulin, homocysteine, total and LDL cholesterol, triglycerides, inflammatory markers and liver enzymes, blood pressure and heart rate decreased and LDL particle size increased to a greater extent with the liquid diet; LDL particle size increased in the liquid food group, whereas there was no change in the solid food group [67,94,95], although Metzner *et al* [67] found that while serum homocysteine increased in the CCR group, folate increased in the meal replacement group and a similar study by Noakes *et al* showed that both folate and β-carotene were higher in the meal replacement group [98], possibly indicating the benefit of added micronutrients in the meal replacements, not present in self-selected food. Wing *et al* found that a lower calorie group had improved glycaemic control and insulin sensitivity after loss of 11% body weight compared to a higher calorie group [96]. There was generally little difference in compliance between groups, which was good or reasonable, and incidence of binge eating declined with time [93]. Nevertheless, Das *et al* [35], who compared CR with high or low glycaemic load, found that in the high glycaemic load group only there was a decrease in satisfaction with the provided foods and a significant increase in the desire to eat non-study foods during the first three months of the study.

Summary of results: Diet composition has little effect on weight and fat loss in caloric restriction, although a low carbohydrate diet improves the blood lipids, insulin and insulin resistance. Taking calories in liquid form can be helpful for weight and fat loss and improves biochemistry but greater caloric restriction was not necessarily more effective than less caloric restriction, except possibly in T2D.

Caloric Restriction with Oral Supplements

Table 4 shows the six RCTs investigating the effect of CR with or without additional oral supplementation, three of which investigate ω3 fish oils, known to enhance lipid oxidation in healthy humans. The study by Su *et al* [99] shows that with the addition of protein and/or ω3 fish oils to CR, most groups had significant reductions in BMI and waist circumference but the reductions in weight and total body mass were not significant and the addition of protein and/or fish oils did not cause significantly greater reduction in BMI and waist circumference relative to CR alone, even after 12 weeks. However, the study by Munro *et al* [100] showed that ω3 fish oils can significantly enhance reduction in weight and BMI in calorically restricted obese adults, possibly through reducing insulin resistance, although there was no difference between groups in fat mass or hip measurement. Kunesova *et al* [101] also found that the addition of ω3 fish oils resulted in significantly increased loss of weight, BMI and hip circumference. The reason for the beneficial effects of ω3 fish oils in the studies by Munro *et al* and Kunesova *et al* but none in the study by Su *et al* may be due to the much higher dosage of docosahexaenoic acid (DHA) in the latter two studies, since others have shown benefit for weight loss when DHA intake is considerably greater than that of eicosapentaenoic acid (EPA) [102], possibly due to its

Table 4: RCTs of caloric restriction with oral supplements

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets and Supplements	Length of study	Short-term outcome for weight/ BMI
Su *et al*, 2015 [99]	143	>40	F Taiwanese	Overweight or obese + met syn	1500 kcal/day ± protein ± ω3 fish oils (1280mg/ day EPA + 850mg/day DHA)	12 weeks	No difference
Munro *et al*, 2013 [100]	42	18-60	F	Obese	VLED ± ω3 fish oils (420 mg/day EPA+ 1620 mg/ day DHA)	4 weeks	Weight + BMI: ω3 fish oil
Kunesova *et al*, 2006 [101]	20	Mean 52	F	Obese	VLCD ± 2.8g/day ω3 fish oils (EPA:DHA ratio 2:1)	3 weeks	Weight + BMI: ω3 fish oil
Coker *et al*, 2012 [103]	12	65-80	-	Obese	1200 kcal/day ± whey protein and essential amino acids meal replacement	8 weeks	Weight: no difference; fat loss: amino acids
Georg-Jensen *et al*, 2012 [105]	80	20-55	-	Obese	CR ± low viscous alginate fibre	12 weeks	Alginate fibre
Georg-Jensen *et al*, 2011 [104]	24	20-45	-	Obese	CR ± low viscous alginate fibre	2 weeks	No difference

Key: CR = caloric restriction; VLED = very low energy diet; BMI = body mass index; Met Syn = metabolic syndrome; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; EGCG = epigallocatechin gallate

anti-inflammatory or lipogenesis suppression effects [100].

Coker *et al* showed that the addition of whey protein and essential amino acids to CCR had no effect on weight loss but increased fat reduction by 30% relative to CCR alone in an 8 week study of the obese elderly [103]. Furthermore, in two studies by Georg-Jensen *et al* investigating the effect of CR with or without low viscous alginate fibre, the earlier [104], which comprised 24 subjects and lasted two weeks, failed to find any benefit for reduction of weight and waist circumference with the additional fibre but the later study [105], which comprised 80 subjects and lasted 12 weeks, showed a significant benefit of the alginate fibre on weight and percentage of body fat.

Su *et al* [99] showed that, despite the lack of effect on weight and BMI, CR supplemented with protein and ω3 fish oils resulted in a 1.5-fold greater recovery from metabolic syndrome (as shown by the Z-score) compared to CR alone. On the other hand, Munro *et al* [100] found no significant difference between CR with and without fish oil in the reduction in fasting glucose, total, LDL and HDL cholesterol, triglycerides, leptin and inflammatory markers. Kunesova *et al* [101] found that the addition of ω3 fish oils to CR generated a higher increase in β-hydroxybutyrate, indicating higher ketogenesis and possibly higher fatty acid oxidation or decreased lipogenesis. In the study of the elderly by Coker *et al* [103], the addition of whey protein and essential amino acids did not significantly alter the change in fasting glucose or lipids relative to CR alone. The larger study of CR with or without alginate fibre found no difference in fasting glucose, insulin, HOMA-IR, total, LDL or HDL cholesterol, triglycerides, ghrelin, inflammatory markers or heart rate but there was a greater reduction in the alginate fibre group in HbA1c and systolic and diastolic blood pressure [105].

Summary of results **:** The addition of ω3 fish oils to CR aided weight and fat loss, with greater ketogenesis, provided the dosage of DHA was sufficiently high. Whey protein and fibre may also be of benefit.

Caloric restriction and optimal meal timing

Table 5 shows the three RCTs that have investigated optimal meal timing with caloric restriction. Hoddy *et al* [106], investigating ADF with lunch only, dinner only or three small isocaloric meals, found no difference in weight between meal timing groups but systolic blood pressure was significantly lower in the small meals group only, while heart rate decreased in the lunch group only and resting metabolic rate reduced in the dinner group only, suggesting that dinner should not be the one meal of the day. A study by Williams *et al* [107] compared obese diabetics randomised to CR either one day per week per five weeks or to five consecutive days every five weeks, with behavioural therapy provided to achieve the goal of 1,500-1,800 kcal/day in order to determine the optimum interval for ICR but there was no difference between the two groups with respect to weight or fasting plasma glucose.

