MINERVA
GASTROENTEROLOGICA
E DIETOLOGICA

VOL. 56 · SUPPL. I · N. 2 · GIUGNO 2010

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EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A. P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 0026-4849 TAXE PERÇUE

"This work is dedicated to
Tommaso Iannitti's family,
namely Concetta, Vincenzo and Felice
for their unconditional love and support and
their constant encouragement during all these years"

MINERVA GASTROENTEROL DIETOL 2010;56(Suppl. 1 al N. 2):1-65

The obese patient: clinical effectiveness of a high-protein low-calorie diet and its usefulness in the field of surgery

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Obesity has become a concern of epidemic proportion involving globally both children and adults. Although genetically linked, lack of physical activity and the outstanding growing of the food market are the main behavioral causes of obesity. Furthermore, it is related to several diseases which may impair the life quality, but also lead to death. Atkins nutritional approach has become really popular since the publication of Dr Atkins' first book "Dr. Atkins' Diet Revolution" in 1972. This approach, although very criticized by some dieticians, has been used as a model for a lot of high-protein, low-carbohydrate diets that are nowadays widely used. The evidence that obese people experience a more adverse outcome in a medical and surgical Intensive Care Unit, compared with non-obese pairs, has risen the issue of the importance of an appropriate feeding. Could obese people benefit from a high-protein diet? Is this approach related to adverse effects? Can a high-protein diet bring benefits to obese patients undergoing surgery? This review deals with this matters reporting the use of high-protein diets in clinical trials involving obese subjects.

Key words: **Diet - Obesity, surgery - Fatty acids, polyunsaturated.**

Obesity is the nominal form of obese, from the Latin *obesus*, which means "stout, fat, or plump". *Esus* is the past participle of *edere* (to eat), with *ob* added to it. In Classical Latin, this verb is seen only in past participial form. Its first attested usage in English was in 1651, in Noah Biggs's "Matæotechnia Medicinæ Praxeos" (see "The Oxford English Dictionary", online). Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health may be impaired.[1] In the clinical setting it is commonly defined as a body mass index (BMI) of 30 kg/m^2 or higher.[2] The BMI or Quetelet index was developed in the 19th century by the Belgian

Both the authors contributed equally to this work.

Funding. This review was not supported by any grant.

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

The authors hereby certify that all the work contained in this review is an original work by Tommaso Iannitti and Beniamino Palmieri. All the pieces of information taken from other articles, including tables and pictures, have been referenced in the "Bibliography" section. The authors claim full responsibility for the contents of the article.

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statistician and anthropometrist Adolphe Quetelet and it is calculated by dividing the subject's weight in kilograms by the square of his/her height in meters. Commonly four classes of increasing severity which the World Health Organization (WHO) has defined consistent with the notion of graded risk are used (BMI 18.5 – 24.9 kg/m^2 = normal; 25.0 – 29.9 kg/m^2 = pre-obese/overweight; ≥30.0 kg/m^2 = obese).[3]

Epidemiology

Obesity has become epidemic in many countries.[4] Worldwide 400 million adults are obese and 1.6 billion are overweight,[5] 155 million children are overweight, including 30-45 million obese children.[6] Obesity levels have risen sharply across the globe. Even in those countries that have historically had lower rates of obesity, there is now evidence of increasing overweight.[7] In the Americas, the United States is by far the fattest country.[8] Approximately two thirds of US adults and one fifth of US children are obese or overweight. During 1980-2004 obesity prevalence among US adults doubled and recent data indicate that an estimated 33% of US adults are overweight (BMI: 25.0-29.9 kg/m^2), 34% are obese (BMI ≥30.0 kg/m^2) including nearly 6% who are extremely obese (BMI ≥40.0 kg/m^2).[9] Prevalence of childhood obesity has increased at least two- to threefold in the Western societies during the last few decades. Consequently, currently ~20% of the adolescents are overweight or obese.[10] In Europe the prevalence of obesity (BMI ≥30 kg/m^2) in men ranges from 4.0% to 28.3% and in women from 6.2% to 36.5%.[11] In modern societies this situation makes obesity one of the five major health risks which could lead to a life expectancy decrease, for the first time in recent history, due to numerous comorbid disorders.[12]

Obesity: causes, associated diseases and lipotoxicity

When energy intake exceeds energy consumption, the surplus of energy is stored as adipose tissue. This situation of positive energy balance (EB) is responsible for overweight and obesity. Overweight and obesity are becoming endemic, particularly because of increasing nourishment and a decrease in physical exercise.[13] The influence on various complex neuroendocrine systems can genetically determine approximately 50% of the inter-individual variation in BMI; ultimately it is the interaction between genetic predisposition and environment that finally determines the attained body weight (BW).[14] The rising of obesity rates is due to the changes in eating habits. Commercially prepared food is higher in fat and sugar, the average daily calorie intake has increased across the globe, the consumption of foods high in fats and sweeteners is increasing and the intake of fruits and vegetables remains inadequate.[15] In the literature there is evidence that diet seems to exert a key role in overweight and related pathologies. About 25% of the population produces excessive insulin in response to rapidly absorbed carbohydrates (CHOs). These insulin-resistant individuals may be at greater risk of obesity if they consistently eat CHOs with a rapid absorption rate. This occurs because excessive insulin facilitates glucose oxidation at the expense of fatty acids (FAs) oxidation; it also stimulates the synthesis of very low-density lipoprotein cholesterol (LDL-C) in the liver and fat storage in adipose tissue.[16] Being overweight leads to the raise of different pathologies like type 2 diabetes, metabolic syndrome, cardiovascular diseases (CVD), hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), some immuno-mediated disorders such as asthma, dementia, obstructive sleep apnea and several types of cancer. Some of these pathologies can be due to inadequate insulin produced by the pancreas to control blood sugar (relative insulin deficiency), decreased insulin effects on peripheral tissue (insulin resistance) or a combined effect of both.[4, 12, 17, 18] However, Cave *et al.*[19] underline that not all the obese patients develop obesity associated diseases because both the location (adipose tissue is preferable to central (visceral) adipose tissue which is preferable to more vital non-adipose organs such as

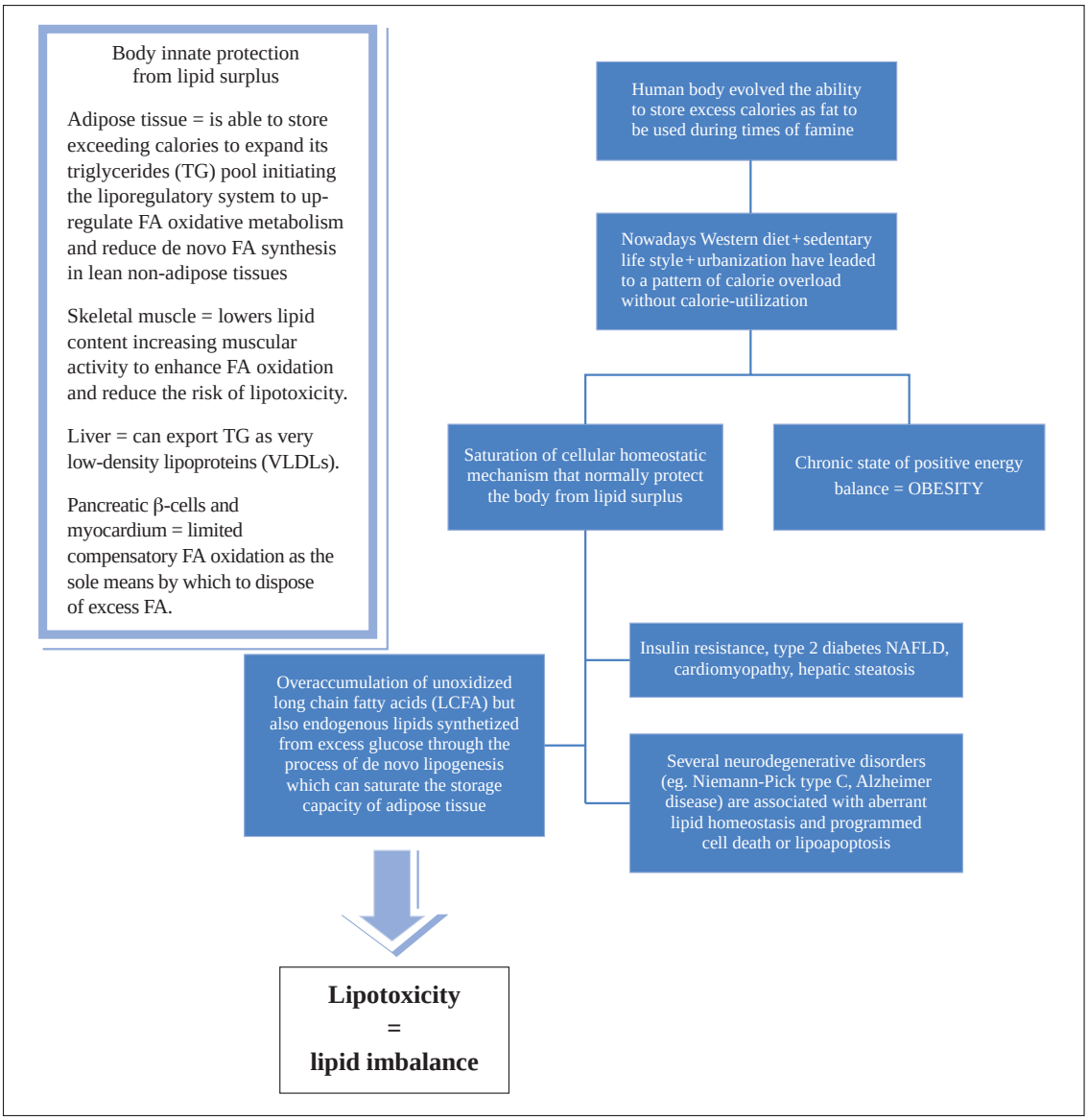

Figure 1.—The relationship between obesity and lipotoxicity.[25-31]

heart and liver) and type of lipid accumulation (Figure 2) determine the presence or absence of disease considering that different tissues vary greatly in the quantity of lipid they can store. In fact, evidence has emerged that FA overload may damage the myocardium through excessive FA oxidation and accumulation of toxic lipid species within the myocardium, a phenomenon called "lipotoxicity".[20] A number of investigators have implicated specific lipid species, such as long-chain saturated FAs (palmitate), in the pathogenesis of cardiomyocyte dysfunction , while unsaturated FAs (oleate) are considered cardioprotective.[21] The term "lipotoxicity" refers to the processes leading to end organ damage and/or dysfunction following excess overload that results from not only unoxidized FAs but also from endogenous lipids synthesized from excess glucose through the

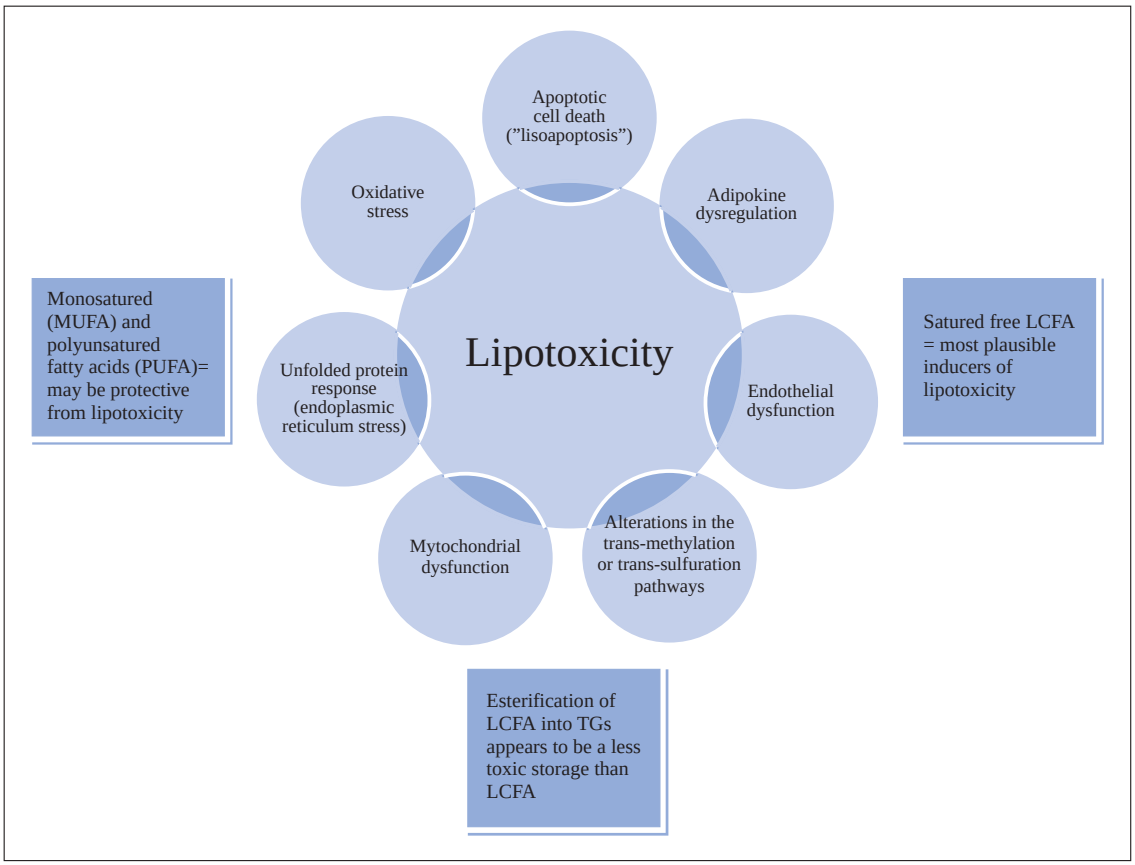

Figure 2.—Intracellular and extracellular mechanisms responsible for lipotoxicity.[19]

process of the novo lipogenesis (Figure 2) [22, 23] and it has been demonstrated to occur in the presence of excess lipid accumulation in non-adipose tissues such as liver (NAFLD), pancreas (diabetes), muscle (insulin resistance) and hearth (diabetic cardiomyopathy).[24] The relationship between obesity and lipotoxicity is summarized in Figure 1. Intracellular and extracellular mechanisms which may be responsible for lipotoxicity are shown in Figure 2.

