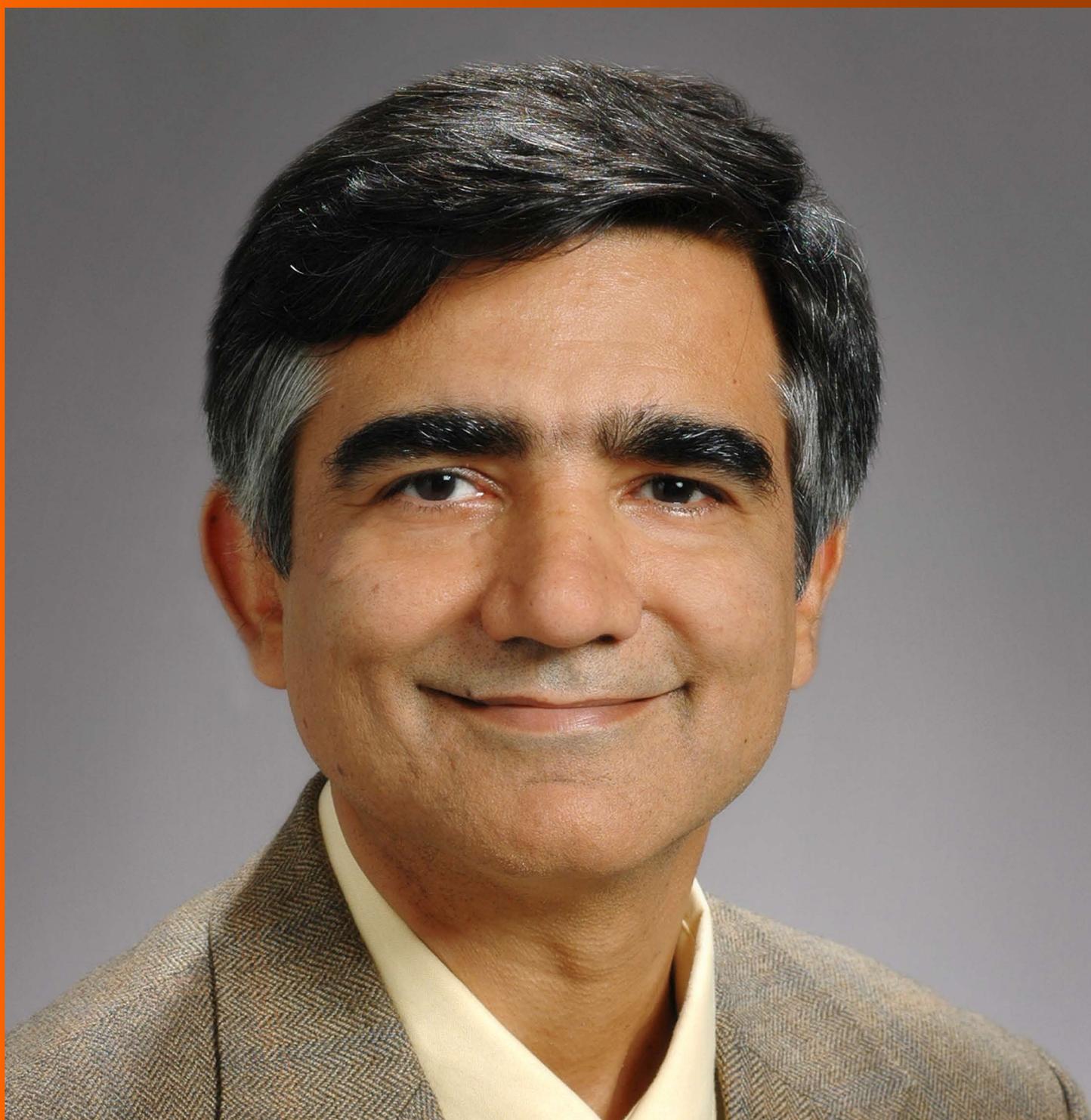


# World Journal of *Diabetes*

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## Assessing the evidence for weight loss strategies in people with and without type 2 diabetes

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### Abstract

This review will examine topical issues in weight loss and weight maintenance in people with and without diabetes. A high protein, low glycemic index diet would appear to be best for 12-mo weight maintenance in people without type 2 diabetes. This dietary pattern is currently being

explored in a large prevention of diabetes intervention. Intermittent energy restriction is useful but no better than daily energy restriction but there needs to be larger and longer term trials performed. There appears to be no evidence that intermittent fasting or intermittent severe energy restriction has a metabolic benefit beyond the weight loss produced and does not spare lean mass compared with daily energy restriction. Meal replacements are useful and can produce weight loss similar to or better than food restriction alone. Very low calorie diets can produce weight loss of 11-16 kg at 12 mo with persistent weight loss of 1-2 kg at 4-6 years with a very wide variation in long term results. Long term medication or meal replacement support can produce more sustained weight loss. In type 2 diabetes very low carbohydrate diets are strongly recommended by some groups but the long term evidence is very limited and no published trial is longer than 12 mo. Although obesity is strongly genetically based the microbiome may play a small role but human evidence is currently very limited.

**Key words:** Protein; Glycemic index; Very low calorie diet; Very low carbohydrate diet; Low fat diets; Intermittent energy restriction; Alternate day fasting

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**Core tip:** Very low energy or very low calorie diet (VLCD) may reverse early type 2 diabetes and very low carbohydrate diets may offer a short term advantage in reducing medication use and/or lower HbA1c more than a more conventional diet. Intermittent energy restriction may be helpful in some people but more data is required. Long term weight maintenance after VLCD may be helped by a higher protein lower glycemic index diet but drugs and partial meal replacements are also helpful.