Stote *et al* investigated three meals per day compared with an isocaloric one meal per day and found that the one meal per day was significantly more beneficial for weight and fat mass reduction, although blood pressure increased, as well as total, LDL and HDL cholesterol and liver enzymes, which remained in normal range, but cortisol and blood urea nitrogen were decreased [108]. This was a short study, carried out in healthy normal weight subjects and it remains to be seen what the longer term outcome would have been and whether the same intervention would have raised glucose, lipid and enzymes levels in obese or diabetic subjects.

***Summary of Results*:** The studies are unclear whether one meal per day is more effective for weight and fat loss than three meals of the same total calories.

Studies of Caloric Restriction vs Bariatric Surgery

Although not all of the seven studies shown in Table 6 are RCTs and the study period is usually short, they do provide an interesting comparison of bariatric surgery versus caloric restriction. Four studies [109-112] found no difference between Roux-en-Y gastric bypass (RYGB) and caloric restriction of 700 or 1000 kcals/day or the standard post-surgery protocol (around 500 kcals/ day), but little information is provided about the content of the diet. One study [113] found that a higher level of daily caloric allowance provided greater reduction in

Table 5. Caloric restriction: optimal meal timing

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets	Length of study	Short-term outcome for weight/ BMI
Hoddy *et al*, 2014 [106]	74	25-65	-	Obese	ADF lunch only; ADF dinner only or ADF small meals.	8 weeks	No difference
Stote *et al*, 2007 [108]	21	40-50	F	Normal weight	3 meals/day or 1 meal/ day (between 1600 and 2000 hrs)	2 x 8 weeks	1 meal/day
Williams *et al*, 1998 [107]	54	30-70	-	Obese diabetics	Intermittent CR: 1 day/ week or 5 consecutive days every 5 weeks	20 weeks	No difference

Key: VLCD = very low calorie diet; BMI = body mass index; ADF = alternate day fasting weight and BMI than RYGB, with a steady daily weight loss during caloric restriction but rapid loss following RYGB; this was a study of predominantly African American females, whereas the majority of the other study participants were Caucasians and it is not known if the ethnicity would have made a difference. Two studies [68,114] found that RYGB was more effective at weight and BMI reduction compared to CR but one of these [68] was a low fat, high carbohydrate diet, which has already been shown to have little effect on weight; little information was provided on the diet content in the other study.

All studies of bariatric surgery focus mainly on incretins but those investigating other parameters generally found no difference in changes in fasting plasma glucose, insulin, HOMA-IR, C-peptide, thyroid hormones, leptin and other adipokines, inflammatory markers and liver enzymes [68,109-112,114]. The fact that glycaemic control tends to be similar in the CR and RYGB groups suggests that it is the weight loss following caloric restriction after RYGB that brings about the improvements, rather than an incretin-mediated mechanism due to bypassing the duodenum [111, 113]. Nevertheless, Lingvay *et al* [113], who found CR more effective than RYGB in African American females, also showed that fasting glucose and HbA1c were lower in the CR group vs RYGB, despite lower caloric intake in the RYGB group; insulin requirements were also significantly lower. Although Steven *et al* found greater weight loss with RYGB than CR, triglycerides rose after RYGB but fell in the CR group [114], while in the only study to test fasting glucagon, it was found to decrease to a greater extent with diet than RYGB [110].

Since these studies show that in most cases the results from CR on weight, fasting glucose, insulin and other biomarkers of T2D, are indistinguishable from those produced by RYGB plus CR, this suggests that rather than undergo expensive and potentially dangerous surgery with its known long term adverse effects, it may be preferable to attempt CR in the first instance. Where RYGB shows greater success than CR is in maintenance of weight loss, possibly since the

Table 6. Caloric restriction vs bariatric surgery

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets	Length of study	Short-term outcome for weight/BMI
Steven *et al*, 2016 [114]	-	25-65	-	T2D for <15 years	RYGB or 700 cal/day	7 days	RYGB
Lips *et al*, 2013 [109]	74	Mean 49.4	F Caucasian	Obese with/ without T2D	RYGB or CR (700 kcal/ day)	3 weeks	No difference
Lingvay *et al*, 2013 [113]	10	Mean 53	F Afr. Amer.	Obese, T2D mean 7.4 yr	Post-RYGB CR (1313-2107 kcal per day), with/ without RYGB	10 days	CR without RYGB
Jackness *et al*, 2013 [112]	25	18-65	F	Obese ± T2D	RYGB or VLCD of 500kcal.day	3 weeks	No difference
Mitterberger *et al*, 2010 [68]	19	Mean 39	F Caucasian	Normal weight, obese	Post-RYGB 40% CR (low fat, high carb), with/ without RYGB	6-9 months	RYGB
Campos *et al*, 2010 [111]	22	21-65	F	Obese	Post-RYGB CR, with/ without RYGB	2 weeks	No difference
Laferrere *et al*, 2008 [110]	19	<60	F	Obese + T2D for <5 years	RYGB (600-800 kcal/day) or CR (1000kcal/day)	1 month	No difference

Key: T2D = type 2 diabetes; CR = caloric restriction; BMI = body mass index; RYGB = Roux-en-Y gastric bypass consequences of overeating for RYGB patients are so unpleasant.

Summary of results: There is little difference in weight and fat loss, glycaemic control or other biochemistry between RYGB and CR, suggesting that the health benefits following RYGB are due to the caloric restriction following the surgery rather than the surgery itself.

Caloric Restriction and Weight Regain after Unsupervised Period

The benefits of CR for weight loss maintenance was seen in a 2001 meta-analysis [115] of 29 US studies of subjects who had carried out a structured weight-loss programme. It found that continuous very low energy diets (VLEDs) of <800 kcal/day were significantly more successful at weight loss maintenance than continuous hypoenergetic balanced diets (HBDs) (not precisely defined) after 5 years. Table 7 shows 11 RCTs, the majority of which show no difference between CCR and ICR in respect of weight or fat loss maintenance, regardless of a low carbohydrate, low fat or low glycaemic load element or whether the calories were provided as liquid or solid food. The only factors that appear to make a difference are the addition of protein to a very low energy diet, which reduced weight regain [116,117] and zero calorie ADF, which slowed fat and lean mass regain [87].

Most studies did not measure other parameters but three found no difference in resting metabolic rate, fasting insulin, glucose, insulin sensitivity, total, LDL and HDL cholesterol, triglycerides, leptin or ghrelin between the two study groups [35,86,87], although after follow-up brain-derived neurotrophic factor (BDNF), important for cognition and weight loss, had increased in ADF but decreased in CCR [87]. Two studies of very low energy intake, with or without added protein, found that leptin and triglycerides were significantly lower in the protein group [116,117], while others found that all parameters had returned to baseline in both study groups [87,92].