High-protein diet

Atkins diet books sold millions of copies, gained tremendous consensus, and became very popular due to the epidemic spreading of the diet among obese people. Dr. Atkins' diet recommends that dieters can eat as much energy from fat and protein as desired as long as CHOs are severely restricted (the diet is composed of 4 phases; phase 1 allows approximately 4 g CHO per day, and phase 4 allows no more than 40 to 60 g CHO per day).[32] The main objection to the Atkins's diet is that it is not only synonymous with a high-fat (HF) one, but also that it is high in saturated fat. However, the Atkins' Nutritionals have recently recommended lowering its saturated fat content.[33] Atkins diet has been widely used as a starting point for high-protein (HP) based diet either low in fat or not (ketogenic diet = replacing the majority of the CHO with both protein and fat). The WHO recommends that dietary protein should account for ~10-15% of energy intake when in EB and weight stable.[34] Given the

range of the normal protein (NP) intake, a NP diet, given in EB, contains 10-15% of energy from protein, and a HP diet in EB contains 20-30% of energy from protein.[35] Veldhorst *et al.* consider an average of ~10-15% of energy intake from protein, when in EB and weight stable, as a NP intake, and >15% of energy intake from protein, when in EB and weight stable, as a HP intake.[36] The benefits of the Atkins' diet, which has been endorsed by an estimated 20 million people worldwide, are claimed to be weight loss, maintenance of weight loss without hunger, good health and disease prevention.[37] Proponents of the HP approach argue that, because CHOs are the major stimuli for insulin release, restricting CHOs will reduce insulin levels and encourage fat oxidation.[38] It appears that larger BW loss on a sustained relatively HP diet depends on HP diet-induced satiety, energy expenditure, and sparing fat free mass (FFM).[35] It has been shown that, a relatively HP intake sustains weight maintenance by 1) inducing regain of FFM at the cost of fat mass, at a similar physical activity level;[39] 2) reducing the energy efficiency with respect to the body mass regained,[39] and 3) increasing satiety.[40] Some of the possible mechanisms, behind the weight loss associated with a HP diet, are summarized in Figure 2.

In the last few years (yrs) soy protein, an important component of soy beans, has aroused the interest of many scientists and dieticians because it is able to provide an abundant source of dietary protein with a high biological value. Soybeans contain an amount of protein between 36% and 56%. Their predominant proteins are 7S globulin (conglycin) and 11S globulin (glycin), called storage proteins, which represent together the 80% of the total proteins. The remaining 20% is made up of 2S, 9S and 15S. Soybeans also contain lectin and protease inhibitors such as Kuntz and Bowman Burk.[41-43] Velasquez *et al.*[44] report that soy protein and its isoflavones may have a beneficial role in obesity reducing BW, in particular body fat mass and reducing plasma lipids. However, the Authors also report that soybean has been implicated as a possible cause of food allergy being cited as one of the 8 most common

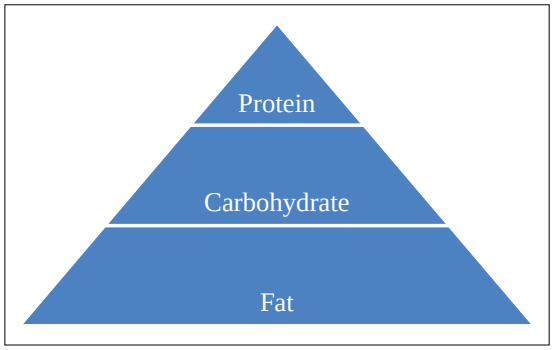

Figure 3.—Hierarchy observed for the satiating efficacies of the macronutrients protein, carbohydrate and fat, with protein as most satiating and fat as least satiating.[50]

allergenic foods containing allergens like b-conglycinin, glucinin, soy vacuolar protein, Kunitz trypsin inhibitor and other proteins. The only remedy in case of allergy is, at the moment, to avoid these products.

Tovar *et al.*[45] analyzed the contribution due to the type of dietary protein to obesity and its metabolic consequences. They report that consumption of soy protein stimulates insulin secretion to a lower extent than casein due to the amino acid profiles of soy protein and its isoflavones. They underline that soy protein increases insulin sensivity (proteins from soy and other plant foods are higher in non-essential amino acids compared with food from animal foods) [46] whereas casein has the opposite effect. Moreover the same Authors report that soy protein is able to lower the Sterol Regulatory Element-Binding Protein-1 (SREBP-1) expression in the liver leading to low accumulation of hepatic TG, despite the consumption of a HF diet. Furthermore, soy protein is reported to reduce adipocyte hypertrophy, hyperleptinemia and free FA concentration leading to a decrease in lipid depots and ceramide, which reduce hepatic lipotoxicity (casein has the opposite effect) and is able to increase the thermogenic capacity of brown adipose tissue. Soy protein is also known to have hypocholesterolemic properties [47] and may influence estrogen metabolism decreasing the risk of hormone-dependent cancers.[48]

Newby *et al.*[49] report that legume protein is more slowly absorbed than animal protein

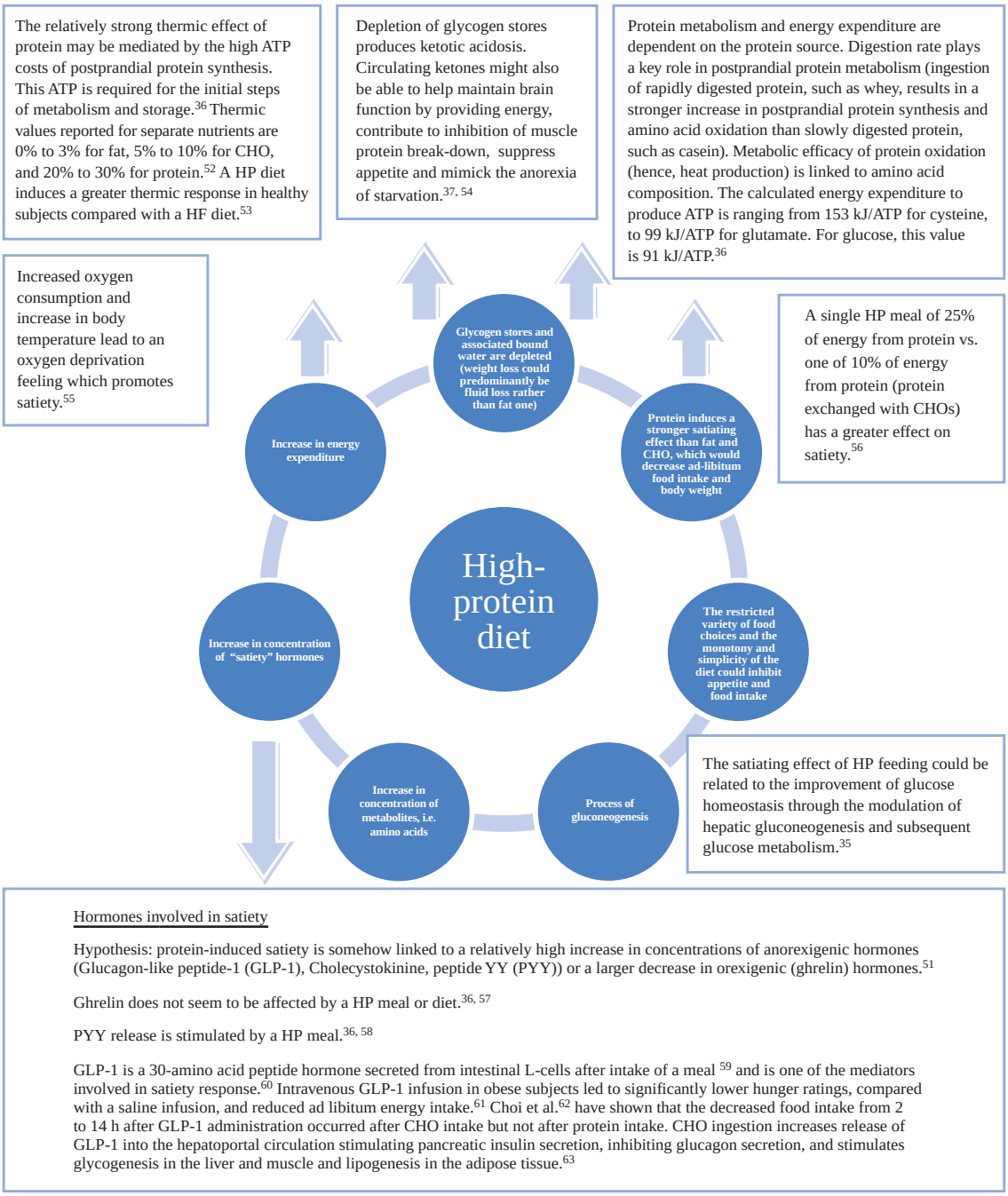

Figure 4.—Possible mechanisms behind the weight loss associated with a high-protein diet.

and isolated soy protein increases the release of glucagon. Both of them enhance fat oxidation and inhibit lipogenesis by down-regulating lipogenic enzymes. As far as the use of HP diet for weight control or loss is concerned all the studies, involving this type of diet, have used a mix of proteins with predominating animal protein and there is

no evidence showing that there is a difference in efficacy between protein types (Figures 3, 4).[50]

Safety of low-carbohydrate/high-protein diets

With the spreading of low-carbohydrate (LC)/HP diets there has been a lot of discussion about the potential risks of such a type of diet. HP diets have also been associated with an increase risk of kidney stones [64] and uric acid stone.[65] Siener *et al.* underline that increasing dietary protein is first related to an increase in glomerular filtration rate (GFR), second to an increase in endogenous acid production, that may require buffering from bone leading to an increasing calcium resorption, and third to a decrease in renal reabsorption of calcium from distal tubular cells. Major attention should be paid to hypercalciuric patients because the calciuric effects of a HP intake may be, for them, even greater. Brenner *et al.*[66] observe that, in populations with established renal disease, limiting protein to the recommended daily amount (RDA) level may slow the progression of the disease. Eisenstein and Roberts in 2002,[67] after reviewing the existing studies, conclude that there is little evidence supporting adverse effects of HP diets on renal function in individuals without a history of renal disease. Knight *et al.*[68] show that women, with impaired renal function, have an increased decline in renal function with increased protein intake in contrast with women with normal renal function who show none. As far as calcium oxalate stones are concerned, there are contradictory studies: Hess *et al.*[69] report that HP intake is associated with an increase in calcium stones while Hiatt *et al.*[70] compare HP diet to a LP diet group observing a decrease in calcium stones in the first group. Munger *et al.*[71] report that HP diets, in particular when they involve a great quantity of meat, are related to an increase in urinary calcium loss. However, the same Authors underline that these diets reduce the risk of fractures, probably related to an improvement in bone strength, due to the HP intake. Comparing NP diets with HP diets, less bone loss is observed in the latter.[72] Diets rich in beef, lamb and pork meat, show an increase risk of colorectal cancer.[73] Atkins diet has been associated with constipation (relieved by the use of fiber supplementation), renal stones in children (effect not observed in adults) and, if maintained in the long term, it may lead to an increased risk of gastrointestinal tract cancer and vitamin and mineral deficiency.[74] Moreover Tay *et al.*[75] observe that an elevation in LDL-C (predominant lipoprotein carrier of TGs) levels occur in 24% of people following the Atkins' diet, compared with 10% of people on a high-carbohydrate (HC) weight-loss diet. Jenkins *et al.*[76] report a significant decrease in TG and oxidized LDL-C in patients on a HP (27%) diet compared to a control group. Moreover a study performed by Parker *et al.*[77] shows a significantly lower LDL-C level with a HP diet (5.7%) compared to a LP diet (2.7%) ($P<0.01$). Samaha *et al.*[78] report that patients on a HP Atkins' diet (22% protein) have significantly lower TGs compared with the lower protein group (-20% *vs.* 4%, $P=0.001$). Layman *et al.*[79, 80] report that TG levels fall by 21% in patients on an HP diet compared to a LP diet. A significant decrease in plasma TGs associated with HP diets is also observed by Farnsworth [81] and Skow.[82] The latter study also shows a decrease in plasma non-esterified fatty acids (NEFA) and no differences in LDL changes. Nordmann *et al.*[82] realize a meta-analysis involving patients with diabetes and report that for every 10% decrease in CHO intake, TGs decrease by 7.6±0.6% ($P=0.001$). Other findings, supporting these results, are reported by Stoernell *et al.*[84] who find that atherogenic LDL-C have a 46% decrease in the carbohydrate-restricted diet (CRD) group in contrast to a 36% increase in the low-fat (LF) diet group ($P=0.045$). Volek *et al.*[85] show that patient's affected by atherogenic dyslipidemia on a calorie restricted diet show uniform improvements in TGs, high density lipoprotein cholesterol (HDL-C), total cholesterol to HDL-C ratio, postprandial lipemia, apolipo-protein B to apolipoprotein A-I ratio and LDL-C distribution. A systematic review,[86] including all randomized controlled trials of LC/HP diets compared with LF/HC conventional diets, performed between 2000 and 2007, show that