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## OBSERVATION COHORTS

Observational cohorts from the Nurses' Health Study I and II and the Health Professionals Follow up study with a total of 120000 participants have been very useful at examining dietary predictors of weight gain<sup>[1,2]</sup>. In these cohorts there was a weight gain of 1.45 kg over 4 years. A one cup increase in: (1) sugar sweetened beverages increased weight gain by 0.36 kg; and (2) fruit juice by 0.22 kg while a 1 cup increase in coffee decreased weight by 0.14 kg as did tea by 0.03 kg. Substituting water for sugar sweetened beverages decreased weight gain by 0.49 kg. Greater than average increase in weight was associated with potatoes and French Fries, sugar-sweetened beverages, red meat, alcohol, TV watching, short or long hours of sleep (< 6 or > 8 h/night) and quitting smoking. Lower than average weight gain was associated with a high consumption of vegetables, whole grains, fruit, nuts, yogurt and physical activity.

## ISSUES FOR WEIGHT LOSS AND WEIGHT MAINTENANCE

Long term caloric reduction and weight loss induces a reduction in resting metabolic rate that is usually greater than expected by the lean tissue loss<sup>[3]</sup>, and increased energy efficiency of digestion and absorption and movement<sup>[4]</sup> all of which make weight maintenance a difficult proposition. Hunger is increased and appetite and satiety hormones still deranged 12 mo after initial weight loss despite weight stability or even some weight regain<sup>[5]</sup>. Whether the higher thermic effect<sup>[6]</sup> and higher satiety value of protein<sup>[7]</sup> helps maintain weight loss is not totally clear. Higher fiber intake and lower energy density plus increased polyunsaturated fat intake have been associated with better weight maintenance<sup>[8]</sup>. Long term weight maintenance after large weight losses in the National Weight Control Register is associated with frequent self-monitoring of body weight and food intake, consistency of food intake, always eating breakfast, low variety of food, low fat, low fast food intakes and high levels of regular physical activity (10-11 mJ/wk) although none of these behaviors may be causally related to weight maintenance. Once these successful maintainers have maintained a weight loss for 2-5 years, the chances of longer-term success greatly increase<sup>[9,10]</sup>.

## LOW FAT DIETS

Low fat ad libitum diets have been recommended for many decades on the basis of several observations: (1) energy from fat is less satiating than energy from carbohydrate, and a high fat/carbohydrate ratio (and

thus higher energy density) in the diet can promote passive overconsumption, a positive energy balance and weight gain in susceptible individuals as most individuals eat a fixed volume of food<sup>[11-13]</sup>; (2) fat is more readily absorbed from the intestine than carbohydrate and faecal energy loss is much lower with a high dietary fat/carbohydrate ratio; (3) carbohydrate is more thermogenic than fat<sup>[14]</sup> and energy expenditure is lower during positive energy balance produced by a diet with a high fat/carbohydrate ratio than during positive energy balance produced by a diet with a low fat/carbohydrate ratio<sup>[15]</sup>; and (4) a high fat diet may damage the intestinal barrier and cause intestinal dysbiosis<sup>[16,17]</sup>.

Low fat diets were reviewed many years ago by Astrup *et al*<sup>[18]</sup>. Summaries for all the diets are found in Table 1. He found that low-fat diets cause weight loss proportional to pretreatment body weight and weight loss is correlated positively to the reduction in dietary fat content. A reduction of 10% fat energy produces an average 5-kg weight loss in obese persons. After major weight loss, an ad libitum low-fat diet program appeared to be superior to caloric counting in maintaining the weight loss 2 years later. A recent meta-analysis from Tobias *et al*<sup>[19]</sup> found low diets were not different to high fat weight loss diets but worth 5 kg compared with no intervention. A Cochrane meta-analysis from Hooper confirmed the weight loss effects of a low fat diet compared with usual diet with an effect size of 1.5 kg<sup>[20]</sup>.

## HIGH PROTEIN DIETS

High protein weight loss diets reduce the intake of carbohydrate and fat but maintain protein intake to take advantage of their greater satiety (10%-15% less food intake after a protein preload<sup>[21]</sup>) and thermic effects. Atkins and South Beach diets maintain protein intake but in addition dramatically reduce carbohydrate and replace it with fat. Omitting a major food group inevitably leads to weight loss but long term adherence is difficult.

Clifton *et al*<sup>[22]</sup> performed a meta-analysis of planned high protein diets vs normal protein weight loss diets with at least 10% protein difference planned or expected (*e.g.*, Atkins diets) and followed up for 12 mo or more. The actual reported difference in protein intake at the end of the study was usually 2%-5% of energy. Thirty-two studies with 3492 individuals were analyzed with data on fat and lean mass, glucose and insulin data was available from 18 to 22 studies and lipids from 28 studies. This meta-analysis included the large but very negative Sacks study<sup>[23]</sup>. A difference in favor of the high protein of about 0.4 kg for weight and fat mass was found. A difference of 5% or greater in percentage protein between diets at 12 mo was associated with a 3-fold greater effect size compared with < 5% ( $P = 0.038$ ) in fat mass (0.9 vs 0.3 kg). Fasting triglyceride and insulin were also lower with high protein diets.