In an interesting study by Westerterp-Plantenga *et al* [118], higher caffeine intake was associated with increased reduction in weight, BMI, waist circumference, fat mass and percentage body fat during the weight loss period, with lower resting energy expenditure and increased satiety and fat oxidation. Nevertheless, during the weight maintenance phase, a caffeine and epigallocatechin gallate (green tea) supplement was associated with significantly lower weight, BMI, waist circumference, fat mass, percentage body fat, fasting insulin and triglycerides and significantly increased fat oxidation and β-hydroxybutyrate among those with a normally low, but not high, caffeine intake and in fact this group regained no weight at all, while the other three groups regained varying amounts. This effect in low caffeine consumers only was hypothesised to be because the effect of caffeine appears to depend upon habitual intake, possibly due to lack of sensitivity with a habitually high intake.

Among the non-RCT studies, the beneficial effect of protein is echoed in a study by Arciero *et al* [119], who investigated 24 overweight or obese adults who had been on a high protein CR diet for 10 weeks, resulting in significant decreases in body weight and fat mass. The subjects then chose whether to continue with this diet or switch to a traditional 'healthy heart' diet of low fat, low protein and high carbohydrate for a further 52 weeks. Those in the high protein CR group regained significantly less weight (<1% increase), total body fat and abdominal fat compared to the 'healthy heart' diet group (who gained 6.1% of their weight). Fasting glucose and insulin were unchanged from the beginning of the 52 weeks, indicating that the subjects retained their enhanced insulin sensitivity from the weight loss phase, despite the 'healthy heart' group regaining the weight and total body fat, suggesting that factors other than body weight and fat mass may mediate insulin resistance. An interesting study by Mutch *et al* [120]

Table 7: Caloric restriction and weight regain after unsupervised period

Authors	No. of subjects	Age	Main gender/ ethnicity	Condition	Diets	Unsuper-vised period	Outcome for weight and BMI
Catenacci et al, 2016 [87]	26	18-55	F Caucasian	Obese	Zero calorie ADF or CCR (-400 kcal/day)	24 weeks	Weight: no difference; % fat/lean mass regain: ADF
Keogh et al 2014 [171]	65	≥ 18	F	Overweight/ obese, some with T2D	CCR vs ICR: (1 week on; 1 week off)	44 weeks	No difference
Harvie et al, 2013 [85]	115	20-69	F Caucasian	Overweight or obese	Low carb 25% ICR; 25% CCR or 15% ICR ICR or CCR	4 weeks	No difference
Arguin et al, 2012 [86]	25	Mean 60.5	F	Obese	30% CR high GL vs 30% CR low GL	1 year	No difference
Das et al, 2007 [35]	34	24-42	-	Overweight	1400-1700 cal/ day: ICR liquid 4/7 days or food	24 weeks	No difference
Ash et al, 2003 [42]	51	<70	M	Overweight or obese	CCR or CCR + low fat	18 months	All parameters returned to initial levels
Pascale et al, 1995 [92]			F	Obese with T2D or FH	CCR 1000 or 400 calories/ day	38 weeks	All parameters returned to initial levels
Wing et al 1994 [172]	90	Mean 45			Continuous very low energy ± 30g protein/day		Weight: 400 calories/day
Lejeune et al 2005 [116]	93	30-70	F	Obese + T2D Overweight/obese	VLED ± 45mg/day EGCG + 25mg/day caffeine	50 weeks	With protein
Westerterp-Plantenga et al, 2005 [118]	113	18-60	-	Overweight/obese	Continuous very low energy ± 48g protein/day	6 months	Weight: low caffeine intake + supplement
Westerterp-Plantenga 2004 [117]	76	18-60	-	Overweight/obese		3 months	With protein
	148	Mean 42	-			3 months	

Key: T2D = Type 2 diabetes; CCR = continuous caloric restriction; ICR = intermittent caloric restriction; Carb = carbohydrate; BMI = body mass index; ADF = alternate day fasting; GL = glycaemic load investigated 40 female Caucasians who followed an 8 week low calorie diet after which they all lost weight. After a six month weight maintenance phase, they were then stratified according to whether they were weight maintainers (0-10% of weight regain) or weight regainers (50-100% weight regain). Part of the difference between the two groups was genetic but the remainder was because weight maintainers experienced a significant reduction in insulin secretion in response to an oral glucose tolerance test, whereas no changes in insulin secretion were observed in the weight regainers.

Summary of Results: There is little difference between CCR and ICR or diet composition in terms of weight loss maintenance, although adequate protein and zero calorie ADF proved to be most beneficial. Increased caffeine and green tea among those with normally low caffeine intake may also help. Whether or not an individual experiences a reduction in insulin secretion may help determine whether or not they will maintain the weight loss.

Alternate Day Fasting (ADF) Studies

The only RCT comparing ADF with CCR was by Catenacci *et al* using zero calorie ADF; the results proved to be just as successful as CCR for weight loss over eight weeks and in preventing weight regain over 26 weeks in obese subjects [87]. Another zero calorie fasting study investigated severely obese patients prescribed either VLCD or zero calorie ADF but there was again no significant difference in the reduction in weight experienced by both groups [121]. In a study to investigate the feasibility of zero calorie ADF in non-obese subjects for 22 days, participants were told that on the non-fasting day they should double their usual intake to make up for the calories lost the previous day. Despite these instructions, participants lost 2.5% of baseline weight and 4% of baseline fat mass and fat-free mass; insulin was also significantly reduced but resting metabolic rate did not vary, indicating that separate 24 hour fasts did not cause adaptation by the body. Hunger increased on day 1 but did not increase further, whereas feelings of fullness increased over the course of the study; no subjects left the study and compliance appeared to be good. [122] Similarly, a small study of obese vs non-obese young female patients in a Korean medical centre found that after nine days of zero calorie fasting there was a significant decrease in weight and BMI in both groups; although both experienced hunger, this decreased only in the non-obese subjects [123].

ADF studies employing 25% of energy needs on the fasting day include one by Hoddy *et al* showing that in obese subjects ADF generated significant reductions in body weight, fat mass, fat-free mass and visceral fat mass; hunger had not increased from Day 1 and feelings of fullness on the fasting day increased as the study progressed [124]. An Iranian study also investigated ADF with 20-30% of normal energy intake for six weeks in obese females and found significant decreases in body weight, BMI, fat mass, waist circumference, systolic blood pressure and diastolic blood pressure [125].