LC/HP diets are more effective at six months and are as effective, if not more, as LF diets in reducing weight and CVD risk up to one year. Hu *et al.*[87] observe that a higher protein intake (24% *vs.* 15% of calories) is associated with a decreased risk of coronary heart disease during 14 years of follow-up, due to both animal and plant proteins. Several studies show that a low animal protein intake is associated with hemorrhagic stroke.[88] As far as blood pressure (BP) is concerned, an increase in protein of about 5% of energy in exchange for CHO lowers BP by about 5 mmHg in hypertensive people.[89]

Vedhorst *et al.*[51] underline that long-term consumption of HP diets may have adverse effects on the kidney and consequently on BP. The Authors observe that amino acids, involved in gluconeogenesis and/or ureagenesis, may have a BP lowering effect, whereas acidifying amino acids may have a BP raising effect. Subjects with subclinical renal injury, such as elderly subjects, subjects with low renal functional mass, such as renal transplant recipients and subjects with obesity-related conditions, such as the metabolic syndrome and type 2 diabetes, will be more susceptible to the BP raising effects than others. Moreover they report that sulphur-containing amino acids (cysteine, homocysteine, methionine, taurine) may compromise long-term renal maintenance of acid-base homeostasis, and cause a BP raising effect. Then acid-base homeostasis is maintained through excretion of the excess acid load by the kidneys. The kidneys compensate by increased excretion of ammonia, resulting from stimulated ammoniagenesis with the amino acid glutamine as substrate. Chronic ingestion of large amounts of sulphur-containing amino-acids may have an indirect effect on BP, by induction of renal subtle structural damage, ultimately leading to loss of nephron mass and a secondary increase in BP. Soenen *et al.*[55] underline that subclinical renal injury, such as elderly individuals, individuals with low renal functional mass such as renal-transplant recipients, and individuals with obesity-related conditions, such as metabolic syndrome and type 2 diabetes, are more susceptible to the BP raising. A meta-analysis,[90-92] aiming at analyzing the correlation between CRDs and glucose control in type 2 diabetes, suggest that this diet is related to significantly greater improvements in fasting glucose (4.5% predicted decrease for each 10% decrease in proportion of caloric intake from CHOs; 3.2% predicted decrease after controlling of weight loss) and hemoglobin A1c (4.4% predicted relative decrease for each 10% decrease in proportion of caloric intake from CHOs; this is not significant after controlling for weight loss). This study also shows that CRDs rapidly affect glucose control with patients showing changes in A1c at two weeks (wks). Shai *et al.*[93] confirm these findings reporting that, after 24 months, participants with diabetes in the CRD group have a significant ($P<0.05$) decrease in hemoglobin A1c compared to LF and Mediterranean diet groups. Moreover Promintzer *et al.*[94] report that epidemiological studies have shown a positive correlation between meat intake and the risk of type 2 diabetes while experimental amino acid infusion directly induces insulin resistance and stimulates endogenous glucose production. Astrup *et al.*[37] report that studies of epileptic children on a LC diet for seizure control, show an adverse effect on blood lipids that persist over two years, and ketosis may also pose a risk of cardiac arrhythmias. Moreover the same Authors report that LC diets are associated with constipation and headache, which is readily explained by the reduced intake of fruit, vegetables, and whole-grain bread and cereals. Restricted intake of these foods is not commensurable with long-term nutritional adequacy, and might pose a second-line increased risk of CVD and cancer. Halitosis, muscle cramps, diarrhea, general weakness, and rashes have also been more often reported on LC than on LF diets.

Review criteria

A Medline search was conducted between October 2009 and February 2010 using the keywords “high-protein” and “diet” combined with the key words “obesity” and “surgery”.

TABLE I.—*Bowen* et al. *Study results.*[96]

Weight loss	During ER, BW decreased by 10% independently of diet and gender (DP; -9.0±0.6 kg, MP; -9.3±0.7 kg). No further weight loss was observed during EB (DP; -9.4±0.7 kg, MP; -9.5±0.8 kg).
Total bone mineral density (BMD)	During ER, BW decreased by 10% independently of diet and gender (DP; -9.0±0.6 kg, MP; -9.3±0.7 kg). No further weight loss during EB was observed (DP; -9.4±0.7 kg, MP; -9.5±0.8 kg).
Urinary sodium, calcium, phosphate	Changes in these parameters were independent of diet and gender. Urinary sodium excretion did not change throughout the study (173±14, 160±12, 184±12 mmol/d for baseline, ER, and EB, respectively). There was a decrease in urinary calcium excretion from baseline to the end of ER which was significant at the end of the EB phase (33% lower urinary calcium excretion compared with baseline (-1.13±0.3 mmol/d, P=0.004)). ER (29.9±1.5 mmol/d) was associated with an 18% reduction (-6.4±2.7 mmol/d, P=0.012) in urinary phosphate compared with baseline (36.4±2.7 mmol/d) and returned to baseline level by EB (32.8±1.9 mmol/d).
Pyridinoline (Pyr) and deoxypyridinoline (Dpr) (markers of bone resorption) /nmol creatinine (Cr; a marker of dietary protein intake)	Dpr:Cr and Pyr:Cr increased during ER and EB. The increase in Pyr:Cr was independent of diet. The increase in Dpr:Cr was significantly smaller in the DP diet group than in the MP diet group at the end of ER and EB. Dpr excretion at wk 16 in the MP group differed from that of the DP group (256.9±17.5 nmol/24 h vs. 207.4±16.6 nmol/24 h, respectively, (P=0.05). Total Pyr excretion did not differ between groups. Plasma osteocalcin (a bone formation marker) did not change from baseline to the end of the ER and EB periods in the DP group. The MP group had a significant increase above baseline (+2.16±0.63 µg/L [+0.63±0.11nmol/L], P=0.001) during the ER period and this remained elevated during EB.

Clinical trials

HIGH-PROTEIN DIETS AND OBESITY

Bowen *et al.*[96] assessed whether a diet, high in calcium and protein, could minimize bone resorption during weight loss compared with a lower calcium, protein-rich diet. The study involved obese adults (N.=50, BMI: 33.4±2.1 kg/m^2; aged 20-65 yrs) and was organized in 12 wks of energy restriction (ER) followed by four wks of EB. Subjects were randomly assigned to isoenergetic diets (5.5 MJ/day, 34% energy from protein, 41% CHO, 24% fat) high in either dairy protein (DP, 2 400 mg Ca/day) or mixed-protein (MP, 500 mg Ca/day) sources. The results are summarized in Table I.

The Authors conclude that weight loss due to HP diets is associated with increased urinary excretion of bone resorption markers. This is moderately higher in MP subjects and weight loss is accompanied by an increase in markers of bone formation in this group. Additionally, increased bone turnover occurred despite a reduction in urinary calcium excretion. The reduction in calcium excretion is independent of diet and may reflect the mixed nature of the foods in the prescribed diet.

Bowen *et al.*[97] designed a randomized, parallel study (12 wks of ER, 4 wks of EB; wk 0=baseline data; wk 16=end of EB phase) to compare the effects of two HP diets that differ in dietary calcium (DP 2 400 mg Ca/day; MP 500 mg Ca/day) and protein source (DP: milk, meat, skim milk powder, reduced fat cheese, LF yoghurt, egg; MP: meat, ham, milk, egg, almonds, legumes) on weight loss, body composition, glucose and lipid metabolism, markers of liver function, fibrinolysis and endothelial function and BP. The study involved 50 healthy, overweight (age 25-64 y; BMI 25-35 kg/m^2) males (N.=20) and females (N.=30). Loss of total weight (-9.773.8 kg), fat mass (-8.370.4 kg) and lean mass (-1.670.3 kg) were independent of dietary group. BWs were measured and overnight fasting (12 hours) venous blood samples were collected

TABLE II.—*Bowen* et al. *study results.*[97]

Weight Loss	Females in the DP treatment group had greater total and abdominal fat at baseline compared to females in the MP treatment group (P<0.05).
Body composition	Cr excretion increased 18% above baseline level (34.3±1.0) during ER (42.0±1.3; P<0.02) and remained elevated during EB (42.0±1.8; P<0.02) independently of the dietary group. Total energy and percentage of energy from protein, fat and CHO during ER and EB were similar between diets. Protein intake during ER and EB was 106±3 and 116±4 g/d, respectively, and did not differ between groups. Males and females consumed approximately 1.1 and 1.3 g protein/kg total BW, respectively. Dairy sources provided most dietary protein (62%) in the DP diet compared to the MP diet (5%). Calcium intake was greater in the DP group compared to the MP group. Dietary cholesterol was 28% lower in the DP group compared to the MP group during ER and 36% lower during EB. Mean weight loss during ER was 10% (-9.7±3.8 kg) and this was independent of diet and gender. There was no change in weight during EB (wk 12–16). Total fat decreased by 21.871.3% and abdominal fat decreased by 26.372.2% (P<0.0001) with no effect of dietary group. There was no significant change in LBM in females after weight loss, and a small reduction in men (P=0.004), which was independent of total weight loss and diet.
Glucose/Insulin (improvements independent of dietary intervention)	Fasting insulin was reduced by -1.4±0.3 mU/L at wk 16 compared to baseline (9.1±0.7 mU/L) independent of diet and gender (P<0.05). Fasting glucose did not change throughout the study (wk 0 6.4±0.1 mmol/L). In wk 0, the insulin concentration at 120 min was 36% higher in the MP group compared to the DP group (P<0.05), although insulin area under the curve (AUC) was similar for both groups (DP 75±9 mU/L/min; MP 77±7 mU/L/min respectively). By wk 16, there was a reduction in insulin AUC independently of diet group (AUC DP -26.0±8.8 mU/L/min; MP -28.5±4.1 mU/L/min; P<0.01) and baseline temporal differences were no longer observed. In wk 0, the postprandial glucose response at 30 and 60 min was significantly higher in the MP group compared to the DP group reflected by a difference in glucose AUC at wk 0 (MP 3.8±0.4 mU/L/min; DP 1.7±0.4 mU/L/min; P<0.05). By wk 16, the glucose response was significantly lower in the MP group, and AUC was reduced. In wk 0, there was no difference in the insulin response to the OGTT between treatments at any time point or for AUC. By wk 16, the insulin AUC was significantly reduced independently of dietary group (DP -41.5±9.4; MP -42.4±8.4 mU/L/min; P<0.01). The glucose response was not different between dietary groups in wk 0. There was a significant reduction in glucose AUC in wk 16, which was similar for both dietary groups (DP -1.6±0.6; MP -2.7±0.5 mU/L/min; P<0.01).
Lipids (improvements independent of dietary intervention)	Fasting plasma levels of lipids did not differ between dietary groups and genders throughout the study. Fasting plasma TGs decreased by 0.35±0.06 mmol/L during ER. By wk 16, there was a 0.24±0.06 mmol/L decrease in TG concentration compared to baseline (P<0.001). Total cholesterol decreased by 0.62±0.11 mmol/L during ER and increased by 0.21±0.10 mmol/L during EB, resulting in a net reduction in total cholesterol (-0.41±0.07 mmol/L; P<0.001). LDL-C decreased 0.60±0.10 mmol/L after 12 wks of ER (P<0.001). At wk 16, LDL-C remained 0.36±0.10 mmol/L below baseline concentration (P<0.001). Fasting plasma HDL-C remained unchanged during the ER and EB phases.
Markers of fibrinolysis, endothelial and liver function	The changes in these markers were independent of dietary treatment. The fibrinolysis marker PAI-1 was lower at wk 16 compared to baseline (-4.571.4 AU/mL; P<0.001). Endothelial and liver function markers were also reduced at wk 16 compared to baseline (intracellular adhesion molecule-1 [s-ICAM] -19.2±9.8 mg/L; P<0.05, CRP -1.7±0.4 mg/L; P<0.001, GGT -9.2±2.0 U/L; P<0.001, AST -5.4±1.7 U/L; P<0.001 , TP-2.2±0.6 g/L; P<0.001).
Blood pressure (improvements independent of dietary intervention)	No relationship between baseline BP and weight loss or dietary group was observed. Systolic and diastolic BP significantly lower at wk 16 compared to baseline (independent of dietary group and gender). Systolic BP decreased by 9.4±1.4 mmHg from baseline to wk 16 (P<0.001). The largest decrease occurred between wk 0 and 4 (-7.6±1.3 mmHg; P<0.001) and remained relatively stable between wk 4 and 16. Diastolic BP decreased by 2.5±0.9 mmHg from baseline to wk 16 (P<0.001). Largest decrease between baseline and wk 4 (-4.470.9 mmHg; P<0.001) and remained stable from wk 4 to 12. Diastolic BP increased by 2.1±0.8 mmHg from wk 12 to 16 (P<0.01).