**Table 1** Weight loss diets in people without diabetes

Type of diet	Type of summary document	Effect size	Long term data	Recommendation	Risk markers
Low fat diet	Systematic review <sup>[18]</sup>	10% reduction in fat lowers weight by 5 kg			
Low fat diet	Meta-analysis <sup>[19]</sup>	Not different to high fat weight loss diets			
Low fat diet	Cochrane <sup>[20]</sup> meta-analysis 32 RCT, 54000 participants At least 6-mo duration	Mean reduction 1.5 kg for low fat without intention to lose weight	No reduction with time	High quality evidence-effect seen in almost all studies A useful strategy well worth pursuing	
High protein diet	Meta-analysis of 12 m or greater weight loss studies 3492 individuals <sup>[22]</sup>	SMD 0.14 for weight $P = 0.008$ and 0.22 for fat mass, $P < 0.001$ for 2%-5% energy differences in protein. > 5% energy protein difference 0.9 kg weight loss	Data out to 5 yr still shows a small residual effect		Lower triglyceride (SMD 0.17, $P = 0.003$ ) and lower insulin (SMD 0.22, $P = 0.042$ )
High protein diet	Meta-analysis of controlled short term studies <sup>[24]</sup>	0.79 kg weight 95%CI: -1.50, -0.08 kg), 0.8 kg greater fat mass loss (-0.87 kg; 95%CI: -1.26, 0.48 ), 0.43 kg (95%CI: 0.09, 0.78) reduction in lean loss			Lower triglyceride (-0.23 mmol/L; 95%CI: -0.33, -0.12 mmol/L). Reductions in falls in REE (595.5 kJ/d; 95%CI: 67.0, 1124.1 kJ/d)
Conclusion				Small effects. Difficult to maintain a higher protein intake long term as other sources of calories creep in	
Very low carbohydrate diets	Energy controlled < 45% CHO vs < 30% fat 23 trials 2788 participants <sup>[31]</sup>	Weight outcomes same			Slightly lower LDL, TG, increased HDL
Very low carbohydrate diets	Meta-analysis of 6 mo studies, 11 studies <sup>[25]</sup>	Atkins diet better by WMD -2.17 kg; 95%CI: -3.36, -0.99	Not long term	No long term benefit, possible adverse CVD effects	Triglyceride was lowered WMD -0.26 mmol/L; 95%CI: -0.37, -0.15 by the low carbohydrate diet; LDL elevated by WMD 0.16 mmol/L; 95%CI: 0.003, 0.33). HDL elevated WMD 0.14 mmol/L; 95%CI: 0.09, 0.19
Very low carbohydrate diets	Meta-analysis of 12 mo or > studies, $n = 5$ <sup>[25]</sup>	Weight outcomes same		No long term benefit	
Conclusion				No long term benefit	
Very low calorie diet	Review of 12 studies <sup>[35]</sup> of VLCD vs behavioural program and diet change	VLCD was worth an additional 3.9 kg at 12 m and 1.4 kg at 24 m and 1.3 kg at 38-60 m. Dropouts were the same at 19%-20% which was lower than expected	Long term benefit seen	Worth trying with weight loss maintenance programs	
Very low calorie diet	Single hospital based clinic $n = 1109$ <sup>[36]</sup>	19% still attending at 3 yr and the mean weight loss of this group was 6.4 kg. Weight loss was 7.7% vs 2.3% for drugs (topiramate plus phentermine or sibutramine) compared with no drugs			
Conclusion				Well worth trying if large weight loss required	
Weight maintenance after VLCD	8 European centres <sup>[38]</sup> 11% weight loss with VLCD after 8 wk Randomised to high or normal protein 25% vs 13% and high or low GI 15U different	Fewer participants in the high-protein and the low glycemic-index groups than in the low-protein-high-glycemic-index group dropped out of the study (26.4% and 25.6% vs 37.4%; $P = 0.02$ and $P = 0.01$ )	The difference in weight regain after 1 yr <sup>[39]</sup> between protein groups was 2.0 (0.4, 3.6) kg ( $P = 0.017$ ) (completers analysis, $n = 139$ ) or 2.8 (1.4, 4.1) kg ( $P < 0.001$ ) (intention-to-treat analysis, $n = 256$ )	In the shop centres (where food was provided) protein had a more powerful effect (2.7 kg compared with low protein, $P < 0.001$ ) while low GI had less effect (0.48 kg, NS)	

Weight maintenance after VLCD	189 participants on VLCD for 3 mo then high or normal protein for 12 mo <sup>[40]</sup>	No difference between diets Weight regain over 9 mo was modest at 2 kg with a final weight loss of 14.5 kg overall. Overall dropout rate was 53% and compliance measures to the high protein diet were limited		Protein may have modest long term weight maintenance effects Because compliance measures were limited conclusions on benefit (or absence of benefit) are limited
Conclusions				Protein may be of some benefit, GI isn't long term. More trials required
Intermittent energy restriction Conclusion	2 d partial fast and 5 normal days or alternate day fasting	Weight loss similar to CER over 3-6 mo <sup>[40-42,44,45]</sup>	No long term data	No additional metabolic benefit <sup>[47,48]</sup>  Insufficient data, no long term data. More work required
Glycemic index	23 young adults <sup>[50]</sup> low GI ad lib vs Low fat diet with energy reduction of 250-500 kcal	Weight loss 7.8% vs 6.1% (NS)		Triglyceride was lowered by 37.2% and 19.1% ( $P = 0.005$ ) at 6 mo with no difference at 12 mo. PAI-1 was lowered by 39% with the low GI diet vs a 33% rise (despite the weight loss) CVD risk markers the same
Glycemic index Conclusion	73 young adults low glycemic load diet vs low fat diet <sup>[51]</sup>	No difference at 6, 12, 18 mo Insulin above the median (57.5 $\mu$ IU/mL; $n = 28$ ) at 30 min of OGTT -5.8 vs -1.2 kg on low GL diet vs low fat diet ( $P = 0.004$ ) and body fat percentage (-2.6% vs -0.9%; $P = 0.03$ ). No difference in insulin sensitive group		Insufficient data for any conclusions
Mediterranean diet Conclusion	Mediterranean vs low fat diet in 322 people in a workplace setting <sup>[51]</sup>	Weight loss in the 272 completers was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group; a moderate reduction only ( $P < 0.001$ for the interaction between diet group and time)	During 6 follow-up period, participants had regained 2.7 kg of weight lost in the low-fat group, 1.4 kg in the Mediterranean group, and 4.1 kg in the low-carbohydrate group ( $P = 0.004$ for all comparisons) For the entire 6-yr period, the total weight loss was 0.6 kg in the low-fat group, 3.1 kg in the Mediterranean group, and 1.7 kg in the low-carbohydrate group ( $P = 0.01$ for all comparisons) with the Mediterranean group and the low-carbohydrate group not different from each other ( $P = 0.22$ ) <sup>[52]</sup>	Mediterranean diet best long term and has the longest follow up along with VLCD