Unsupervised ADF for weight loss maintenance was also been investigated in the RCT by Catenacci *et al* [87]. Using zero calorie ADF versus CCR, they found that after 24 weeks there was no difference in weight regain between the two groups but the ADF group showed a lower amount of fat mass regain. Other ADF studies include Klempel *et al* [44], who studied obese subjects undergoing controlled 500 kcal/day ADF for four weeks, followed by a further four weeks of unsupervised feeding and found that after the unsupervised feeding, body weight reduced further than was found after the controlled feeding; hunger decreased after approximately two weeks and there was no hyperphagic response on the non-fasting day. Similar studies were carried out by Varady *et al* [43] and Bhutani *et al* [64], both using a 25% energy requirement ADF, which significantly reduced body weight, waist circumference, percentage of body fat and fat mass, with a similar amount of weight lost in the supervised and unsupervised periods, indicating that this form of ADF can be maintained away from a clinically controlled environment, although there were weekly meetings with a dietician. There was no change in fat-free mass, suggesting that ADF preserved lean mass. Compliance was good at 86% during the controlled feeding and 89% during the unsupervised feeding; there were no complaints of fatigue [43,64].

Alhamdan *et al* [126] carried out a meta-analysis in 2016 comprising 10 quality studies of overweight or obese healthy adults aged 18-70, comparing the efficacy of interventions lasting 3-12 weeks using ADF (4 studies) or CCR using very low calorie diets (VLCDs) of <800 calories per day (6 studies). Because of the few published ADF studies to date, the authors included non-randomised clinical trials in this category but all studies are recent (published after 1999). Interestingly, the authors noted that the ADF studies were all grant funded, while the VLCD studies were all industry funded. Some of these studies focused on weight maintenance after weight loss, rather than weight loss *per se*, but overall there was no significant difference in mean body weight loss or lean mass between ADF and CCR with VLCDs but ADF subjects lost significantly more fat mass than VLCD subjects. The authors also noted that in some VLCD studies, subjects had suffered headaches, fatigue, dizziness and hair loss, which had not been experienced in the ADF studies. Furthermore, they observed that ADF had been found to decrease hunger and increase satiety and dieting satisfaction, which may increase compliance, and there was no hyperphagic response on the non-fasting day. The authors commented that another reason for the increased compliance with ADF may be that no change in food type is required but merely a change in meal timing. Heilbronn *et al* [122] had previously observed that unsupervised individuals who do not have their food portion provided may have great difficulty estimating energy intake in CCR, whereas with zero calorie ADF, there is no estimation required.

The principal concern about CR is the reduction in lean mass along with fat mass, with loss of bone and muscle during proteolysis, as reflected in increased blood urea nitrogen, which is often seen during fasting but usually only in fasts lasting >60 hours. In a 2015 review of ICR studies, Tinsley *et al* [34] showed that while ADF studies consistently showed reduction in weight and fat mass, among those that measured lean mass, 50% showed no change while 50% showed a reduction, although two of these three studies required zero calorie ADF, suggesting that a small protein-rich meal should be added to the regimen if ADF is continued for any length of time.

***Summary of Results*:** Although there are few studies, zero calorie ADF appears to be at least as beneficial as other forms of CR for weight and fat loss but may not cause a reduction in metabolic rate or lean mass. ADF may be more helpful for weight/fat loss maintenance, with good compliance and fewer adverse effects.

Adipose Tissue

The RCTs show that a significantly greater amount of reduction in BMI and fat mass, as well as abdominal, visceral and subcutaneous fat, is experienced with CR compared to other weight loss regimens. There is generally little difference in reduction in adiposity between CCR and ICR, either in the initial weight loss period or during an unsupervised period, although in a few studies more fat loss may be found with ICR; a zero calorie ADF regimen slowed fat mass regain in the unsupervised period. More fat mass was lost with one meal per day rather than an isocaloric three meals per day.

Other studies show that CR of mean 1437 kcal/day for 3 weeks results in a significant decrease in waist circumference and intra-abdominal fat area [127]. Similarly, a VLCD administered for two weeks gave a significant reduction in BMI, abdominal adipose tissue and visceral adipose tissue but there was no difference in subcutaneous tissue [128], while obese females given a VLCD for four weeks had a two-fold increase in lipolysis of abdominal adipose tissue, potentially contributing to a reduction in adipocyte size [129]. A study of 15% or 25% CR for 24 weeks could also reduce visceral fat cell size in proportion to weight loss [130]. A 2011 review by Varady [69] noted that weight loss through CR was roughly proportional to loss of visceral fat mass, with CCR and ICR being similarly effective at reducing visceral fat mass. Animal studies reflect the effect of CR on adipocyte size, reducing white adipose tissue but increasing 'beige' fat deposits [131] and preventing visceral adipose tissue accumulation [132]; greater reductions in body weight were associated with more fat loss but not necessarily reduction in fat cell number [133].

The initial effect of CR is water loss as a result of depleted glycogen stores [14]. Following this, CR appears to function through increased lipolysis resulting in net fat loss from cells, leading to decreased adipocyte size and therefore reduced secretion of leptin and other pro-inflammatory adipokines [14,133]. Interestingly, Johnstone notes that some studies have shown that the slowest rate of weight loss (with an LCD, rather than a VLCD) is associated with the greatest loss of fat mass and the smallest loss of lean mass [14].

Summary of Results: There is little difference in the effectiveness of ICR and CCR for adipose tissue reduction, although zero calorie ADF may be of advantage in slowing fat mass regain. CR appears to reduce the more dangerous visceral fat, decreasing adipocyte size, while having less effect on subcutaneous fat. The slowest rate of weight loss may have the greatest impact on fat mass.

Lean (fat-free) Mass

Several of the RCTs of CR versus no CR show lean body mass decreasing with body weight and fat mass [79-81], although one showed that this did not affect bone mineral content. Some of the RCTs also showed a reduction in resting metabolic rate and total daily energy expenditure. In comparisons of CCR with ICR, generally a similar amount of lean mass is lost, although one found increased loss of lean mass with ICR compared to CCR [86]. This occurred particularly among postmenopausal females, where the reduction was twice as great in ICR as in CCR, although in this study there was no association between lean mass reduction and change in resting metabolic rate. Among studies of weight regain during an unsupervised period, zero calorie ADF slowed both fat and lean mass regain [87]. Despite this possibly adverse effect of ICR vs CCR, a 2011 review by Varady [69] noted that a higher proportion of lean mass was lost with CCR relative to ICR, although this could in part be due to different fat measurement techniques.

A non-randomised study by Arciero *et al* [119] put 40 overweight or obese adults on a high protein CR diet for 10 weeks, following which there were significant decreases in weight and fat and lean mass. Curiously, resting metabolic rate increased, whereas in most other CR studies it decreased, causing the authors to hypothesise that the addition of increased protein prevented RMR from falling. Lean body mass is the single greatest predictor of resting metabolic rate and these two moved in tandem during the initial 10 weeks.

Summary of Results: Both CCR and ICR can generate loss of lean as well as fat mass, although studies differ on which type of CR is more detrimental to lean mass. The addition of protein to CR was able to increase resting metabolic rate and lean body mass.