TABLE III.—*Westerterp-Platenga* et al. *Study results.*[98]

Body weight loss	The following parameters changed over time, but were not significantly different between groups. BW decreased (6.4 kg ±1.8 [SD] or 7.5%±2.0 [SD] of their original BW [P<0.001]); this decrease consisted of 3.9±3.2 kg fat mass (61%) and 2.5±2.2 kg FFM (39%). Waist circumference (WC) decreased. Attitude toward eating showed an increase in cognitive dietary restraint. REE, respiratory quotient (RQ), and total energy expenditure (TEE), reduced, while physical activity level (PAL) remained the same. The blood parameters from the fasting blood samples (glucose, insulin, triacylglycerol, and leptin) significantly decreased, while b-hydroxybutyrate, glycerol and free FAs increased.
Weight maintenance	During the weight-maintenance phase, the "additional protein group" showed compliance by a significantly higher amount of nitrogen in 24 h urine collection, representing a significantly higher protein intake. Percentage of energy intake from protein appeared to be 18% in the 'additional-protein group' (significantly higher than the 15% in the control group). Dietary restraint remained at the level reached during weight loss, with no differences between the groups, indicating no different role of dietary restraint. Satiety ratings in the fasted state before breakfast were increased significantly more in the additional protein group, despite lack of difference in 24 h energy intake. The body mass regained, the resulting BMI, the fat mass regained, the resulting % body fat and the regained WC were significantly lower in the additional-protein group. Energy efficiency, calculated as kg body mass regain/energy intake, was significantly lower in the "additional protein group". Changes in REE expressed as a function of FFM, PAL, TEE, and core body temperature did not differ significantly between the groups. Increase in triacylglycerol and in leptin was significantly lower in the 'additional protein group. Increases in glucose, insulin, and decreases in b-hydroxybutyrate, glycerol, and free FAs did not reach the original values again. They did not differ between the groups. In both groups, the decrease in leptin during weight loss was related to the BW lost (r^2=0.3; P<0.0001) and to the decrease in REE (r^2=0.5; P<0.0001). The increase in leptin during body weight regain was related to BW regain (r^2=0.3; P<0.0001), to the increase in REE (r^2=0.5; P<0.0001), and to the increase of maximum core body temperature of 30 min moving average per 24 h (r^2=0.4; P<0.0001). The increase in leptin was only related to the increase in fat mass in the non additional-protein group (r^2=0.2; P<0.0001); there was no relationship with the increase in FFM.

in wk 0, 4, 8, 12 and 16. In wk 0 and 16, body composition was assessed and insulin and glucose responses, following meal tolerance test (MTT), were tested. The MTT meals (day 1) (1 330 kJ, 32% total energy from protein, 27% fat, 41% CHO, energy density 6.8 kJ/g) comprised foods consistent with subjects' allocated diet (DP: LF cheese, wholemeal bread, margarine and LF yoghurt; MP: lean ham, egg, wholemeal bread and fruit biscuit). The glucose load (oral glucose tolerance test [OGTT], day 2, 75 g) was provided in a 200 mL solution. Subjects consumed the meal/beverage in 10 min. Venous blood samples were collected at baseline, 30, 60, 120 and 180 min after commencing the meal/beverage. In wk 0, 12 and 16, urine samples (24 hours) were collected for assessment of urea/Cr ratio. Both diets were isoenergetic, (5.5MJ/day), HP (34% energy), moderate CHO (41% energy) and LF (24% energy). EB was achieved by increasing energy intake by 2MJ/day for each 0.5 kg weight loss per wk (averaged over wk 8-12). The two diets differed in the percentage of fat from monounsaturated, polyunsaturated and saturated FAs. At baseline there were no significant differences in the physical characteristics, dietary intake or metabolic variables between groups, except that females in the DP group had significantly higher BMI compared to females in the MP group due to withdrawals that occurred during the intervention. The results are summarized in Table II.

The Authors conclude that weight loss following energy restricted, HP diets is not affected by dietary calcium or protein source. Glycemic control, lipid profile, markers of liver and vascular function and BP improve with weight loss independent of dietary protein source or calcium intake.

Westerterp-Plantenga *et al.*[98] investigated whether addition of protein could improve weight maintenance after weight loss of 5-10% in moderately obese subjects. They

TABLE IV.—*Brinkworth* et al. *Study results.*[99]

Subject attrition, diet composition and compliance	No significant differences between the two dietary groups for the subjects physical characteristics. Energy intake did not differ between the diet groups during either the 12-wk ER, 4-wk EB or the 12-month follow-up phase. The protein intake was higher and the CHO intake was lower with the HP diet compared to the SP diet during the ER and EB periods (P<0.001). During the 12-month follow-up, protein intake increased significantly with the SP diet and decreased with the HP diet, while CHO intake increased with the SP diet but remained unchanged in the HP group (P<0.001). No difference between the two diet groups for either CHO or protein intake after 3 and 6 months of follow-up, respectively was observed. Dietary cholesterol was higher and dietary fiber lower with the HP diet than with the SP diet during the ER and EB phases. During the 12-month follow-up cholesterol intake increased and fiber intake decreased to a greater extent with the SP diet than with the HP diet such that there was no difference in either cholesterol or fiber intake between the diet groups (P<0.001). Urinary urea/Cr ratio was not different between diets at wk 0 (P=0.48) and increased by wk 16 in HP (P=0.001). During the 12-month follow-up whereby the urinary urea/Cr ratio increased in SP and decreased in HP, such that there was no difference between the diets during this period (P=0.62), indicating poor long-term dietary adherence for both dietary patterns.
Body weight and body composition	After 12 wks of ER and 4 wks of EB, the mean weight loss was 8.570.6 kg. The decrease in weight was not affected by the diet composition (SP -9.1±0.7%, HP -8.7±0.7%; P=0.44). At wk 68, there was a significant regain in weight, but weight remained significantly lower (3.5%) than baseline, with no effect of dietary composition (SP -2.9±0.8%, HP -4.1±1.3%; P=0.44). For all subjects, fat mass and lean body mass (LBM) were significantly reduced with weight loss at wk 16. During the 12-month follow-up, LBM returned to baseline levels, and although fat mass also increased, it remained significantly lower than baseline at wk 68. There was no effect of dietary composition on either tissue compartment. In males, bone mineral content (BMC) was higher than baseline at wk 68 (P=0.01) whereas no significant change was evident in the females.
Blood pressure	Systolic BP did not change significantly in either group during the study. At baseline, diastolic BP was significantly higher in the male compared to female subjects. For all subjects, diastolic BP did not change significantly during the first 16 wks of the study (P=0.10). During the 12 month follow-up phase diastolic BP fell significantly in the male subjects (P=0.03), but did not change in female subjects, such that there were no differences between genders at wk 68. There was no effect of diet observed for changes in diastolic BP.
Fasting glucose, insulin, HOMA	Fasting glucose concentrations did not change significantly in either group during the study. At wk 68, CRP, sICAM-1, fasting insulin concentrations and HOMA had decreased significantly from baseline by 14–30%, but this was not affected by dietary composition.
Serum lipids	Fasting serum triacylglycerol, total cholesterol and LDL-C concentrations were reduced by both dietary interventions during the first 16 wks of the study, but increased during the 12 month follow-up, such that there was no difference compared to baseline at wk 68. Fasting serum HDL concentrations had increased by 15% in both diet groups at wk 68. There was no significant effect of diet or gender for changes in any of the blood lipid variables during the study.
Creatinine clearance	Creatinine clearance was only assessed in some of the subjects (SP, N.=15; HP, N.=14) and significantly increased from baseline to wk 68 in both dietary groups (P=0.01), with no effect of dietary composition evident (P=0.38).

designed a randomized parallel study involving 148 male and female subjects (age 44.2±10.1 y; BMI 29.5±2.5 kg/m^2; body fat 37.2±5.0%) who followed a very low-energy diet (2.1 MJ/day) during 4 wks. For subsequent three months weight-maintenance assessment, they were stratified according to age, BMI, BW, restrained eating and resting energy expenditure (REE) and randomized over two groups. One group (N.=73) received 48.2 g/day additional protein to their diet. No different effects of additional protein con-

TABLE V.—*Brinkworth* et al. *Study results.*[100]

Body weight and composition	In both groups, the mean weight loss was 5.3 kg (5.7% loss of initial BW) after the first 12 wks. There was a significant weight regain during follow-up but BW remained significantly lower at wk 64 than at baseline (LP diet: -2.2± 1.1 kg; HP diet: -3.7±1.0 kg, time effect P<0.01), with no significant differential effect of sex or diet. Significant reduction in lean body mass (LBM) and fat mass with weight loss observed at the end of the 12 wk intervention period. Fat mass increased , after follow-up, at wk 64 to baseline levels; FFM remained significantly lower than baseline. No effect of diet or sex was observed for changes in either tissue compartment.
Bone mineral content	Bone mineral content was not different between diet groups at baseline and did not change during the study.
Blood pressure	Systolic BP was not significantly lower in the LP group than in the HP group at baseline. Systolic BP decreased by 6 mmHg during weight loss after 12 wks with both diets, but there was no effect of diet composition (P=0.95). During the follow-up, systolic BP increased by 8.1 mmHg more in the LP than in the HP group, with a significant time by diet interaction (LP: 10.0±3.2 mmHg; HP: 1.9±1.9 mmHg; P=0.04). Diastolic BP was significantly lower in the LP than in the HP group at baseline. By wk 12, it decreased by 3 mmHg with weight loss, but there was no effect of diet composition (P=0.48). There was a significant time by diet interaction during follow-up, with diastolic BP 5.7 mmHg higher in the LP group than in the HP group (LP increase: 4.7±1.6 mmHg; HP: -1.0±1.3 mmHg; P=0.008). The time by diet interaction effects for both systolic and diastolic BP were present after controlling for baseline differences. The differences between the experimental groups for the changes in systolic and diastolic BP during the follow-up had 82% and 88% power respectively to be significant with a type 1 error of 5% (two-tailed).
Glycaemic control	Fasting glucose, insulin, HOMA and HbA1c concentrations significantly reduced with ER by wk 12, but increased during the follow-up period such that no difference from baseline levels was detected at wk 64. No significant effect of diet or sex observed for changes in any of these variables during the study.
Albumin	No statistical difference in urinary albumin excretion between the groups and no change throughout the study.
CRP	CRP decreased by 14% (P=0.04) during the intervention, with no effect of dietary composition or sex.
Blood lipids	HDL-C ratio fell significantly in both groups at wk 12, but increased during the follow-up, such that at wk 64 there were no significant differences compared to baseline. The changes in these variables did not differ significantly between the treatment groups. Fasting serum HDL-C did not change during ER, but a main effect of time was that levels had increased by 17% (0.16±0.02 mmol/L) in both diet groups by wk 64; this was not affected by either diet or sex. The change in HDL-C was not correlated with changes in BW (r=-0.03, P=0.88) and fat mass (r=0.07, P=0.66). The fluctuations in serum LDL-C did not differ between the treatment groups (8% higher in the LP group vs. -6% in the HP group).
Dietary compliance and composition	The urinary urea : Cr ratio was not different between the two dietary groups at wk 0 (LP: 35.6±1.7; HP 33.7±1.6; P=0.42). The urinary urea : Cr ratio increased by 27.4±6.1% from baseline at Wk 12 in the HP group, but did not change in the LP group. During the next 12 months, urinary urea : Cr remained stable in both groups, leaving urinary urea : Cr at wk 64 significantly higher than baseline in the HP group (P=0.01), with no difference to baseline in the LP group (P=0.78). These results indicate that compliance with the protein prescription in the two diet groups was good. A significant difference in weight regain of 4.5 kg between the diet groups (P=0.05) was observed. The effect of diet composition showed non-statistically significant effects for LDL and triacylglycerol.

sumption for men or women were observed; no adverse events occurred. The results are summarized in Table III.

The Authors conclude that additional protein consumption, during weight maintenance after weight loss resulting in 18 *vs.* 15

TABELE VI.—*Clifton* et al. *Study results.*[101]

Weight loss	Weight loss between the 2 groups was not significantly different (HP: 4.6±5.5; HC: 4.4±6.1 kg. Ratios of urinary urea to Cr at 64 wk were not significantly different. When actual protein intake, calculated from dietary records at 64 wk returned by 72 participants, was used as a criterion, weight loss was greater (P=0.03) in the reported HP group (RHP; >88 g protein/d; upper tertile) than in the reported LP group (RLP): 6.5±7.5 kg (N.=27) compared with 3.4±4.4 kg (N.=45). A similar weight loss (P=0.05) was observed when the group was divided by urinary urea excretion, at wk 64, into the upper tertile and the lower 2 tertiles (6.3±7.9 compared with 3.6±4.2 kg; high compared with low urinary urea).
Dietary intake	There was poor compliance with the original assigned diet. Energy intake increased with time by ~24% (P<0.001), with no difference between original diet groups. By 64 wk, the percentage of energy as protein declined with time overall (P=0.001), with a time by diet interaction(11% decrease in the HP group compared with a 2% increase in the HC group; P=0.001), so that there was only a 3.6% difference in energy as protein (statistically significant but not large enough to be of biological significance). Absolute protein intake decreased in the HP group by 10 g/d and increased in the HC group by ~20 g/d (time-by-diet interaction; P < 0.001). Fat intake increased by 20 g/d (P < 0.001), with no differences between groups, whereas CHO intake increased by 41 g in the HP group and did not change in the HC group (time effect: P=0.013; time-by-diet interaction: P < 0.001). At 64 wk, the CHO intake in grams was the same in both groups.
Body composition by DXA (dual-energy X-ray absorptiometry)	Total body fat at 64 wk, after adjustment for baseline total fat, was related to CHO intake in grams (P=0.001) and inversely to protein intake in grams (P=0.052) (r^2=0.83 for the whole equation). Abdominal fat at 64 wk after baseline adjustment was also related to CHO intake in grams (P=0.001, r^2=0.55). When dietary variables expressed as a percentage of energy were entered into the model, the percentage of energy as protein was inversely related to abdominal fat (P=0.013) and to limb fat (-2.3, P=0.026), which accounted for 48% and 83% of the variance in these variables, respectively, after adjustment for baseline variables. The change in total body fat was related to the reported percentage of energy as protein at 64 wk (r=0.43, P=0.006) and inversely related to the percentage of energy as CHO (r=-0.47, P=0.003), but, on multiple regression, only the latter remained significant. Changes in total and limb fat were also inversely related to CHO intake in grams (P=0.001 and P=0.004; r^2=0.25 for the whole equation) and protein intake in grams (P=0.044 and P=0.017; r^2=0.23 for the whole equation) on multiple regression. Changes in abdominal fat were related only to CHO in grams (r=-0.35, P=0.015). The ratio of fat to lean tissue at the end of the study was related (r^2=0.8), after baseline adjustment, to CHO intake in grams (P=0.001) and to CHO intake as a percentage of energy (P=0.004). The change in the ratio was also inversely related to CHO intake in grams at 64 wk (r=-0.48, P=0.001), to CHO intake as a percentage of energy (P=0.04), and to total energy intake (P=0.026; r^2=0.18 for the whole equation). Greater changes in total weight were associated with greater changes in the ratio of fat to lean tissue (r=0.46, P=0.001), *i.e.*, there was no proportional loss of fat and lean tissue with greater weight loss.
Glucose, insulin, lipids, and C-reactive protein	Glucose decreased significantly by the end of the study, by 11.5% (from 6.1±0.6 to 5.4±0.7 mmol/L; P<0.0001 for time), with no difference between allocated or reported protein groups. The change in glucose was positively correlated with weight change (r=0.293, P<0.01). Insulin decreased overall by 23% (P=0.01), with no difference between allocated or reported protein groups. CRP was reduced at the end of the study (from 5.4±4.9 to 4.1±4.9 mg/L; P<0.05), with no differences between groups and no relation with macronutrient composition. At the end of the study, triacylglycerol was reduced by 0.21 mmol/L (P<0.01), with no difference between groups. HDL cholesterol was higher at the end of the study with no effect of reported protein intake (1.26±0.31 to 1.58±0.4 mmol/L; P<0.001). Change in HDL cholesterol was related to CRP group at 64 wk (r=0.269 P<0.018), with an increase of 0.39 mmol/L in those with a CRP concentration below the median (<2.5 mg/L) and an increase of 0.27 mmol/L in those with a CRP concentration above the median. In the group with an above-median CRP but a low triacylglycerol concentration, changes in HDL cholesterol were greater in the HP group (0.29 compared with 0.17 mmol/L; diet-by-triacylglycerol interaction, P=0.013). Changes in triacylglycerol and HDL were inversely related (r=-0.33, P=0.003), but the change in weight was unrelated to the change in HDL cholesterol. The change in LDL cholesterol at 64 wk was considerable (-0.55±0.80 mmol/L; P<0.001), with no difference between diet groups. The change in LDL cholesterol was significantly greater in the high triacylglycerol group (>1.5 mmol/L at baseline) than in the low triacylglycerol group (<1.5 mmol/L at baseline), with a change of-0.97 mmol/L compared with-0.39 mmol/L (P=0.005), *i.e.*, a change of 30% compared with 12%.