Low sugar diet	Meta-analysis of 30 trials and 38 cohorts <sup>[53]</sup>	Adults decrease in body weight (0.80 kg, 95%CI: 0.39 to 1.21; $P < 0.001$ ) Cohort studies sugar caused increase weight increase of 0.75 kg, 95%CI: 0.30 to 1.19; $P = 0.001$ ) Interventions in children SSB vs control beverage 1 kg (95%CI for the difference, -1.54 to -0.48) <sup>[54]</sup>	12 mo difference in weight of 1.9 kg SSB vs water disappeared 12 mo after trial stopped <sup>[55]</sup>	
Conclusion				Strong evidence for the benefit of sugar reduction in beverages
Multicomponent	33 RCTs of at least 1 yr's duration <sup>[56]</sup>	Weight loss vs exercise 3.2 kg, 95%CI: -4.8 kg to -1.6 kg) Type of diet not important	Low-fat diets, some with meal replacements, with physical activity and behavior change training gave most effective long-term weight change in men (-5.2 kg after 4 yr)	
Multicomponent	Commercial weight loss programs <sup>[57]</sup>	Pooled results from five study arms in commercial weight management programs showed significant weight loss at 12 mo (-2.22 kg, 95%CI: -2.90 to -1.54) Two commercial weight loss arms (mean difference -6.83 kg, 95%CI: -8.39 to -5.26) GP interventions mean difference -0.45 kg, 95%CI: -1.34 to 0.43)		
Conclusion				Commercial plans of some value
Calcium	Meta-analysis of calcium RCTs	RCTs of about 600 overweight and obese individuals from 7 trials dietary calcium supplementation of about 1000 mg was associated with weight loss and fat loss of approximately 1 kg over 6 mo and had a greater effect in pre - than in postmenopausal women <sup>[59]</sup>	Calcium (1000 mg) and vitamin D after 3 yr of follow-up women with daily calcium intakes of < 1200 mg at baseline on supplements were 11% less likely to experience weight gain <sup>[61]</sup>	
Conclusion				Marginal effect only
Dairy	Meta-analysis of 27 trials of dairy added to energy restriction <sup>[62]</sup> Meta-analysis of added calcium or dairy without weight restriction-no effects seen <sup>[60]</sup>	A greater reduction in body weight [-1.16 kg (95%CI: -1.66 to -0.66), $P < 0.001$ , $I^2 = 11%$ , QR = high, $n = 644$ ] and body fat mass [-1.49 kg (95%CI: -2.06 to -0.92), $P < 0.001$ , $I^2 = 21%$ , $n = 521$ , QR = high) smaller loss of lean mass of 0.36 kg (0.01, 0.71 kg), $P = 0.04$ , $I^2 = 64%$ , $n = 651$ , QR = moderate)	No long term data	
Conclusion				Dairy may be useful component of a weight loss diet but does nothing by itself in the absence of weight loss

CER: Continuous energy restriction; CHO: Carbohydrate; GI: Glycemic index; PAI-1: Plasminogen activator inhibitor-1; QR: Quality rating; RCT: Randomised control trial; SMD: Standardized mean difference; VLCD: Very low calorie diet; WMD: Weight mean difference.

Other lipids and glucose were not different. A meta-analysis of short term calorie controlled interventions was performed by Wycherley *et al*<sup>[24]</sup>. Despite the similar

energy prescription weight loss was greater on the high protein, low fat diet with a difference in weight of -0.79 kg and fat mass of 0.8 kg with lower triglycerides. There

was also mitigation of reductions in fat-free mass of 0.43 kg and resting energy expenditure.

There have been several meta-analysis of low carbohydrate diets<sup>[25-31]</sup>. One compared low carbohydrate diets (< 45%) vs low fat (< 30%) diets in an energy controlled, constant protein design. In 23 trials containing 2788 participants weight outcomes were the same with slightly lower low-density lipoprotein (LDL), increased high-density lipoprotein and lower TG<sup>[31]</sup>. In a meta-analysis of 5 studies<sup>[25]</sup> of 12 mo or more duration there was no difference in weight although 11 studies of 6 mo or more duration<sup>[25]</sup> showed a 2 kg difference in favor of the Atkins diet. Although triglyceride was lowered as expected by 0.35 mmol/L by the low carbohydrate diet LDL cholesterol was still elevated by 0.2 mmol/L by the high saturated fat diet which could increase the risk of cardiovascular disease (CVD) suggesting the Atkins diet may not be the best diet for those at risk of CVD<sup>[25,32-34]</sup>. Flow mediated dilatation which is a reasonable proxy for CVD risk is impaired after an Atkins diet despite weight loss and blood pressure and glucose reduction<sup>[35]</sup>. South Beach style diets which use unsaturated fats instead may be better for those at risk of CVD<sup>[34]</sup>.

## MEAL REPLACEMENTS AND VERY LOW CALORIE DIETS

Another variant of a high protein diet is the meal replacement which provides mostly protein with a small amount of carbohydrate or fat but also provides a very structured, controlled intake especially in its very low calorie diet (VLCD) form. The latter is not frequently used because of rapid weight regain after its cessation but if drugs are used better weight maintenance can be achieved.

A recent review examined 12 studies with 974 participants comparing VLCD to behavioural programs that would be conducted in a medical clinic. Compared with behavioural programs (mostly diet alone) VLCD was worth an additional 3.9 kg at 12 m and 1.4 kg at 24 m and 1.3 kg at 38-60 m. Dropouts were the same at 19%-20% which was lower than expected<sup>[36]</sup>. A follow up of an obesity clinic hospital population of 1109 hospital patients given VLCD showed that 19% were still attending at 3 years and the mean weight loss of this group was 6.4 kg. Weight loss was 7.7% vs 2.3% for drugs (topiramate plus phentermine or sibutramine) compared with no drugs<sup>[37]</sup>.

## WEIGHT MAINTENANCE AFTER VLCD

Larsen *et al*<sup>[38]</sup> completed a large pan European trial in 8 centres which randomised participants to a normal or high protein diet or a low glycemic index or moderate glycemic index. After 773 completed the VLCD phase they were randomised to the maintenance diets for 6 mo. Although the high protein diet was planned to be 25% of energy compared with 13% in the normal diet the difference between the two was only 5%.