Age, Gender and Ethnicity

Although almost all the RCTs analysed above investigated subjects who are aged <65, CR appears to be effective in all age groups. Yet in general, studies of the elderly show that they may be more successful with dietary restriction than younger individuals, possibly due to altered biochemistry but maybe also because they are more prepared to follow the instructions of health professionals [134]. It is also thought that the usual definitions of obesity and overweight based on BMI may not be applicable in the elderly due to the change in stature and body composition that accompanies ageing and that waist circumference may be a better measure of adiposity in this age group [70]. Since in the elderly, overweight or mild obesity can protect against osteoporosis, fractures and mortality, there is particular concern that CR may impact bone density and muscle mass, triggering or worsening the known ageing condition of sarcopenic obesity, where depleted muscle mass is combined with a redistribution of body fat to the abdomen [70]. One study in this review focusing specifically on the obese elderly showed that the addition of protein may aid fat reduction and should also promote lean mass retention, and the addition of resistance exercise may also be of benefit. There are as yet no long term RCTs of the effects of CR in the elderly.

Virtually all studies employ female, or predominantly female, subjects, yet there is no suggestion in any study that gender impacts the effectiveness of CR or any form of CR. The three exclusively male RCTs showed that CR was effective for weight and BMI reduction in those who were obese or had T2D and that the findings were in line with those for females in studies lasting 12 weeks to two years. Few studies analyse ethnicity but where details were given, it appears that the results are similar regardless of whether the subjects are predominantly Caucasian or Asian (Japanese, Taiwanese, Korean), although a study which compared ethnicities found that Caucasians aged 50-59 achieved significantly greater weight loss than other age and ethnic groups [134]. One of the RCTs analysed above [113] was a comparison of RYGB or CR in African American females and was the only one of the bariatric surgery versus CR studies to demonstrate that CR alone was significantly more effective for weight reduction than the CR following RYGB. Another study provided a comparison of Caucasian and African American premenopausal females who were calorically restricted for 12 weeks and found an ethnic difference only among those with greater baseline weight, where Caucasians lost significantly more weight than African Americans but African Americans had a greater decrease in waist:hip ratio [135]. However, a study of Caucasian males and matched South Asians showed that the South Asians were more insulin resistant at baseline, although the results of an eight day VLCD were the same for weight loss [136].

***Summary of Results*:** CR is beneficial for weight and fat loss in all age groups but particularly the elderly, with added protein to aid lean mass retention. It appears helpful for both males and females and in all ethnicities, but possibly particularly for Caucasians.

Fasting and Exercise

There are many RCTs investigating caloric restriction and exercise but since this paper is concerned with the optimum dietary regimen, only an overview of the exercise studies will be provided. Because of the multitude of these studies, only those published after 2011 (10 RCTs in total) have been considered. Seven of these show that, although significant weight loss occurred in all groups, there was no difference in the weight loss between diet, exercise or diet + exercise [137-143]. Two studies investigating body composition found that body mass did not decrease in the resistance training group but in the resistance training + CR group there was a significant reduction, particularly in abdominal obesity [70,144]; similarly, the resistance training + CR group showed a significantly greater reduction in metabolic syndrome prevalence, VLDL, triglycerides and systolic and diastolic blood pressure relative to resistance training alone [145]. Only one study found that the combination of exercise + ADF was more effective than either alone, although exercise on its own was significantly less effective than ADF [146].

Summary of Results: In general, exercise has little or no impact on weight loss when compared with or combined with CR.

Compliance, Adverse Efects and Qualitative Assessment of the Dietary Regimen

Among the RCTs, those comparing CR with no CR found no serious decline in mood or cognition among the CR subjects and no increase in serious adverse clinical events. Similarly, where there was a difference between CCR and ICR, compliance was slightly improved in the ICR group and there was no disordered eating or overconsumption on non-restricted days [65,85]. Incidence of binge eating in ICR, where present, declined with time [93]. A notable feature of some of these RCTs is that subjects consistently fail to achieve the target calorie or energy restriction; in Ruggenenti *et al* [82] the goal was 25% caloric restriction but only 15% was achieved, while in Ravussin *et al* [80] the goal was again 25% caloric restriction but only 12% was achieved. Although significant weight loss nevertheless occurred, this provides an indication of how difficult a goal of 25% caloric restriction can be unless all meals are provided. Hunger was in general higher at the start of the study and declined as the body adapted to lower intake, however, a small study of young female Koreans found that after nine days of zero calorie fasting, all had experienced hunger but this decreased only in the non-obese but not in obese subjects [123]. Increased protein intake is normally found to aid satiety.

In studies of ADF, compliance was generally good, both during controlled and unsupervised feeding [43,64,83], although hunger was reported on fasting days early in the study but lessened with time [122]; other studies reported increased feelings of fullness [146]. There were no complaints of fatigue. The meta-analysis by Alhamdan *et al* [126] noted that with VLCDs some subjects suffered headaches, fatigue, dizziness and hair loss, which were not experienced in the ADF studies. Furthermore, they observed that ADF had been found to decrease hunger and increase satiety and dieting satisfaction, which may increase compliance, and there was again no hyperphagic response on the non-fasting days. The authors commented that a reason for the increased compliance in ADF may be that no change in food type was required but merely a change in meal timing. Nevertheless, Hoddy *et al* [124] noted that these were subjective ratings of hunger and fullness, taken in the evening of a fast day, so that a post-prandial assessment before and after ADF were not given. Objective measures of hunger and satiety, such as ghrelin or PYY were not assessed. In their study, Hoddy *et al* [124] showed that despite considerable weight loss after eight weeks of ADF, ghrelin, an indicator of hunger, was unchanged from baseline and PYY, an indicator of fullness, increased during the study, corresponding with the subjective assessments. Nevertheless, Hoddy *et al* recognise that these findings are not in accordance with the usual findings in CR studies. Johnstone [14] notes that some ADF studies appear to suggest that there may be a difference in perception of hunger between those of normal weight, who continue to feel hunger throughout the study, and obese subjects, whose hunger declines as the body adapts, although a small study by Halberg *et al* showed that non-obese males habituated to ADF after approximately two weeks and felt more satisfied with the diet after about four weeks [147].

Finally, Johnstone noted that in an unsupervised study comparing fasting, LCD and VLCD, that after 12 months it was the fasting group that best maintained the initial weight loss. This could be explained by the subjects' reports that they had confidence that they could restrict food intake for a period of time with no ill effects and they now employed the technique to maintain their weight, although Johnstone pointed out that this was not an RCT and the subjects had volunteered for the fasting group, suggesting that this more radical approach might suit them better. [14]

Summary of results: CR appears to carry no significant risk of serious clinical events or decline in mood or cognition. ICR generated slightly improved compliance with no disordered eating or overconsumption on non-restricted days. Headaches, fatigue and dizziness were avoided with ADF. Hunger generally declined with time, especially with higher protein intake.