(Continue)

TABLE VI.—*Clifton* et al. *Study results.*[101]

Bone markers and bone mineral density	Weight loss had a positive effect on both biomarkers of disease and plasma vitamins and minerals, with significant decreases in homocysteine and increases in vitamin B-12 and ferritin. As a consequence of increased iron intake, transferrin decreased and transferrin saturation and hemoglobin increased significantly. Serum vitamin B-12 was related to protein as a percentage of energy ($P<0.001$) and protein in grams ($P<0.001$) at 64 wk after adjustment for baseline levels. Overall, decreases in the 24-h urinary bone turnover markers ratio of Dpr to Cr (from 21.0±8.9 to 18.0±6.0 nmol/mmol; $P<0.05$) and the ratio of Pyr to Cr (from 73.6±33.8 to 64.5±18.6 nmol/mmol; $P<0.05$) were observed at the end of the study, with no differences between diets and no relation with weight loss or any dietary components. Calcium excretion was not different from baseline (wk 0) at 64 wk (4.2±2.6 compared with 4.0±2.9 mmol/24 h). The ratio of calcium to Cr decreased ($P<0.001$), with no relation with weight changes, treatment, or reported diet. Bone density had not changed significantly by the end of the study (from 1.03±0.1 to 1.04±1.0 g/cm^2; not significant).

en% protein, results in a 50% lower BW regain, only consisting of FFM and related to increased satiety and decreased energy efficiency.

Brinkworth *et al.*[99] designed a parallel, clinical intervention study (68-wk study protocol) of two groups of obese non-diabetic subjects (mean age 50.2 yrs, mean BMI 34.0 kg/m^2, mean fasting insulin 17.8 mU/L) with hyperinsulinemia randomly assigned to either a standard protein (SP) (N.=22) or HP diet (N.=21), during 12 wks of ER (~6.5 MJ/day) and 4 wks of EB (~8.3 MJ/day). They compared the long-term compliance and effects of two LF diets differing in CHO to protein ratio on body composition, BP, blood lipids, fasting glucose, insulin, C-reactive protein (CRP), homeostatic model assessment (HOMA) and soluble sICAM-1, measured at baseline and at wks 16 and 68 and urinary urea/Cr ratio which was measured at baseline, wk 16 and at three monthly intervals thereafter. Subsequently, subjects were asked to maintain the same dietary pattern for the succeeding 52 wks with minimal professional support. During the 12-wk ER period, the prescribed HP diet consisted of 30% of energy from protein (B110 g/day), 40% of energy from CHO (B140 g/day) and 30% from fat (B50 g/day), while the SP diet consisted of 15% of energy from protein (B60 g/day), 55% of energy from CHO (200 g/day) and 30% from fat (B50 g/day). During the succeeding four-wk EB period, caloric intake was increased by approximately 30% with a further 7 g of protein in the SP diet and 21 g in the HP diet. For the 12-month follow-up period, subjects were asked to continue the same dietary pattern followed during the previous periods of the study. The results are summarized in Table IV.

The Authors conclude that in obese, hyperinsulinemic subjects, over a 68-wk period, prescribing a LF, HP diet offers no greater advantages or disadvantages for weight loss, markers of CVD and dietary adherence compared to a conventional SP diet. However, due to poor dietary compliance, no conclusions can be made in relation to the direct long-term metabolic effects of a HP diet.

Brinkworth *et al.*[100] compared the long-term weight loss and health outcomes at one-year follow-up, after a 12-wk intensive intervention consisting of two LF, weight-loss diets, which differed in protein content. Sixty-six obese patients (BMI: 27-40 kg/m^2) with type 2 diabetes were randomly assigned to either a low-protein (LP; 15% protein, 55% CHO) or HP diet (30% protein, 40% CHO) for 8 wks of ER (~6.7 MJ/day) and four wks of EB. During the eight-wk ER period, the prescribed HP diet consisted of 30% of energy from protein, 40% from CHO and 30% from fat; the LP diet consisted of 15% of energy from protein, 55% from CHO and 30% from fat. Both diets were matched for FA profile (8% saturated FAs, 12% mono-unsaturated FAs, 5% polyunsaturated FAs) and dietary fibre intake (~30 g/day). During the subsequent four-wk EB period, caloric intake was increased by 30%, with a further 7 g protein in the LP diet and 21 g in the HP diet. Subjects were asked to maintain the same dietary pat-

TABLE VII.—*Due* et al. *Study results.*[102]

Dropping out	During the 6 months provision of food, only two subjects dropped out of each intervention group. After 12 months of dietary intervention, seven (28%) in the MeP group and two (8%) in the HP group had dropped out (P<0.07). At the 24 months follow-up, 19 (76%) subjects in the MeP group and 14 (56%) in the HP group no longer attended.
Dietary intervention	At baseline, there were no significant differences between the groups. During the 6 months provision of food, the average protein intake increased from 89.1 (81.1–97.2) to 127.6 g/day (117.0-138.2)corresponding to an increase of 8.2% of total energy in the HP group. The protein-E% decreased by 3.1% in the MP group and the difference in the protein-E% between the two groups was significant during the 6 months intervention (P<0.0001). During the dietary counseling period, the protein-E% remained higher in the HP than in the MP group, which was also reflected in a significant difference in 24-h urinary nitrogen excretion between the groups throughout the study (time x group interaction: P<0.001). The CHO-E% increased in the MeP group, but remained unchanged in the HP group and the difference between the groups was significant during all 12 months of dietary intervention. No difference in fat-E% between the groups was found. Consistent with the greater weight loss, the average energy intake was lower in the HP than in the MeP group during the 6 months provision of food (P=0.001), but no difference was found during the counseling period.
Anthropometrical measures	No significant differences between the groups at baseline. After 6 months, the HP group had a 3.5 (0.8-6.2) kg greater weight loss than the MeP group (P<0.05). During the following 6-12 months period, the weight regain was higher in the HP than in the MeP group (P<0.05). After 12 months, the average weight loss from baseline was 6.2 (3.8-8.6) and 4.3 (2.2-6.4) kg in the two groups and the difference between the groups was no longer significant. At the 24 months follow-up visit, the maintained weight loss was doubled in the HP than in the MeP group (6.4 [2.6–10.2] vs. 3.2 (-1.5-7.9) kg), but the difference was not significant due to the low number of subjects attending this visit.
Body composition	After 6 months, the HP group experienced a greater loss of body FM compared to the MeP group (P<0.0001). During the following 6-12 months, FM increased in both groups and no longer there was any difference between the groups. After 6 months, the HP group had a greater decrease in waist-to-hip ratio (W/H) compared to the MeP group (P<0.01), due to a greater decrease in WC (P<0.01). After 12 months, the HP group still maintained a greater decrease in waist (P<0.001) and W/H ratio (P=0.001) compared to the MeP group. The decrease in intra abdominal adipose tissue (IAAT) was greater in the HP group than the MeP group both after 6 months (P<0.01) and 12 months intervention (P<0.05). The difference in intra-abdominal adipose tissue (IAAT) between the groups was maintained after adjustment for body weight loss (P<0.05). Gender influenced IAAT (P<0.05), but no difference between the groups was detected, due to too few male subjects. No significant differences between the groups with respect to lean body mass were found during the intervention.
Blood parameters	No differences were seen between the MeP and HP groups at baseline and after 6 or 12 months of dietary intervention with the exception of FFA. After 6 months, the FFA concentration was significantly lower in the HP than in the MeP group (P=0.01). These results were unaltered after adjustment for changes in BW.

tern for a further 12 months of follow-up. The results are summarized in Table V.

The Authors conclude that both do not achieve long-term net fat loss, but prescription of the HP diet has a more favourable effect on CVD risk by lowering BP to a greater extent than a conventional LP diet in overweight patients with type 2 diabetes.

Clifton *et al.*[101] determined the efficacy of a higher protein intake on the maintenance of weight loss after 64 wks of follow-up. Seventy-two healthy women (no history of renal or liver disease or type 1 or type 2 diabetes) with a mean (±SD) age of 49±9 yrs and a BMI (in kg/m^2) of 32.8±3.5 completed an intensive 12-wk weight-loss program and 52 wks of follow-up to compare the effects on weight-loss maintenance of a HP diet (34% of

TABLE VIII.—*Dumesnil* et al. *study results.*[103]

Dietary intake	The average protein intake during regimen 2 (1.67 [SD 0.24] g/kg BW) was approximately twice the recommended dietary allowance of 0.86 g/kg BW whereas protein intake during regimen 3 (0.89 [SD 10] g/kg BW) was 20% less than during regimen 1 (1.06 [SD 0.09] g/kg BW) and approximately corresponded to the recommended dietary allowance. Relative lipid intake was not substantially different (approximately 30%) among the three regimens whereas regimen 2 resulted in an increase in the relative intake of proteins (31 [SD 2] % vs. 15 [SD 1] %, P<0.001) and a decrease in the relative intake of CHOs (37 [SD 5] % vs. 55 [SD 1] %, P<0.001) in comparison with regimen 1. No major difference was found in the FA composition of the diet with the exception of the relative intake of saturated fat which reached 14 (SD 4) % on regimen 2. Regimens 2 and 3 were characterized by a decrease in total energy intake in comparison with regimen 1. Regimen 3 was associated with increases in hunger and desire to eat before meals (P<0.0002) and with decreases in fullness and satiety levels after meals (P<0.007).
Weight loss	When subjects ate ad libitum the AHA phase I diet, no change in BW nor in waist and hip circumferences was noted at the end of the 6-d intervention period. In contrast, the low-glycemic index-LF-HP diet (regimen 2) induced significant decreases in all three anthropometric indices. On average, weight loss was 2.3 (SD 1.6) kg (P<0.001) and was accompanied by a 3.2 (SD 2.3) cm (P<0.001) reduction in waist girth and by a 2.7 (SD 3.0) cm decrease in hip circumference (P<0.02). Regimen 3 also induced significant weight loss (21.4 [SD 0.9] kg, P<0.001) and a reduction in WC (22.0 [SD 2.2] cm, P<0.02) whereas the change in hip girth did not reach statistical significance. Furthermore, these changes were not significantly different from those observed during regimen 2.
Blood pressure	No effects of the three diets on plasma cholesterol levels were noted. However, the ad libitum version of the AHA phase I diet induced a 28% increase (P<0.05) in fasting triacyglycerol levels which was accompanied by a 10% reduction in HDL-C concentrations (P<0.01). This decrease contributed to the significant increase in cholesterol:HDL-C following this regimen. In contrast, the ad libitum low-glycemic index-LF-HP diet was associated with a substantial reduction in plasma triacyglycerol levels (235 %, P<0.0005) whereas this diet had no effect on plasma HDL-C levels as well as on other variables. The energy-restricted version of the AHA phase I diet (diet matched to the energy intake consumed during the ad libitum low-glycaemic index-LF-HP diet) failed to induce any significant beneficial change in any of the lipid variables. Moreover, total cholesterol:HDL-C (a commonly-used index of CHD risk) was significantly increased within a wk with regimens 1 and 3 (from 5.42 [SD 1.21] to 5.98 [SD 1.36], P<0.05 vs. 5.26 [SD 1.57] to 5.65 [SD 1.59], P<0.0001), such deterioration not being observed on the low-glycemic index-LF-HP diet (from 5.71 [SD 1.30] to 5.53 [SD 1.28], NS). It was also found that the response of plasma triacylglycerols,HDL-C,HDL3-cholesterol and in cholesterol:HDL-C to the regimen 2 was significantly different from changes noted in response to the ad libitum consumption of the AHA phase I diet.
Fasting plasma insulin, apolipoprotein B levels and LDL peak particle diameter	The AHA phase I diet (condition 1 and 2) did not induce any significant change in these variables. The ad libitum low-glycaemic index–LF–HP regimen induced a significant decrease in fasting insulin levels and a significant increase in LDL peak particle diameter whereas there was no change in apolipoprotein B levels following this 6-d experimental condition. Furthermore, the change in LDL size observed with diet condition 2 was significantly greater than for the response of this variable to the dietary condition 1 and condition 3. There was a similar rise in glucose levels after breakfast during the three diet conditions whereas much smaller increases in glucose levels were noted after lunch and dinner with the low glycemic index-LF-HP diet compared with the two other nutritional conditions. Plasma insulin levels during the test day (day 6 on the diet) were markedly reduced with the low-glycemic index-LF-HP diet compared with the other two conditions, particularly at lunch and dinner, whereas the hypoenergetic version of the AHA diet (condition 3) showed intermediate levels compared with the other two conditions. Moreover, the ad libitum version of the AHA diet showed the highest increase in plasma insulin levels in response to the dinner meal. There was also a substantial increase in plasma triacylglycerol levels occurred in the daytime with the ad libitum version of the AHA phase I diet. Both the ad libitum consumption of the low-glycaemic index-LF-HP diet and the restricted intake of AHA phase I diet were associated with lower triacylglycerolaemia throughout the day. However, no difference was observed in the AUC of daytime triacylglycerol levels between diet conditions 2 and 3. Plasma glucose and insulin levels during the glucose tolerance tests performed on day 1 and day 7 of each experimental condition were compared. When this standardized 75 g glucose challenge was used, no evidence for an improved glucose tolerance was found after 1 wk of the Montignac diet or under the energy-restricted AHA phase I diet. For example, the change in glucose area under the curve observed with the regimen 2, was even significantly different from the change noted with the ad libitum Phase I diet. However, the insulin response to the glucose load was significantly decreased after only 1 wk on the lowglycaemic index-LF-HP diet whereas it remained unchanged after 1 wk on ad libitum or energy-restricted AHA phase I diets.