The GI was planned to be 15 U different but only a 5 U difference was achieved. In an intention-to-treat analysis, the weight regain was 0.93 kg less in the high-protein group than in the low-protein group ( $P = 0.003$ ) and 0.95 kg less in low-GI diet than in the high GI diet ( $P = 0.003$ ). Only the low protein, low GI group gained a significant amount of weight over the 6 mo (1.67 kg;  $P < 0.01$ ). The follow up was extended to 1 year in 2 of the centres. The difference in weight regain after 1 year between protein groups was 2.0 kg ( $P = 0.017$ ). No consistent effect of GI on weight regain was found<sup>[39]</sup>.

Contrary results were found by Delbridge *et al*<sup>[40]</sup> who placed 180 participants on a VLCD for 3 mo and then randomised them to a high protein weight maintenance diet or a normal protein diet. Weight regain over 9 mo was modest at 2 kg with a final weight loss of 14.5 kg overall. Overall dropout rate was 53% and compliance measures to the high protein diet were limited so it is difficult to draw any firm conclusions from this study.

## ALTERNATIVE APPROACHES TO FULL VLCD

Intermittent energy restriction consists of either 2 d of 600-880 kcal/d with 5 d of a normal diet or alternate day fasting. The weight loss results are very similar to a 25%-30% calorie reduction every day over 3-6 mo<sup>[41,42]</sup>. Similar results have been seen with alternate day fasting<sup>[43]</sup> and week on/week off diets<sup>[44]</sup> and there is some evidence of usefulness in people with type 2 diabetes<sup>[45,46]</sup>. Alternate day fasting may be just as efficacious as full VLCD<sup>[47]</sup>. The suggestion there may be metabolic benefit of intermittent energy restriction is currently unproven<sup>[48,49]</sup>.

## GLYCEMIC INDEX

There are very limited studies for weight loss in people without diabetes. Ebbeling *et al*<sup>[50]</sup> studied 23 young obese adults over 12 mo comparing an ad libitum low GI diet to a low fat diet with an energy reduction of 250-500 kcal/d. Body weight was lowered by a similar amount at 12 mo. Plasminogen activator inhibitor-1 was lowered by 39% with the low GI diet vs a 33% rise (despite the weight loss). In a second study of 73 young obese adults a low glycemic load diet was not different from a low fat diet at 6, 12 and 18 mo<sup>[51]</sup>. For those with a high insulin concentration at 30 min after a 75 g OGTT (*i.e.*, insulin resistant) the low-glycemic load diet produced a greater decrease in weight (-5.8 kg vs -1.2 kg;  $P = 0.004$ ) than the low-fat diet at 18 mo. No differences were seen in the insulin sensitive group. CVD risk markers were not influenced by insulin response status.

## MEDITERRANEAN DIET

Shai *et al*<sup>[52]</sup> compared a Mediterranean to an Atkins and a low fat weight loss diet in 322 subjects with a mean body mass index (BMI) 31 of whom 86% male in

a controlled workplace setting in the Negev desert (The DIRECT study). At 2 years 84.6% were still enrolled in the study. Weight loss in the 272 completers was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group (a moderate reduction) (only  $P < 0.001$  for the interaction between diet group and time). Predictors of successful weight loss at 6 m were increasing the intake of vegetables and decreasing the intake of sweets and cakes.

At 6 years after study initiation, 67% of the participants had continued with their originally assigned diet, 11% had switched to another diet, and 22% were not dieting ( $P = 0.36$  for all comparisons). For the entire 6-year period, the total weight loss was 0.6 kg in the low-fat group, 3.1 kg in the Mediterranean group, and 1.7 kg in the low-carbohydrate group ( $P = 0.01$  for all comparisons) with the Mediterranean group and the low-carbohydrate group not different from each other ( $P = 0.22$ )<sup>[53]</sup>.

## LOW SUGAR DIETS

Te Morenga *et al*<sup>[54]</sup> performed a meta-analysis of low sugar diets. In trials of adults with ad libitum diets reduced intake of dietary sugars was associated with a decrease in body weight of 0.80 kg,  $P < 0.001$ . Isoenergetic exchange of dietary sugars with other carbohydrates showed no change in body weight. In cohort studies increased sugar intake was associated with a weight increase of 0.75 kg,  $P = 0.001$ . In children a controlled randomised beverage trials of sugar sweetened beverages vs artificially sweetened over 18m demonstrated a weight increase of 6.35 kg in the sugar-free group as compared with 7.37 kg in the sugar group<sup>[55]</sup>. In 223 overweight/obese adolescents home delivery of water and diet beverages in children who were regular consumers of sugar sweetened beverages for 1 year induced changes in weight (-1.9 kg,  $P = 0.04$ ) compared with the control group at 1 year but this disappeared at 2 years<sup>[56]</sup>.

## MULTICOMPONENT AND COMMUNITY-BASED INTERVENTIONS

Robertson *et al*<sup>[57]</sup> examined weight loss studies in men of at least 1 year's duration and 33 RCTs were located which met the inclusion criteria. Reducing diets tended to produce more favorable weight loss than physical activity alone (mean weight difference after 1 year from a reducing diet compared with an exercise program of 3.2 kg). The type of reducing diet did not affect long-term weight loss. A reducing diet plus physical activity and behavior change gave the most effective results. Low-fat reducing diets, some with meal replacements, combined with physical activity and behavior change training gave the most effective long-term weight change in men of 5.2 kg after 4 years.

Hartmann-Boyce *et al*<sup>[58]</sup> examined multicomponent interventions delivered in a routine clinical practice environment with assessment at 12 mo. Pooled results from five study arms in commercial weight management programs showed significant weight loss at 12 mo of 2.22 kg. Results from two arms of a study testing a commercial program providing meal replacements also showed a significant weight loss of 6.8 kg. In contrast, pooled results from five interventions delivered by primary care teams showed no evidence of an effect on weight. Clearly commercial weight loss programs can be of value.