Discussion

Our findings show that some form of supervised caloric restriction is highly beneficial for reduction in weight, BMI, fat mass and various other measures of adiposity over periods from 12 weeks to two years. The exception was where CR was carried out with a low fat diet, when a CR Mediterranean diet or low carbohydrate diet proved more effective; it has consistently been shown that a low fat diet does not facilitate weight loss. Significant reductions in fasting lipids, glucose and insulin resistance were also found in most studies. Where intermittent is compared with continuous caloric restriction (ICR vs CCR), both generally prove to be equally effective in reducing weight and fat mass. In

some studies, compliance is better in the ICR group and, contrary to concerns, there was little or no hyperphagic or disordered eating on the non-fasting days. Several studies show improved fasting glucose, insulin and insulin resistance for ICR compared to CCR. There is also a suggestion that weight loss may be greater once subjects have normalised HbA1c.

Neither CCR nor ICR studies show any difference in weight loss or fat mass reduction between a low fat, high carbohydrate diet or a high fat, low carbohydrate diet in non-diabetic subjects. There also appears to be no difference between a low and high glycaemic load diet on overweight subjects, whereas a liquid diet may be more effective than solid food for reduction of weight and other parameters. There was little difference in compliance between groups and hyperphagia appeared to decline with time, although CCR with a high glycaemic load was easier to follow than a low glycaemic load. A number of food supplements have been trialled to aid CR. The three studies investigating the addition of ω3 fish oils found that it was significantly effective in increasing weight loss and BMI reduction provided the dose of docosahexaenoic acid (DHA) was high, and could increase ketogenesis. Fat, but not weight, reduction may be aided by the addition of whey protein and essential amino acids or alginate fibre. Only a few studies have investigated CR and meal timing but there seems to be little consensus in the results.

Studies comparing bariatric surgery with CR using the same post-surgery CR diet have found little difference in weight and fat mass reduction, except where the CR involved a low fat diet, when RYGB was more effective. There was similarly no difference in reduction of fasting glucose, insulin, insulin resistance and adipokines, indicating that it is the post-surgery CR which accounts for the success of RYGB in reversing obesity and T2D, rather than the surgical effect on incretin production. This would suggest that rather than undertake expensive and potentially dangerous surgery with its known adverse effects, CR should be attempted first.

Analysis of the studies of weight regain following significant weight loss indicate that CR can be effective in maintaining weight and fat loss and that in general CCR and ICR are equally beneficial, regardless of whether they are low carbohydrate, low fat or low glycaemic diets or whether the calories are provided as liquid or solid food. The only factors which may impact compliance are the addition of protein or employment of ADF rather than CCR. A caffeine and green tea supplement also aided weight loss but only in those with low habitual caffeine intake.

Although there are few studies of ADF, and particularly zero calorie ADF, the regimen appears to be at least as beneficial as other forms of CR for weight and fat loss but may not cause a reduction in metabolic rate or lean mass. ADF may be more helpful for weight/fat loss maintenance, with good compliance and fewer adverse effects. All forms of CR appear to reduce the more dangerous visceral fat and decrease adipocyte size, while having less effect on subcutaneous fat. All forms of CR similarly induce loss of lean as well as fat mass, although the addition of protein to CR was able to increase resting metabolic rate and lean body mass. In general, exercise had little or no impact on weight loss when compared with or combined with CR.

CR has been found to be beneficial for weight and fat loss in all age groups, but particularly the elderly, both genders and in all ethnicities, but possibly particularly for Caucasians. It appears to carry no significant risk of serious clinical events or decline in mood or cognition. ICR generated slightly improved compliance with no disordered eating or overconsumption on non-restricted days, while headaches, fatigue and dizziness were avoided with ADF. Hunger generally declined with time, especially with higher protein intake.

Does Caloric Restriction have the Same Result on all Subjects, Regardless of Condition?

The RCTs analysed above comprise a mixture of subjects who are of normal weight, overweight, obese and/or with T2D. Although no study has set out to compare the impact of CR between diabetics and non-diabetics or groups with different BMI, CR appears to benefit all. Yet there are a few differences, which it may be worth highlighting. Firstly, Pascale *et al* [92] found that CR with a low fat diet enhanced weight loss in those with T2D but made no difference in those without, whereas three other RCTs comparing CR with high and low fat diets in non-diabetics all showed no difference. Pascale *et al* further found that total cholesterol was reduced to a greater extent in non-diabetics on CR with low fat, compared to diabetics. The fact that a low fat diet can aid weight loss in diabetics is a somewhat surprising finding since in general a low fat diet has not been found to support weight reduction. Furthermore, in non-diabetics the degree of CR appears to make little difference to the extent of weight, BMI and fat loss but in diabetics those on 400 kcals/day lost significantly more weight than those on 1000 kcal/day. A difference in effect between diabetics and non-diabetics is not a phenomenon that has previously been highlighted but the number of studies in which it has been found are small and this should be tested in larger studies. With respect to baseline weight, Varady [69] noted that whether a subject was overweight or obese did not affect the relative amount of fat to lean mass lost during weight loss using CCR, although this meant that obese subjects lost more weight in absolute terms than overweight subjects.

Although none of the RCTs investigated type 1 diabetes, in which the incidence of obesity also appears to be growing, nevertheless a study of obese type 1 diabetics showed that caloric restriction for 21 days in a controlled environment could safely result in reduction in weight, BMI, fat mass and waist circumference and allowed a significant reduction in insulin dose [148]. There is, however, a recognised risk of hypoglycaemia with caloric restriction in type 1 diabetes, so regular monitoring would be required.

How much CR is Enough?

The RCTs analysed above are not homogeneous, since some consider energy deficit while other prescribe a set number of calories, but it appears that a 25% calorie deficit has a better weight loss response relative to a 15% deficit [85], while zero calorie ADF resulted in less fat regain during unsupervised weight maintenance than a 400 kcal/day deficit [87]. Yet other than these, and the study showing that among diabetics only a lower calorie intake led to greater weight loss, the majority of studies show that there is little difference between greater or lesser caloric restriction for reduction of weight and fat mass.

However, the Dietary Guidelines for Americans recommend that an energy deficit of at least 500 kcal/day is necessary for weight loss. This was tested in 54 overweight or obese adults, who were given the goal to lose 5% of their total body weight in 14 weeks through creating an energy deficit of ≥500 kcal/day. It was found that those who averaged an energy deficit of >500 kcal/day lost nearly 4 times the weight of individuals whose energy deficit was smaller, while those who achieved the goal of 5% weight loss carried out self-monitoring nearly twice as often as those who failed. [149] In terms of absolute amounts, a retrospective study of 1887 outpatients found that 520 kcal/day versus 850 kcal/day for 12 weeks produced significantly greater weight loss and improved weight maintenance, although after controlling for baseline body weight there was no significant difference between diets for initial weight loss or weight regain. In fact the 850 kcal/day diet had a lower incidence of adverse events and less need for medical monitoring [150]. Several other studies have also shown that the degree of energy restriction is not always reflected in the weight loss results, which may in part be due to techniques to measure food intake [69].