TABLE IX.—*Evangelista* et al. *Study results.*[104]

Weight loss	Participants in the HP diet group had significantly greater weight loss compared with the SP or conventional diets (-9.9 vs. -5.5 kg vs. 1.51 kg, respectively, P<0.001). Patients on the HP diet also demonstrated greater reductions in percent body fat (P=0.036) and WC compared with the other 2 diets over time. No differences in LBM were found among the 3 groups, but a trend toward increased LBM was noted in the HP group.
Hemoglobin A1c	Patients in all 3 groups demonstrated significant reductions in hemoglobin A1c (baseline to 12 wks)
QOL	Patients in all 3 groups demonstrated significant improvements in overall QOL over time (baseline to 12 wks). Patients on the HP diet demonstrated significantly greater reductions physical QOL scores (P=0.022) compared with those on SP and conventional diets.
Between-group differences from baseline to 12 weeks	Patients on the HP diet demonstrated significantly greater reductions in total cholesterol (P=0.016), triglyceride concentrations (P=0.034), and LDL-C (P=0.041) and greater improvements in functional status (6-minute walk [P=0.010] and VO_2 peak [P=0.003] and HDL-C [P=0.006]) compared with those on SP and conventional diets.
Patients satisfaction	Four of the 5 participants in the HP group indicated that following the diet was ''easy'' and that they were ''very satisfied'' with the food choices they were given. The fifth participant assigned to the HP group rated the diet as ''neither difficult nor easy'' to follow and indicated being ''satisfied'' with the food choices.

energy) or a HC diet (64% of energy). The results are summarized in Table VI.

The Authors conclude that a higher protein intake appears to confer some weight-loss benefit after 64 wk but, although CVD risk markers improved, protein intake does not appear to confer any extra benefit.

Due *et al.*[102] after reporting that a fat-reduced HP diet had more favorable effects on BW loss over six months than a medium-protein diet ,tried to extend this observation by a further 6-12 months less stringent intervention and a 24-month follow-up. The Authors designed a randomized six months strictly controlled dietary intervention followed by 6-12 month dietary counselling period, and a subsequent 24 month follow-up, comparing an ad libitum, fat-reduced diet (30% of energy) either high in protein (25% of energy, HP) or medium in protein (12% of energy, MeP) in a total of 50 overweight and obese subjects (age: 19-55 yr; BMI: 26-34 kg/m^2). The results are summarized in Table VII.

The Authors conclude that a protein content up to 25% of total energy is favorable to induce weight loss and does not adversely affect weight maintenance. In addition, the beneficial effect on IAAT was maintained after 12 months, and may have important implications in the prevention of complications of obesity.

Dumesnil *et al.*[103] investigated the short-term(6-d) nutritional and metabolic effects of an ad libitum low-glycaemic index-LF-HP diet (prepared according to the Montignac method) compared with the American Heart Association (AHA) phase I diet consumed ad libitum, as well as with a pair-fed session, consisting of the same daily energy intake as the former but with the same macronutrient composition as the AHA phase I diet. Twelve overweight men (BMI 33 [SD 3.5] kg/m^2), without other diseases, were involved in three experimental conditions with a minimal washout period of two wks, separating each intervention. The first two conditions were administered randomly whereas the pair-fed session had to be administered last. The results are summarized in Table VIII.

The Authors conclude that a low-glycemic index-LF-HP diet can produce a marked

TABLE X.—*Nickols-Richardson* et al. *Study results.*[105]

Weight loss	Mean BW significantly decreased in both diet groups over time (P<0.01). Specifically, after 1, 2, 3, and 4 wks of dietary compliance, average weekly BW loss was 2.2, 0.7, 0.5, and 0.3 kg, respectively, in the LC/HP group and 0.8, 0.4, 1.0, and 0.4 kg, respectively, in the HC/LF group. During wks 5 and 6 combined, women in the LC/ HP group lost an average of 1.2 kg, and women in the HC/LF group lost an average of 0.8 kg. Women in the LC/HP diet group lost more BW (5.7%) compared with women in the HC/LF diet group (3.3%) after 6 wks of dietary intervention (P<0.05). Women in both diet groups experienced significant changes in BMI (P<0.0001) over time, although the mean reduction in BMI was not different between diet groups. These changes in BW and BMI suggest that both dietary interventions were effective at inducing short-term changes, with the LC/HP diet promoting greater reductions in percentage of BW loss compared with the HC/LF diet. These results are consistent with other studies that report similar short-term BW and BMI losses in individuals complying with LC/HP diets.
Hunger and cognitive eating restraint and energy intake	The LC/HP diet group had a significant decrease (P<0.03) in self-reported hunger score from baseline to wk 6 (6.3±4.1 vs. 3.2±2.4, respectively), whereas the HC/LF diet group did not (7.1±4.0 vs. 5.9±3.8, respectively). The mean cognitive eating restraint score significantly increased (P<0.01) in both diet groups (N.=28) from baseline (7.3±4.4) to wk 1 (13.4±3.9) and remained stable to wk 6, with no statistically significant differences between groups over time. No other significant differences were observed at any other time points for hunger or cognitive eating restraint scores. Estimated average daily energy intake did not significantly differ between diet groups at any time point. Macronutrient composition of the two diets did differ at wks 1, 2, 4, and 6.

decrease in ad libitum energy intake without increasing hunger or decreasing satiety while having rapid and marked effects on metabolic risk variables.

Evangelista *et al.*[104] conducted a study to evaluate the impact of three dietary interventions on BW and adiposity, functional status, lipid profiles, glycemic control, and quality of life (QOL) in overweight and obese patients with heart failure (HF) and type 2 diabetes mellitus. Fourteen patients, with HF with a BMI greater than 27 kg/m^2, were randomized to an HP (hypoenergetic diet [40% total energy from CHOs, 30% from protein, and 30% from fat]) diet (N.=5) , a SP (55% total energy from CHOs, 15% from protein, and 30% from fat) diet (N.=5) or a conventional diet (N.=4). The composition or intake levels of different macronutrients for the SP and conventional diets were the same; they were both based on the AHA recommendations for healthy adults. The SP diet was hypoenergetic and the conventional diet had no ERs. Data were obtained at baseline and 12 wks. There were no significant differences among the three groups with regard to NYHA functional class, HF etiology, left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD). Rates of angiotensin converting enzyme inhibitor (93%), β-blocker (86%), loop diuretic (79%), statins (57%), and digoxin (29%) use were also similar in all three groups. BW and adiposity were comparable among the three diet groups at baseline. The results are summarized in Table IX.

This study suggests that a 12-wk dietary intervention with HP content shows promise in being able to reduce adiposity and improve functional status, lipid profiles, glycemic control, and QOL while preserving LBM in overweight and obese patients with HF. No adverse effects of an HP diet were noted in this study.

Nickols-Richardson *et al.*[105] examined the impact of a LC/HP diet compared with a HC/LF diet on ratings of hunger and cognitive eating restraint. Overweight premenopausal women consumed a LC/HP (N.=13) or HC/LF diet (N.=15) for six wks. Women in the LC/HP diet group, during the first two wks, consumed ≤20 g CHO/day;

TABLE XI.—*McAuley* et al. *Study results.*[106]

Weight loss	The HF and HP groups lost a comparable and significantly greater amount of weight and fat mass, and reduced WC compared to the HC group during the first 6 months but significant increases in weight, fat mass and WC occurred in the HF group between 6 and 12 months. The increases in fat mass and WC were significantly greater than that seen in the HP group. Overall, the HC group achieved a smaller reduction in weight, fat mass and WC compared to the other groups; however, reductions were sustained between 6 and 12 months. Weight at 12 months for all groups was considerably lower compared to baseline and weight lost was predominantly from fat rather than lean mass. More women in the HP and HF groups had lost more than 10% of initial BW at 12 months compared to the HC group (36 and 25 vs. 4%, respectively, P=0.027), but the difference between the two alternative diet groups was not significant. When considering the difference between groups in measures of adiposity at 12 months, none achieved statistical significance.
Blood lipids	Final 12-month TG levels were not different between the HF and the HC group, but were significantly lower in the HP group, where the mean difference was -0.4 mmol/L (95% CI -0.71, -0.02; P=0.037). Fasting TGs significantly increased from 6 to 12 months in the HF group losing the benefit obtained in the first 6 months. HDL levels at 12 months remained significantly improved in the HF group compared to the HC group, (0.13 mmol/L [0.01, 0.26]; P=0.035). Initial improvements in LDL-C seen especially in the HP group were not sustained throughout the 12-month period, so that by 12 months there were no significant differences among the groups. Although at 6 months there were more individuals in the HF group who had had a more than 10% increase in LDL levels, by 12 months there was no difference between the groups with five (21%) individuals showing a 10% rise in LDL in the HF group, six (21%) in the HP group and four (17%) in the HC group.
Glucose and insulin	No differences were observed in fasting glucose and insulin levels among the groups at 12 months.
Satiety, hunger, medications and mood	Participants in the three diet groups did not report any differences in satiety or hunger between the three diets and reported similar physical activity levels. Those on the HF diet had reduced bowel frequency and increased use of anti-constipating medication during the first 6 months, but were not significantly different from the other groups at 12 months. Mood scores were similar for all groups at baseline and 12 months.

thereafter, they increased their CHO intake by 5 g/wk to 40 g CHO/day at wk 6 (Atkins Nutritional Approach). Dietary protein and fat intakes were unlimited with no specific level of ER. Women randomized to the HC/LF diet restricted energy intake to 1 500 or 1 700 kcal/day based on each woman's estimated REE to facilitate 0.45 to 0.90 kg of weight loss per wk. Macronutrient composition of the HC/LF diet was designed to provide 60%, 15%, and 25% of total energy as dietary CHO, protein, and fat, respectively. Fasting BW was measured and the Eating Inventory was completed at baseline, wk 1 to 4, and wk 6. Age, height, BW, BMI, and energy intake did not statistically differ between diet groups at baseline. The results are shown in Table X.

The Authors conclude that both diet groups reported increased cognitive eating restraint, facilitating short-term weight loss. In this study the decrease in hunger perception in the LC/HP group may have contributed to a greater percentage of BW loss.