## DAIRY AND HIGH CALCIUM DIETS FOR WEIGHT LOSS

### Calcium

Calcium binds fat in the gut so that an additional dietary calcium intake of 1000 mg increases faecal fat excretion by approximately 5 g/d<sup>[59]</sup> which has the potential to add to weight loss. In a meta-analysis of RCTs of about 600 overweight and obese individuals from 7 trials dietary calcium supplementation of about 1000 mg was associated with weight loss and fat loss of approximately 1 kg over 6 mo and had a greater effect in pre- than in postmenopausal women<sup>[60]</sup>. Booth *et al*<sup>[61]</sup> however found no effect in their meta-analysis. Most interventions used low fat milk as fat intake was not different between intervention and control in these studies. Women who received calcium (1000 mg) and vitamin D had a slightly lower weight gain than did those receiving placebo, and after 3 years of follow-up women with daily calcium intakes of  $< 1200$  mg at baseline who were randomly assigned to supplements were 11% less likely to experience weight gain<sup>[62]</sup>.

### Dairy

There have been several meta-analyses of the effect of addition of dairy foods to an energy restricted diet. The most recent one examined 27 trials of  $> 4$  wk's duration<sup>[63]</sup>. Participants consumed between 2 and 4 standard servings/day of dairy food and 20-84 g/d of whey protein compared to low dairy control diets, over a median of 16 wk. A greater reduction in body weight of 1.16 kg,  $n = 644$  and body fat mass 1.49 kg,  $n = 521$ , 90% of whom were women. These effects were absent in studies that imposed resistance training. Dairy intake resulted in smaller loss of lean mass of 0.36 kg. No between study dose-response effects were seen. A previous meta-analysis<sup>[61]</sup> found no effect of the addition of calcium or dairy on weight, thirty-one with dairy foods ( $n = 2091$ ), and twenty with Ca supplements ( $n = 2711$ ).

## DIETS FOR WEIGHT LOSS IN TYPE 2 DIABETES

In this section we will examine the effects of diets not just on weight but on HbA1c as an HbA1c  $> 7\%$  would

be one of the prime reasons overweight and obese people with diabetes would be recommended to lose weight. Weight stable dietary changes to lower HbA1c will not be examined (Table 2).

## LOWER GLYCEMIC INDEX/LOWER GLYCEMIC LOAD DIETS

Although these diets would be recommended predominantly to lower HbA1c they are also used for weight loss. The Canadian Trial of Carbohydrates in Diabetes<sup>[64]</sup> enrolled 162 people treated by diet alone who were randomly assigned to high-carbohydrate/high-glycemic-index (HGI) diets; high-carbohydrate/low-glycemic-index (LGI) diets or lower-carbohydrate/high-monounsaturated-fat (LC) diets for 1 year. No differences were seen in weight or HbA1c over 1 year but achieved GI differences were small. A second Canadian low glycemic index diet study<sup>[65]</sup> in 210 participants with type 2 diabetes on hypoglycemic medication showed no differences in weight over 6 mo compared with a high cereal fibre diet although HbA1c was lowered by 0.32%<sup>[65]</sup>.

Franz *et al*<sup>[66]</sup> examined randomized clinical trials implementing weight-loss interventions in overweight or obese adults with type 2 diabetes with a minimum 12-mo study duration, a 70% completion rate, and an HbA1c value reported at 12 mo. Eight trials compared different diets while 3 compared diets to usual care. Only two study groups reported a weight loss of  $\geq 5\%$ : A Mediterranean-style diet implemented in newly diagnosed adults with type 2 diabetes and an intensive lifestyle intervention implemented in the Look AHEAD (Action for Health in Diabetes) trial. Both included regular physical activity and frequent contact with health professionals and reported significant beneficial effects on HbA1c, lipids, and blood pressure. All other trials either achieved a weight loss of  $< 5\%$  and no benefit on HbA1c or CVD risk factors or found no differences between macronutrient interventions in weight or HbA1c.

## LOOK AHEAD STUDY

The Look Ahead Study<sup>[67]</sup> enrolled 5145, aged 45-74 years, with BMI  $> 25$  ( $> 27$  if taking insulin) into a weight loss (with meal replacements if required) and exercise intervention. The Intensive lifestyle intervention produced an 8.6% weight loss at 1 year vs 0.7% in control group. Mean HbA1c dropped from 7.3% to 6.6%. At 4 years weight was still 5.3% lower compared with control and HbA1c-0.27% lower<sup>[68]</sup>.

Although the study was ceased after 8 years because of lack of CVD differences compared with the control group<sup>[69]</sup> there were many benefits seen in the intervention in mood, quality of life and physical function<sup>[70]</sup>. It clearly showed that a weight loss of 10% or more could be achieved and maintained at 8 years in 27% of the intensive lifestyle group with 50%

achieving more than 5% weight loss<sup>[71]</sup>. One of the reasons the trial failed to achieve its primary end point was because the support and education control group achieved a weight loss of 10% or more in 17% of the group with 5% or more weight loss achieved by 36%. The intervention led to reductions in hospitalizations (11%,  $P = 0.004$ ), hospital days (15%,  $P = 0.01$ ), and number of medications (6%,  $P = 0.001$ ) compared with control participants who were invited to three sessions of diabetes support and education a year. No benefit was unfortunately seen in the 15% of the population with pre-existing CVD. There were fewer deaths in the intervention group (6.8% vs 7.8%) but this was not significant ( $P = 0.15$ )<sup>[72]</sup>.

In secondary analyses of the full cohort<sup>[73]</sup> (both intervention and control groups), over a median 10.2 years of follow-up, individuals who lost at least 10% of their bodyweight in the first year of the study had a 21% lower risk of the primary outcome [death from CVD, MI, stroke or admission for angina (adjusted hazard ratio  $P = 0.034$ )] compared with individuals with stable weight or weight gain. In analyses treating the control group as the reference group, participants in the intensive lifestyle intervention group who lost at least 10% of their bodyweight had a 20% lower risk of the primary outcome  $P = 0.039$ .