A meta-analysis of six RCTs by Tsai *et al* [32] compared VLCDs to LCDs, with a follow-up of at least 1 year weight maintenance period. VLCDs usually comprise a liquid or partially liquid meal replacement with added protein to preserve lean mass, normally providing <800 kcal/day; they are normally administered only under medical supervision in the US, although this is not a requirement in Europe. The meta-analysis results showed that VLCDs produced significantly greater short term weight loss but similar results at follow-up after the weight maintenance phase due to greater weight regain among the VLCD group; similar numbers dropped out of each group and there were no adverse events in any study. These results show that there is no long term advantage to VLCDs over LCDs, whereas on a VLCD, subjects were more likely to experience increased risk of gallstones, cold intolerance, hair loss, headache, fatigue, dizziness, volume depletion (with electrolyte abnormalities), muscle cramps and constipation, although these symptoms are usually mild and easily managed.

So while it is unclear whether or not an energy deficit of at least 500 kcal/day is necessary for weight loss and maintenance, the reduced need for medical monitoring and lower reports of adverse events may make a higher caloric allowance for CCR more practical, although use of ICR may avoid some of the medical and supervision problems of CCR. Nevertheless, Tsai *et al* make the point that if an easy and reliable method of unsupervised weight loss maintenance could be found, the ideal combination might be a supervised short term VLCD programme followed by the LCD unsupervised weight maintenance programme [32]. This is echoed by Klempel *et al* [95], who suggest combining one day per week of zero calorie fasting with six days per week of 20% energy restriction, possibly through liquid meal replacement for one meal per day, a regimen shown to be highly successful for weight loss in animal models. Furthermore, use of meal replacements largely overcomes the recognised problem of portion size estimation

Meal Timing and Intervals

The RCTs analysed above failed to find a consistent answer to the optimum meal timing. Nevertheless, in perhaps the simplest study, in which three meals per day were compared with an isocaloric one meal per day i.e. time-restricted feeding (TRF), Stote *et al* showed that the one meal per day was significantly more beneficial for weight and fat mass reduction. The authors note that this may be because the participants failed to eat the same number of calories as they would have in three meals per day due to extreme fullness, although the drop-out rate was relatively high in this group. [108] The few other human studies investigating this issue tend to confirm the lack of consistency. Garrow *et al* showed that consuming one meal per day for a week resulted in greater weight loss than an isocaloric diet consumed in five meals per day [151] and Belinova *et al* found that in type 2 diabetics a hypocaloric diet consumed at breakfast and lunch compared to the same diet divided into six small meals per day had a significantly greater effect on weight, plasma ghrelin, hepatic fat content, insulin sensitivity and feelings of hunger [152], although there was no difference in weight reduction in obese males consuming an isocaloric diet in one, three or six meals per day for five weeks [153] or in obese females consuming breakfast and dinner versus 3-5 isocaloric meals per day for four weeks [154]. A study which combined TRF and ADF found no difference in weight after 15 days [147], although when TRF was investigated in resistance-trained male athletes, who were required to consume 100% of energy needs in three meals during an eight hour period for eight weeks, compared to an isocaloric control group, the TRF group had lost a greater amount of fat mass, with no difference in lean mass or blood lipids [155]. A similar trial by the same group, in which the athletes were required to consume all energy needs in a four hour window for four days per week found no difference in body fat composition compared to the control group, despite a reduction in total energy intake [156].

Animal studies reveal a circadian rhythm in the development of obesity, as the time of feeding and fasting affects several genes which are key regulators of glucose and lipid metabolism. This has become known as 'chrononutrition'. Most studies have been carried out on mice, which are mainly nocturnal feeders, making any translation of results to humans problematic. In general, 24 hour fasting mice showed a large reduction in hepatic gene transcripts compared to normal feeding, while day-fed mice demonstrated an altered oscillation of rhythmic transcripts to normal night-fed mice and developed obesity, perturbation in glucose and lipid homeostasis and insulin resistance. Animal models of obesity regularly display disruption in the feeding/fasting rhythms and circadian gene expression, with obese mice choosing to feed during the day as well as at night. Increased propensity to obesity and metabolic syndrome has also been observed among human night shift workers; in a laboratory setting, where subjects had induced dyssynchrony between feeding and fasting times and a disrupted circadian clock, weight gain and metabolic disturbance ensued, with decreased levels of satiety hormones, elevated post-prandial glucose, insulin resistance and mean arterial pressure. [157] Furthermore, there appear to be daily rhythms in glucose homeostasis and insulin sensitivity, which naturally decline over the course of the day. These rhythms are driven by molecular 'clocks' in the hypothalamus, which are affected by light, but peripheral clocks are located in other tissues involved in lipid and glucose metabolism, such as adipose tissue and the liver, which are controlled mainly by feeding times. [158] Another aspect of this is 'food entrainment', the internal mechanism through which the circadian clock genes are controlled by daily scheduled food availability. This allows the body to realign the timing of behavioural and physiological functions focused on the anticipation of food (known as food anticipatory activity). Caloric restriction, and also presumably TRF, have a strong impact on food entrainment, which appears to influence dopaminergic pathways which enhance locomotor sensitisation. [159]

Studies show that in animals with diet induced obesity, *ad libitum* feeding extends for the full 24 hours, with development of metabolic disorders and down-regulation of genes associated with metabolism. Nevertheless, isocaloric TRF can restore the normal feeding pattern and hepatic gene transcripts and protect against or reverse obesity, hyperinsulinaemia, leptin resistance, hepatic steatosis and inflammation, reducing white adipose tissue and protecting brown adipose tissue from 'whitening'; the benefits of TRF were directly proportional to the duration of food restriction. In addition, TRF restores circadian expression of the down-regulated genes. [157,158] In addition, more fat was lost with all calories eaten in one meal a day than *ad libitum*, while brown adipose tissue content increased, although insulin resistance was also increased. [160]