McAuley *et al.*[106] designed a study to assess wheter HC-high-fiber diets are recommended for weight loss and for treating and preventing diseases such as diabetes and CVD. The Authors report a randomized trial comparing HF and HP diets with the conventional approach. A total of 93 overweight insulin-resistant women received advice fol-

TABLE XII.—*McMillan-Price. Study results.*[107]

Weight loss	While all groups lost a similar (mean±SE) percentage of BW (diet 1, -4.2±0.6%; diet 2, <5.%±0.5%; diet 3, <6.2±0.4%; and diet 4, <4.8±0.7%; P=.09), the proportion of subjects in each group who lost 5% or more of BW varied significantly by diet (diet 1, 31%; diet 2, 56%; diet 3, 66%; and diet 4, 33%; P=.01). Women on diets 2 and 3 lost approximately 80% more fat mass (<4.5±0.5 [mean±SE] kg and <4.6±0.5 kg) than those on diet 1 (<2.5±0.5 kg; P=0.007). Mean±SE LDL-C levels declined significantly in the diet 2 group (<6.6±3.9 mg/dL [<0.17±0.10 mmol/L]) but increased in the diet 3 group (+10.0±3.9 mg/dL [+0.26±0.10 mmol/L]; P=.02). The conventional diet (diet 1) was associated with the highest level of postprandial glycemia as well as with the slowest rate of weight loss. Subjects instructed to follow a HC, low-GI (diet 2) or a HP, high-GI diet (diet 3) were twice as likely to achieve the clinical goal of a weight loss of 5% or more. In women in particular (N.=98), these 2 reduced-GL diets were associated with 80% greater fat loss compared with the conventional LF diet (diet 1; P<0.007), without compromising BLM.
Blood lipids	The low-GI, high-CHO diet (diet 2) produced the best clinical outcomes, reducing both fat mass and LDL-C levels. The HP, high-GI diet (diet 3) produced an increase in total and LDL-C concentrations (+8% overall, +10% in women), which contrasted with the decrease in LDL-C concentrations that was seen with both low-GI diets (P=0.01). The GI, but not the protein content, had a significant effect on change in total cholesterol levels (P=0.02) and LDL-C levels (P=0.009).

lowing randomization to HF, HP or HC dietary regimes, to achieve weight loss followed by weight maintenance over 12 months. Weight, body composition and measures of CHO and lipid metabolism were investigated. Dietary targets for the HF group were to consume no more than 20 g CHO/day in the first two wks, increasing up to 50 g/day by eight wks and continuing thereafter on an amount that maintained initial weight loss. The target for the HP group was to consume 40% of total energy from low glycemic index CHOs, 30% from fat (predominantly unsaturated) and 30% from protein. The HC group consumed at least 55% of total energy from CHOs, less than 30% from fat (less than 8% from saturated fat), 15% from protein and to aim for a dietary fiber intake of 25-30 g/day. At the end of four months all participants were instructed to continue their allocated diet without supervision until the 6- and 12-month visits. In all, 28 of the 30 (93%) in the HP group returned for the 12-month follow-up, compared with 24 of 31 (77%) in the HF group and 24 of 32 (75%) in the HC group. The results are shown in Table XI.

The Authors conclude that the conventional high-fiber dietary advice is related to modest but sustained benefits. This study provides strong support for the use of higher protein diets as an alternative to the conventional approach.

McMillan-Price [107] compared low-glycemic index (GI) and HP diets effects on weight loss and CVD. A total of 116 (of the 129 enrolled subjects, 13 females dropped out)) overweight or obese young adults (BMI ≥25) were assigned to 1 of 4 reduced-fat, high-fiber diets for 12 wks. All four diets were designed as reduced-energy, reduced-fat (30% E), moderate-fiber (30 g/day) eating plans with differences in the quantity and quality of available CHO. Diet 1 was a HC (55% E) and average-protein (15% E) diet based on high-GI whole grains, including fiber-rich breakfast cereals and breads. Diet 2 had the same macronutrient proportions but was based on previously verified low-GI foods. Diet 3 was a higher protein (25% E), CHO-reduced (45% E) diet based on lean red meat and high-GI CHO whole grains. Diet 4 had the same macronutrient proportions as diet 3 but specified low-GI CHO choices. The target glycemic load (GL=GI X CHO content), calculated as the sum of foods

TABLE XIII.—*Treyzon* et al. *Study results.*[108]

Weight loss	Both groups lost significant amount of weight at 12 wks (-4.19±0.5 kg for HP group and -3.72±0.7 kg for SP group, P<0.0001 for both groups) and there was no significant difference between the two treatment groups. For both dietary groups, BMI was significantly lower at 12 wks (HP=-1.50±0.58; SP=-1.13±0.24). There were no significant differences in BMI changes between the two dietary groups. Change in WC (cm) at 12 wks was significant in both treatment groups (HP=-6.7±1.1; SP=-5.1±0.8 P<0.0001). No significant differences in change in WC at any time period were observed between diets. Subjects in the HP group lost a significant amount of fat at 12 wks (from 35.2±1.0 kg to 33.6±1.2 kg, P<0.0001) but not the SP group (32.3±1.3 kg to 31.7±1.0 kg, P>0.05). Subjects in the HP group lost significantly more fat weight than the SP group (HP=-1.65±0.63; SP=-0.64±0.79 kg P=0.05). At 12 wks, the two dietary groups had significantly decreased lean BW (kg) (HP=-2.78.1±0.62; SP=-4.06±1.74, P<0.0001). No significant differences were observed between the dietary groups.
Blood lipids	At 12 wks, there were significant reductions in cholesterol and LDL levels (mg/dL) for the HP group (cholesterol -13.2±5.3, P<0.05; LDL -7.47±3.38, P<0.05) but not for the SP group (cholesterol -7.02±4.3 P>0.05; -9.17+5.65, P>0.05). The difference between the two groups was not significant. There were no significant changes from baseline, nor between dietary groups in serum HDL and TG levels.
Blood glucose	Fasting blood glucose levels did not change significantly from baseline for either group at 12 wks.

in sample menus, was the highest in diet 1 and the lowest in diet 4. Subjects were given eating plans that were devised to help them lose weight (providing approximately 1 400 kcal [6 000 kJ] for women and 1 900 kcal [8 000 kJ] for men) and achieve the desired macronutrient distribution. The results are shown in Table XII.

The Authors observe that dietary GL may be more relevant to women than to men. Women generally lose weight more slowly and display differences in postprandial glucose and fat oxidation which might influence the rate of fat loss. The GL may also be more important in individuals with hypertriglyceridemia. In this subgroup the diet with the lowest GL (diet 4) produces the greatest fat loss and improvement in the total HDL-C ratio. Soluble fibers intrinsic to legumes and low-GI whole grains (but not to high-GI whole grains) bind dietary cholesterol and may be critical in the context of a HP diet.

Treyzon *et al.*[108] designed a single blind, placebo-controlled, randomized outpatient weight loss trial (12 wks), involving 100 obese men and women, to determine effects of a protein-enriched meal replacement (MR) on weight loss and LBM retention, by comparison to an isocaloric CHO-enriched MR within customized diet plans, utilizing MR to achieve HP or SP intakes. MR was used twice daily (one meal, one snack). One additional meal was included in the meal plan designed to achieve individualized protein intakes of either: 1) 2.2 g protein/kg of LBM per day (HP diet) or 2) 1.1 g protein/kg LBM/day SP diet. LBM was determined using bioelectrical impedance analysis (BIA). The patients mean age was 49.4±1.1 yrs and the mean BMI at baseline was 33.8±0.53 for HP group and 32.6±0.58 kg/m^2 for the SP group. Fifteen subjects withdrew from the study within the first wk after randomization (non compliance with the meal plan) so that the HP group included 45 subjects and the SP 42 patients. BW, body composition, and lipid profiles were measured at baseline and 12 wks. The meal energy macronutrient composition in the HP group was approximately 30% protein, 30% fat, and 40% CHO. The macronutrient composition in the SP diet was approximately 15% protein, 30% fat, and 55% CHO. Both groups received the same isocaloric MR (Formula 1, Herbalife Intl., Los Angeles, CA,

TABLE XIV.—*Thomson* et al. *Study results.*[109]

Weight loss	Mean weight loss was 9.4±1.9% of weight (P<0.001 with no difference between treatments (P=0.7). Similarly, WC was reduced 11.1% by wk 20 (P<0.001), with no difference between treatments (P>0.5). There was a significant time by treatment interaction for percent body fat (BF%), fat mass, and FFM (P≤0.04), such that DA and DC had 45% greater reduction in fat mass (P<0.01) and 60% lesser reduction in FFM (P<0.03) compared with DO. There was some evidence for a time by treatment effect for abdominal fat mass (AbFM), although this did not reach statistical significance (P=0.08). Also for the exercising groups (DC and DA), there was greater FFM maintenance from wk 10–20 compared with DO, despite continued significant weight loss during this time. Only the exercising groups experienced continual weight loss and reductions in fat mass and AbFM and BF% from wk 10–20.
Blood pressure, glucose, insulin, HOMA, lipids, testosterone, FAI and SHBG	There were significant reductions in BP, fasting glucose and insulin, insulin resistance, HOMA, lipids, testosterone, and free androgen index (FAI) and increases in sex hormone-binding globulin (SHBG) in all treatment groups at wk 20 (P<0.05), with no difference between treatments (P>0.3). Increases in SHBG were inversely related to weight loss (r=0.43; P=0.002) and reductions in BF%(r=0.42; P=0.002), AbFM (r=0.64; P<0.001), and WC (r=0.46; P=0.001). Reductions in testosterone were positively related to reductions in BF% (r=0.30; P=0.03), AbFM (r=0.33; P=0.02), WC (r=0.29; P=0.04) and weight loss (r=0.25; P=0.07), as was the reduction in FAI (weight loss: r=0.30, P=0.04; BF%: r=0.36, P=0.01; WC: r=0.29, P=0.04; AbFM: r=0.27, P=0.06).
Reproductive function data and cardiometabolic and hormonal parameters	Data on reproductive function were included only for 59 subjects due to inconclusive results from PDG analysis and menses calendars for the remaining subjects. At baseline, 53 subjects reported menstrual irregularities (28 irregular cycle length, 13 anovulatory, 12 amenorrheic), and six had regular ovulating periods. Of the 53 subjects with menstrual irregularities, 49.1% reported improvements in ovulation (DO 50% (6 of 12), DA 50.0% (3 of 6), DC 42.9% [3 of 7]) and/or menstrual cyclicity (DO 21.4% [3 of 14],DA 42.9% [9 of 21],DC 44.4% [8 of 18]), with no difference between treatments (P>0.1). There was no difference between groups in the number of menstrual cycles that occurred during the 20-wk study period (DO 2.25±1.35; DA 3.30±1.97; DC 3.00±1.61; P>0.3), but subjects in DA reported a greater number of ovulatory cycles compared with DO (DO 1.33±1.63, DA 3.10±1.97, DC 2.65±1.70; P=0.04). For the subjects that improved in menstrual cycle length, there was an average reduction of 13.8±28.3 d (49.6±25.0 to 32.7±4.3 d), and for those that improved in consecutive intercycle variation, there was an average reduction of 16.0±19.7 d (19.5±20.7 to 3.5±3.5 d). After the intervention, 18 subjects had regular ovulating cycles, five were anovulatory, 27 had irregular cycle lengths, and nine were amenorrheic. There were no differences in baseline characteristics between subjects who improved reproductive function, determined by improvements in ovulation and menstrual cyclicity (responder [R], N.=26) and those that did not (NR, N.=27) (P>0.1). Women who experienced improvements had greater reductions in weight (R vs. non responder [NR], 12.2±4.0 vs. 6.7±3.8 kg; P<0.001), fat mass (8.2 ±3.4 vs. 4.7±3.2 kg; P<0.01), AbFM (0.5±0.3 vs. 0.3±0.2 kg; P<0.02), and WC (13.4±5.1 vs. 10.0±4.8 cm; P<0.02) compared with women who did not. There were no differences in changes in any cardiometabolic or hormonal parameters between R and NR (P>0.1).

USA) with either a protein supplement for the HP group (Performance Protein Powder, Herbalife Intl.) or with a similar tasting CHO placebo for SP group. Two MR and two meals were eaten daily. Subjects were weighed at baseline, and at 2, 4, 8 and 12 wks. Baseline BW was not significantly different between these two groups. The results are shown in Table XIII.

The Authors conclude that both the HP and SP diets result, in the expected weight loss, typical of an MR diet plan at 12 wks.

TABLE XV.—*Stamets* et al. *Study results.*[110]

Weight loss	Both the HP and HC diets resulted in significant weight loss. There was no significant difference in mean weight loss between the two groups. Of the 26 participants who completed the study, 25 lost some weight and only 1 gained weight. The one participant who gained weight was on the HP diet (this particular HP diet participant gained 0.4 kg [0.45% increase from their baseline weight]). The range in weight loss was therefore a +0.4-kg gain to 6.2-kg loss for the HP diet and a 1.7-kg to 7.3-kg loss for the HC diet. In terms of percent weight loss based on intimal weight, this represented a mean of 3.6% weight loss for the HP diet (range -5.8% to +0.5%) and a mean 4.2% loss for the HC diet (range -6.9% to -2.0%).
Blood pressure, glucose, insulin, HOMA, lipids, testosterone, FAI and SHBG	No observable differences existed between diets for a variety of measures including biometric, hormonal, lipid and lipoprotein, and markers of glucose homeostasis and energy metabolism. There was a trend toward decreased WC in women on the HP diet, and a trend toward decreased hirsutism in the women on the HC diet, but neither trend was significant. There were no differences between treatment groups in individual values of glucose, insulin, or leptin during the 3-hour OGTT, or in integrated AUC measurements.

Both diets are well tolerated, sustainable, and do not result in any adverse effects.

Thomson *et al.*[109] evaluated the effects of aerobic and aerobic-resistance exercise when combined with an energy-restricted HP diet (5 000-6 000 kJ/day) on metabolic risk factors and reproductive function in women with polycystic ovary syndrome (PCOS; a common endocrine condition in women of reproductive age associated with obesity which may involve dysregulation of ghrelin, a hormone implicated in appetite regulation). A 20-wk outpatient, randomized, parallel study was conducted in a metropolitan research clinic. Ninety-four overweight and obese women with PCOS (age: 29.3±6.8 yrs; BMI 36.1±4.8 kg/m^2) were randomized to diet only (DO; N.=30), diet and aerobic exercise (DA; N.=31), or diet and combined aerobic-resistance exercise (DC; N.=33). All subjects were prescribed the same energy-restricted, HP diet (5 000-6 000 kJ/day) for a planned weight loss of 8-12 kg over the study period. The diet provided 30% of energy as protein, 40% as CHO, and 30% as fat (<8% saturated fat). BW, body composition, cardiometabolic risk factors, hormonal status, menstrual cyclicity, and ovulatory function were assessed. There were no significant differences at baseline characteristics between treatments. The results are shown in Table XIV.