## ATKINS AND SOUTH BEACH DIETS

There is a small group of advocates for low carbohydrate Atkins style diets for clinical treatment in type 2 diabetes<sup>[74-76]</sup>. A 6-mo study from one group compared Atkins (LCKD) vs calorie-reduced low GI diet (LGID) in volunteers with a BMI 38, of whom 80% were women. There was a high dropout rate with 58.3% (49) participants completing. Body weight fell by 11.1 kg vs 6.9 kg ( $P = 0.008$ ) and HbA1c was reduced by -1.5% vs -0.5% ( $P = 0.03$ ). LDL was higher in the Atkins group by 4% which although small is of some theoretical concern<sup>[77]</sup>. There was no long term follow up which is important as Atkins adherence drops off dramatically after 6 mo. In a 48w study comparing an Atkins diet to a low fat diet plus orlistat in which 32% of the volunteers had type 2 diabetes ( $n = 46$ ) weight loss was excellent in both groups at 8.65% to 9.5% with no differences between groups<sup>[78]</sup>.

In an energy controlled low carbohydrate South Beach diet compared to a usual carbohydrate weight loss diet weight loss was the same as planned (9.8 and 10.1 kg) the overall HbA1c fall was the same but there was a greater effect in the low carbohydrate group at 6 mo if HbA1c was greater than 7.8% (2.6% vs 1.9%). Drug reductions were also greater in the South Beach group. At 12 mo the HbA1c difference had disappeared<sup>[34,79]</sup>.

## VLCD

Somewhat surprisingly the number of publications of

**Table 2 Weight loss diets in people with type 2 diabetes**

Type of diet	Type of summary document	Effect size	Long term data	Recommendation	Risk markers
Low glycemic index/low glycemic load	Canadian Trial of Carbohydrate in Diabetes <sup>[63]</sup> 12 mo study in 162 volunteers The HGI, LGI and LC diets contained 47% ± 1%, 52% ± 1% and 40% ± 1% energy carbohydrate; 30% ± 1%, 27% ± 1% and 40% ± 1% fat with GI 64 ± 0.4, 55 ± 0.4 and 59 ± 0.4	No difference between diets	None		
Low glycemic index	Canadian low glycemic index diet study <sup>[64]</sup> in 210 participants with type 2 diabetes on hypoglycemic medication	No effect on	None		HbA1c lower buy 0.32% on low glycemic index diet compared with high fibre diet
All randomised diets in type 2 diabetes of 12 mo or more duration	Eleven trials <sup>[65]</sup> were identified with 6754 participants were reviewed. Eight trials compared different diets while 3 compared diets to usual care. Only two study groups reported a weight loss of ≥ 5%: A Mediterranean-style diet implemented in newly diagnosed adults with type 2 diabetes and an intensive lifestyle intervention implemented in the Look AHEAD (Action for Health in Diabetes) trial			No value in type 2 diabetes	
Conclusion				Mediterranean diet best	
Look ahead study	The Look Ahead Study <sup>[66]</sup> enrolled 5145, aged 45-74 yr, with BMI > 25 (> 27 if taking insulin) into a weight loss (with meal replacements if required) and exercise intervention	The Intensive lifestyle intervention produced an 8.6% weight loss at 1 yr vs 0.7% in control group	At 4 yr weight was still 5.3% lower compared with control. Weight loss of 10% or more at 8 yr in 27% of the intensive lifestyle group with 50% achieving more than 5% weight loss <sup>[70]</sup> support and education control group achieved a weight loss of 10% or more in 17% of the group with 5% or more weight loss achieved by 36%		Mean HbA1c dropped from 7.3% to 6.6% At 4 yr HbA1c-0.27% lower <i>Post hoc</i> analysis in the whole population (4834) over 10 yr <sup>[72]</sup> showed that those who lost at least 10% of their body weight in the first year had a 21% lower (HR 0.79, 95%CI: 0.64-0.98, <i>P</i> = 0.034) risk of primary outcome (death from CVD, MI, stroke, admission for angina), and a 24% reduced risk of the secondary outcome (primary plus CABG, carotid endarterectomy, stent, heart failure, PVD or total mortality) (adjusted HR 0.76, 95%CI: 0.63-0.91; <i>P</i> = 0.003)

Conclusion				Only non-surgical weight loss study with reduction in hard end points	
Atkins diet	A 6-mo study from one group of Atkins <i>vs</i> calorie-reduced low GI diet in volunteers with a BMI 38, of whom 80% were women <sup>[76]</sup>	Body weight fell by 11.1 kg <i>vs</i> 6.9 kg, $P = 0.008$ 58.3% (49) participants completing			HbA1c was reduced by -1.5% <i>vs</i> -0.5% ( $P = 0.03$ ) LDL was higher in the Atkins group by 4%
Atkins diet	48w study <sup>[77]</sup> comparing an Atkins diet to a low fat diet plus orlistat in which 32% of the volunteers had type 2 diabetes ( $n = 46$ )	Weight loss 8.65% to 9.5% with no differences between groups			
South Beach diet	80 volunteers completed a 12 mo very low carbohydrate diet <i>vs</i> an energy matched high carbohydrate diet <sup>[34,78]</sup>	9.8 and 10.1 kg at 12 mo			HbA1c changes different at 6 mo but not at 12.1% reduction
Conclusions				Low carbohydrate diets good in short term with intensive support	
VLCD	Meta-analysis of 5 studies of VLCD in volunteers with diabetes or no diabetes <sup>[80]</sup>	Weekly weight loss was similar in the two groups at 0.5 to 0.6 kg/wk. Weight losses of > 15%-20% were observed in these studies			
VLCD	Retrospective analysis of 355 patients with diabetes matched with nondiabetics  Total cohort comprised 204 males: 506 females, age $54.0 \pm 9.1$ ; BMI $41.6 \pm 8.1$ ; weight $116.1 \pm 25.1$ kg <sup>[81]</sup>	After 12 wk, there was significant weight loss within each group when compared with baseline (T2DM: $115.0 \pm 24.4$ kg <i>vs</i> $96.7 \pm 21.4$ kg, $P < 0.0001$ ; non-T2DM: $117.2 \pm 25.8$ kg <i>vs</i> $97.3 \pm 22.2$ kg, $P < 0.0001$ ) At 12 wk, weight change ( $-18.3 \pm 7.3$ kg <i>vs</i> $-19.9 \pm 7.0$ kg, $P = 0.012$ ) were significantly less in the T2DM group when compared with the non-T2DM group	No long term data available		
VLCD	40 individuals with type 2 diabetes and no control group	Weight loss of 10 kg at 1 yr after an 8 wk VLCD. Five year data from a comparison of self-selected VLCD (15) to modest caloric restriction ( $n = 15$ ) showed better weight loss in the conventional diet 8.9 kg <i>vs</i> 4.8 kg <sup>[83]</sup> Early use of VLCD can cause remission of type 2 diabetes <sup>[84]</sup>	Long term data shows benefit	VLCD useful	
Conclusion				Although expensive VLCD has long term benefits	
Diet plus exercise	2 controlled studies adding aerobic or resistance exercise to significant weight loss over 12 to 16 wk <sup>[86,87]</sup>	No additional benefit of adding exercise on weight	No long term data		No additional benefit on HbA1c or any other markers
Conclusions				No added benefit	