A review by Rothschild *et al* found that the effect of TRF on weight differs between animals and humans, although the decrease in glucose, insulin, total cholesterol and triglyceride concentrations is comparable. Paradoxically, while a shorter eating window induces considerable weight loss in animals it has no impact on humans, while a 10-12 hour window, which produces inconsistent results in animals produces consistent weight loss and reduction in LDL cholesterol in humans. The reason for this is unknown but the authors note that the animal studies were all RCTs, whereas the human studies had no control group. Interestingly, fewer participants withdrew from TRF studies relative to intermittent fasting studies. [161] Other studies have shown that TRF in humans can increase brown adipose tissue at the expense of white, as well as synchronising circadian rhythms and metabolism, although the mechanism for this is not yet understood. While the optimum time window for TRF is still unclear, studies have shown that morning feeding is more beneficial to weight loss, fasting glucose, insulin sensitivity and lipid profile than evening feeding and that any meal consumed after 1500 hours is more likely to increase weight than a meal consumed before that time; late night eating is also associated with development of coronary heart disease. This may be because gastric emptying is more robust during the daytime and metabolism of glucose is slower in the evening than morning. In addition it is thought that some fasting programmes impose a diurnal rhythm in food intake, leading to improved oscillation in circadian gene expression which reprogramme energy metabolism and body weight regulation. [12,76,162,163]

The Role of Insulin Resistance

The RCTs show that most of the successful CR regimens found a decrease in fasting plasma insulin and insulin resistance, where measured, which in some cases was greater with ICR compared to CCR [85] and was aided by a low carbohydrate diet, a semi-liquid diet and lower versus higher caloric intake [91,96]. The RCT by Wing *et al* [96] suggested that decreased insulin sensitivity is dependent on degree of caloric restriction and the magnitude of weight loss, which are independent of each other.

Two further studies suggest that the role of insulin is closely linked to successful weight loss. Mutch *et al* [120] found that during an unsupervised six month weight loss maintenance phase, those who regained only 0-10% of lost weight experienced a significant reduction in insulin secretion in response to an oral glucose tolerance test, whereas no changes in insulin secretion were observed in those who regained 50-100% of lost weight. Furthermore, Hoddy *et al* analysed their obese non-diabetic subjects into degrees of insulin resistance and found that ADF for eight weeks generated a significantly greater reduction in fasting insulin and HOMA-IR in subjects in the highest insulin resistance tertile, compared to subjects in the lowest tertile, despite equal reduction in weight and fat mass in each tertile [164]. This would indicate that CR provides the greatest improvement in insulin sensitivity to those with the greatest degree of insulin resistance. This is in contrast to another study, which found that those obese non-diabetics with the highest baseline plasma insulin concentrations and the greatest insulin resistance lost the least weight with CCR and regained it more readily [165]; nevertheless, this could perhaps indicate the greater efficacy of ADF vs CCR.

Since any food raises blood glucose and triggers secretion of insulin, which inhibits lipolysis, it is thought that the reduction in food intake and periods of abstinence from food force a switch of fuel substrate from oxidation of glucose to oxidation of fatty acids once glycogen stores are extinguished. This is seen in the elevated levels of plasma β-hydroxybutyrate and fatty acid concentrations, as stored triglycerides are broken down and adipose tissue lipolysis releases fatty acids into the circulation; a decrease in fasting triglycerides is usually also seen. Some studies suggest that the fast must last for >18 and preferably 24 hours to obtain the full benefit, including increased resting energy expenditure. [34]

Can Caloric Restriction Lower the Weight 'Set Point'?

Very few studies have been carried out on the weight set point; it is almost impossible to assess in humans and in animals the set point must be calculated from hoarding behaviour. Nevertheless in the few studies which have calculated it, obese rodents were found to have a higher weight set point but caloric restriction was found to reverse ghrelin resistance and alter neuropeptide secretion on a temporary basis but the lost weight was eventually regained, particularly with a high fat diet, although a low fat diet may have more success. [25,166] Other factors which appear to lower the set point, at least temporarily, in animals include nicotine [167] and acute, but not chronic, exercise [168]. Consequently, although temporary weight loss can be achieved in rodents by caloric restriction, this may not be sufficient to alter the weight set point permanently, leading to rebound weight gain. This suggests that some form of caloric restriction must be maintained for life.

Conclusion

Both CCR and ICR generally proved to be equally safe and effective at reducing weight and fat mass, as well as inducing improvement in risk factors for T2D and cardiovascular disease. Weight loss may be aided by the addition to CR of a semi-liquid diet, adequate protein, fibre and ω3 fish oils containing high dose DHA. Although weight loss success was similar between CCR and ICR, nevertheless ICR subjects often showed improved compliance, did not develop disordered eating or hyperphagia on non-restricted days and exhibited a greater reduction in insulin resistance. CCR and ICR were similarly effective for weight loss maintenance, which was aided by the addition of protein to very low energy diets. In general, a VLCD generates more weight loss in the short term but after the weight maintenance phase the results are broadly similar, suggesting that the VLCD is harder to sustain over the longer term and has more adverse effects. These results were consistent regardless of age, ethnicity or gender and applied in normal weight, overweight and obese individuals and those with and without T2D, although in diabetics a very low calorie (c400 kcal/day) diet which is low in fat appears to enhance initial weight loss. RCTs comparing CR with bariatric surgery showed that in most cases the results from CR on weight, fasting glucose, insulin and other biomarkers of T2D, are indistinguishable from those produced by RYGB plus CR. This suggests that it may be preferable to attempt CR in the first instance, in order to avoid expensive and potentially dangerous surgery with its known long term adverse effects.

Although there are few RCTs of ADF, other studies have shown that ADF brings the advantage of less reduction in lean mass and better compliance overall. Since communities with low economic status and disadvantaged minorities are especially vulnerable to obesity and metabolic syndrome and are more likely to have reduced access to fresh, nutritious food, ADF, and particularly zero calorie ADF, may be easier for them to carry out. It carries the advantages that there is no cost, no complicated weighing and measuring of food and no counting calories, while few seem to experience the expected hunger, irritability and low energy with reduced resting metabolic rate and lean mass, and any hyperphagia on non-fasting days diminishes with time. Fasting is not continued for long enough for the individual to develop nutrient deficiencies, electrolyte abnormalities or metabolic adaptation. Above all, it requires minimal input from the health care profession and can be continued indefinitely without risk. In many respects, zero calorie ADF may be the optimum regimen for sustainable weight and fat loss, although there are not as yet sufficient human studies to conclude definitively on this point. Possibly the optimum regimen is not one rigid procedure but the ability for each individual to choose whether CCR, ICR or ADF is the preferred weight loss method, since it seems to be the degree of adherence and sustainability rather than dietary strategy that determines weight loss. This would improve compliance and return to the individual some degree of choice.

It is recommended that larger RCTs investigate intermittent CR, and particularly zero calorie ADF, as a treatment regimen for weight loss and unsupervised long term weight loss maintenance. If this is carried out in parallel with a cost/benefit analysis for this weight loss programme versus the best alternative with respect to necessary input from the healthcare profession to maintain the weight loss it will be possible to ascertain the precise potential for significant cost savings. Of course this would not take into account the enormous cost to the healthcare system of these patients developing T2D and its co-morbidities.

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