CER: Continuous energy restriction; CHO: Carbohydrate; GI: Glycemic index; VLCD: Very low calorie diet.

the use of meal replacements and VLCD in diabetes is limited<sup>[80]</sup>. In a meta-analysis of 5 studies of VLCD in both people with and without diabetes there was no difference in achieved weight loss between these two groups. Weekly weight loss was similar in the two groups at 0.5 to 0.6 kg/wk. Weight losses of > 15%-20% were observed in these studies<sup>[81]</sup>. In a retrospective analysis<sup>[82]</sup> 355 participants with T2DM were matched for age, BMI and gender to participants without T2DM. The program included a daily intake of 550 kcal in addition to group support and behavior therapy provided by trained facilitators within a community-based setting. At 12 wk, weight change ( $-18.3 \pm 7.3$  kg vs  $-19.9 \pm 7.0$  kg,  $P = 0.012$ ) was significantly less in the T2DM group when compared with the non-T2DM group. In a study of 40 individuals with type 2 diabetes and no control group Dhindsa *et al*<sup>[83]</sup> found a weight loss of 10 kg at 1 year after an 8 wk VLCD. Five year data from a comparison of self-selected VLCD (15) to modest caloric restriction ( $n = 15$ ) showed better weight loss in the conventional diet 8.9 kg vs 4.8 kg<sup>[84]</sup>. Early use of VLCD can cause remission of type 2 diabetes<sup>[85]</sup>.

Johansson *et al*<sup>[86]</sup> reviewed weight maintenance strategies and found that medication, meal replacements and high protein diets were helpful over a 5-18 mo period while exercise and supplements were not.

## DIET PLUS EXERCISE

The final question we will examine in this review is whether exercise has additive benefits to weight loss. Wycherley *et al*<sup>[87,88]</sup> performed 2 studies adding aerobic or resistance exercise to significant weight loss over 12 to 16 wk and found no additional benefit of adding exercise on HbA1c or any other markers.

## THE FINAL WORD FOR THIS REVIEW IS THE MICROBIOME

Rodent studies from Gordon *et al* taking germ-free mice and giving them a "fat" microbial population made them fat, while a lean microbial population keeps them lean<sup>[89,90]</sup>. Fat mice and lean mice<sup>[91]</sup> (and humans<sup>[92]</sup>) have different bacterial populations and the population changes as weight changes (Phyla: Firmicutes up and Bacteroidetes down with increased weight). An increase in calorie intake (from 2400 to 3400 kcal/d) in obese and lean human individuals promotes rapid changes in the gut microbiota (20% increase in *Firmicutes* and a corresponding decrease in *Bacteroidetes*) and this was associated with an increased energy harvest of approximately 150 kcal, the overfeeding in lean individuals being accompanied by a greater fractional decrease in stool energy loss<sup>[93]</sup>.

Increasing dietary fat alters the microbiome, increases gut leakiness and lipopolysaccharide absorption and enhances insulin resistance<sup>[94,95]</sup> while feeding

oligofructans increase Bifido, reduce insulin resistance and inflammation<sup>[96]</sup>. Feeding flaxseed mucilage for 6w improved insulin resistance, altered 33 microbial species, lowered 8 including faecalibacterium. The species change could not be related to the change in insulin resistance<sup>[97]</sup>. Pedersen *et al*<sup>[98]</sup> fed a galacto-oligosaccharide mix (5.5 g/d) for 12 wk or placebo and demonstrated no changes in insulin sensitivity, glucose tolerance, gut leakiness, inflammatory markers or the microbiome. Changes in the bacterial family Veillonellaceae correlated inversely with changes in glucose response and IL-6 levels ( $r = -0.90$ ,  $P = 0.042$  for both) following prebiotic intake. Metformin may mediate some of its therapeutic effects through short-chain fatty acid production, while its intestinal adverse effects may be due to relative increase in abundance of *Escherichia* species. Controlling for metformin treatment, the gut microbiome shifts in T2D with a depletion of butyrate-producing taxa<sup>[99]</sup>.

Weight loss induced by Roux on Y gastric bypass led to reduction of Firmicutes and Bacteroidetes and an increase of Proteobacteria and these species were related to BMI and CRP<sup>[100]</sup>. Faecalibacterium prausnitzii was directly correlated to fasting blood glucose. In an earlier study Faecalibacterium prausnitzii species was lower in subjects with diabetes and associated negatively with inflammatory markers at baseline and throughout the follow-up after surgery independently of changes in food intake<sup>[101]</sup>.

## CONCLUSION

Weight loss occurs with many different diets and there are no clear conclusions on the optimal diet apart from the diet which the individual can stick to long term, whatever the composition. Whether phenotyping (*e.g.*, degree of insulin resistance) or genotyping will help diet choice is not clear.

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