The Authors conclude that weight loss *via* ER improve reproductive function, cardiometabolic abnormalities, and hormonal parameters in overweight and obese women with PCOS. Addition of regular aerobic or combined aerobic-resistance exercise provides no additional improvement for cardiometabolic, hormonal, or reproductive outcomes but it results in more favorable changes on body composition.

Stamets *et al.*[110] randomized 35 overweight/obese (BMI range: 28-45 kg/m^2) women with PCOS to assess the effects of a one-month HP dietary intervention (30% protein, 40% CHO, and 30% fat) or HC (15% protein, 55% CHO, and 30% fat) on the PCOS phenotype. The fat content was held constant in both diets. Energy needs were adjusted to create a 1 000-kcal deficit per day to produce an approximately 1 000 g/wk rate of weight loss. All participants were instructed to consume a multivitamin/mineral supplement daily. Change in BW was the primary outcome. Secondary outcome were biometric, hormonal, lipid and lipoprotein and markers of glucose homeostasis and energy metabolism. No differences existed among the groups in baseline biometric, hormonal, lipid, and parameters of glucose homeostasis. The mean period of amenorrhea for study completers based on their last menstrual periods before their baseline OGTT visit was 86±66

TABLE XVI.—*Gillingham* et al. *Study results.*[111]

Energy intake	During the HP diet phase, energy intake was an average of 6kcal/kg lean mass/day lower (P=0.02), and REE was an average of 4 kcal/kg lean mass/day higher (P=0.05) compared to the HC diet phase. One subject had a proportionately larger change in REE during the HP diet but the difference in mean REE among all subjects remained significant whether this subject was included or excluded from the analysis. Resting RQ was lower during the HP diet phase most likely due to the lower RQ of protein oxidation. The estimated substrate oxidation data confirm this hypothesis: CHO oxidation was lower and protein oxidation was higher during the HP diet phase compared to the HC diet phase but fat oxidation was not different. There was a non significant trend (P=0.07) for the sum of fasting long-chain hydroxyacylcarnitine concentrations to be higher during the HP diet phase. There were no significant differences in the sum of the long-chain acylcarnitine AUC following the HC test meal (4.28±2.8 μmol/L/4 h) and the HP test meal (5.18±3.2 μmol/L/4 h; P=0.09).
Glucose and insulin	Fasting and AUC plasma insulin levels did not differ between the HC and HP diet periods. Fasting insulin levels were not different from control subjects. there was a trend (P=0.054) for plasma glucose AUC to be lower during the HP diet. No episode of hypoglycemia was noted during the entire 2-wk study.
Triglycerides, leptin and ghrelin	Fasting and AUC plasma TG concentrations were low on both diets, but significantly lower during the HP diet than the HC diet. Plasma levels of leptin did not different between the diet phases. However, compared to control values, fasting plasma leptin concentrations were higher in the study participants. Ghrelin data presented here represent samples collected from six subjects to which an appropriate protease inhibitor and acid were added. Fasting and post-prandial ghrelin AUC was similar between the two diets (mean±SD AUC ghrelin: HC diet=5 124±2 178 pg/mL; HP diet=5 017±1 320 pg/mL). Fasting ghrelin concentrations were not significantly different from controls. Maximum ghrelin suppression following the research meal (difference in fasting and 1 h ghrelin concentrations) was approximately 14% in both diets (P=0.5).

days for the HP group (range 6-195 days) and 102±113 days for the HC group (range 12-403 days). The results are shown in Table XV.

The Authors conclude that those who complete a hypocaloric intervention can expect a significant weight loss and significant improvement in their reproductive and metabolic abnormalities but these data demonstrate that no statistically significant increased benefit was associated with a HP diet. Fourteen of the 26 women experience vaginal bleeding during the study, although we cannot ascertain whether this was anovulatory or ovulatory bleeding.

Gillingham *et al.*[111] determined the short-term safety and efficacy of a HP diet on nine subjects with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency, aged 7-14, fed an ad-libitum HP diet and a HC diet for six days, each using a randomized, crossover design. Body composition was determined by dual energy X-ray absorptiometry. Total energy intake was evaluated daily. REE and substrate utilization were determined by indirect calorimetry. Postprandial metabolic responses of plasma glucose, insulin, leptin, ghrelin, acylcarnitines, and TG were determined in response to a liquid meal. Subjects had a higher fat mass, lower lean mass and higher plasma leptin levels compared to reference values. Diets were served in three meals plus a snack each day with a three-day cycle menu. The daily menu provided 1 800, 2 200 or 2 400 kcal per day depending on the age and BW of the subject (110-120% of estimated energy needs). Three males and six females completed the two-wk study. Three of the subjects were classified as at risk of

TABLE XVII.—*Foster* et al. *Study results.*[112]

Energy intake	Subjects on the LC diet lost significantly more weight than the subjects on the conventional diet at 3 months (P=0.002) and 6 months (P=0.03), but the difference in weight loss was not statistically significant at 12 months (P=0.27).
Urinary ketones	During the first three months, the percentage of patients who tested positive for urinary ketones was significantly greater in the group on the LC diet than in the group on the conventional diet, but there were no significant differences between the groups after three months. There was no significant relation between weight loss and ketosis at any time during the study.
Blood pressure	Systolic BP did not change significantly in either group during the study. Diastolic BP decreased in both groups, but there were no significant differences between groups.
Insulin and glucose	The glucose AUC did not change significantly in either group throughout the study. The insulin AUC decreased in both groups, but there were no significant differences between groups. There were no significant differences between groups in insulin sensitivity (assessed by the quantitative insulin-sensitivity check index) throughout the study period. Both groups had significant increases in insulin sensitivity at six months, but the values were not significantly different from base line at one yr.
	There were no significant differences between groups in the total or LDL-C concentration, except at month 3, when values were significantly lower in the group on the conventional diet than in the group on the LC diet. In contrast, the relative increase in HDL-C concentrations and the relative decrease in triglyceride concentrations were greater in the group on the LC diet than in the group on the conventional diet throughout most of the study.

obesity with a BMI ≥95 percentile. Two subjects were classified as underweight with a BMI <5th percentile. Four subjects were within the normal range (5-85 percentile) of BMI for children. BW remained relatively stable over the course of the study with a mean change in BW of +0.6 kg and a range of -0.2 to +1.9 kg. This study aims at assessing the effects of differential dietary macronutrient content without the confounding effects of a change in BW. The results are shown in Table XVI.

The Authors conclude that short-term consumption of a HP diet Is associated with decreased energy intake and increased REE without exacerbating metabolic control or causing hypoglycemia in subjects with LCHAD and TFP deficiency.

Foster *et al.*[112] conducted a one-year, multicenter, controlled trial involving 63 obese men and women who were randomly assigned to either a LC, HP, HF diet (N.=33; this diet involved a limited CHO intake without restricting consumption of fat and protein. For the first two wks, CHO intake was limited to 20 g per day and then gradually increased until a stable and desired weight was achieved) or a low-calorie, HC, LF (conventional) diet (N.=30; 1 200 to 1 500 kcal per day for women and 1 500 to 1 800 kcal per day for men, with approximately 60% of calories from CHO, 25% from fat, and 15% from protein). The results are shown in Table XVII.

The Authors conclude that the LC diet produced a greater weight loss (absolute difference, approximately 4%) than the conventional diet for the first six months did, but the differences were not significant at one yr. The LC diet was associated with a greater improvement in some risk factors for coronary heart disease.

Farnsworth *et al.*[113] compared the effects of two weight loss diets differing in protein-to-CHO ratio on body composition, glucose and lipid metabolism, and markers of bone turnover. They designed a parallel trial including either a HP diet of meat, poultry, and

TABLE XVIII.—*Farnsworth* et al. *Study results.*[113]

Energy intake	Energy intake did not differ between the 2 groups during either the 12-wk ER phase or the 4-wk EB phase. The protein intake was higher and the CHO intake was lower with the HP diet than with the SP diet, and there was no difference between the ER and EB phases (effect of diet, P<0.0001). Total and saturated fat content did not differ between the diets or phases, but dietary fiber was lower and dietary cholesterol was higher with the HP diet than with the SP diet during both phases.
Urinary urea: creatinine	The ratio of urinary urea to Cr rose from 30.3±1.5 at wk 0 to 36.5±1.6 at wk 16 of the HP diet, and it remained constant from wk 0 to wk 16 of the SP diet (32.2±1 compared with 31.8±1) (P<0.001 for time-by-diet effect; P<0.01 for time).
Body weight and body composition	After 12 wk of ER and 4 wk of EB, the mean weight loss was 7.9±0.5 kg (P<0.0001), but the decrease in weight was not affected by the diet composition (7.8±0.7 compared with 7.9±0.6 kg in the HP and SP diet groups, respectively). The men lost more weight than did the women (not statistically significant; men: 9.7%; women: 7.9%). Weight was maintained during the EB phase, with no difference between diets or sexes. Total fat mass was 6.9±0.4 kg less after 16 wk (P < 0.0001), but the decrease was not affected by diet composition. There was a difference in the reduction in fat mass between the sexes, with the men losing a greater amount of fat. At wk 16, AbFM was 3.1±0.2 kg less (P<0.0001), with no effect of diet composition. The reduction in AbFM was greater for the men than for the women. After 16 wk, total lean mass had decreased 1.2±0.3 kg (P<0.0001). There was no effect of diet on the reduction in lean mass. A time-by-diet-by-sex interaction (P=0.002) was present, even after control for baseline lean mass, such that the women lost significantly (P<0.02) less lean mass with the HP diet than with the SP diet.
Glycemic control, insulin sensitivity, and fatty acids	Fasting plasma glucose did not differ between wks 0 and 16, and there was neither an effect of diet nor a time-by diet interaction. There was no effect of sex on fasting glucose at baseline; however, at screening, fasting glucose was higher in the men than in the women. Fasting serum insulin decreased by 33±3.3% at wk 12 and by 29±3.4% at wk 16 (P<0.001), with no effect of either diet composition or sex. The HOMA index for insulin resistance decreased 32±4%, from 4.3 at wk 0 to 2.5 at wk 12 (P<0.001), and by 27±4% to 2.8 at wk 16 (P<0.001). Neither diet nor sex affected the HOMA index. The plasma glucose AUC was smaller after the HP meal than after the SP meal, at both wks 0 and 16 (P=0.027). The plasma glucose AUC was smaller at wk 16 than at wk 0 (P<0.001), but the reduction tended to be greater in the HP diet group than in the SP diet group (8.7±2.2% compared with 1.9±2.1%; P=0.08). Analyzing the glucose values with a repeated-measures ANOVA, the response of plasma glucose to the test meals decreased after 16 wk (P<0.001), and there was a time-by-diet interaction (P<0.05) such that the plasma glucose response decreased more after the HP diet meal than after the SP diet meal. At wk 16, plasma glucose concentrations at all time points were lower after the HP diet meal than after the SP diet meal (P<0.001 for diet effect). At wk 16, the response of serum insulin to the test meals was less than it had been at wk 0 (P<0.001). There was no effect of diet composition on the reduction in postprandial serum insulin at wk 16. After 16 wk, fasting serum FAs decreased 26% (P<0.001), with no effect of either diet or sex. At wk 0 during the MTT, serum FA concentrations decreased from 0.43±0.02 mmol/L at baseline to 0.006±0.003 mmol/L at 120 min, but no further decrease occurred after 16 wk. There was no effect of either diet or sex on the FA response curves after the MTT.
LDL, and HDL cholesterol and triacylglycerol	Fasting serum total cholesterol at wk 12 decreased by 10.0% compared with that at wk 0 and decreased by 5.3% at wk 16 (P<0.0001), with no effect of diet. There was an effect of sex on the decrease in fasting serum total cholesterol from wk 0 to wk 12 (P<0.005) such that total cholesterol decreased more in the men (1.0±0.2 mmol/L) than in the women (0.42±0.1 mmol/L). Fasting serum LDL-

(Continue)

TABLE XVIII.—*Farnsworth* et al. *Study results.*[113]

	C was 12% lower at wk 12 and 6% lower at wk 16 (P<0.0001), with no effect of diet. At both wks 12 and 16, the decrease in LDL-C was greater for the men than for the women (P<0.02). Fasting serum HDL-C increased 2% by wk 12 and 5% by wk 16 (P=0.001), with no effect of either diet or sex. Fasting serum triacylglycerol concentrations decreased 15.8% by wk 12 and 14.1% by wk 16 (P<0.0001). A time-by-diet effect was observed (P<0.05) such that the decrease in serum triacylglycerol concentrations was 29% by wk 12 and 23% by wk 16 with the HP diet, but the decrease was only 12% by wk 12 and 10% by wk 16 with the SP diet.
Urinary calcium, markers of bone turnover, blood pressure	Urinary calcium excretion was unchanged at wk 16 compared with wk 0 (4.7±0.4 compared with 4.4±0.3 mmol/24 h), and there was no effect of either diet or sex. The concentrations of bone-turnover markers (Pyr: 62.5±2.2 compared with 62.1±2.6 nmol/mmol Cr; Dyr: 18.6±0.7 compared with 18.5±0.9 nmol/mmol Cr) also did not differ between baseline and wk 16 in both groups. Systolic BP decreased from 130±1.9 mmHg at wk 0 to 126±1.8 mmHg at wk 12 (P=0.022), but, by wk 16, systolic BP (126±2.3 mmHg) not differ from that at wk 0. At both wks 12 and 16, diastolic BP (72±1.3 and 72±1.4 mmHg, respectively) was significantly (P<0.04) lower than that at wk 0 (74±1.4 mmHg). There was no effect of either diet or sex on systolic or diastolic BP.

dairy foods (HP diet: 30% of energy as protein [~110 g/day], 40% as CHO, and 30% as fat) or a SP diet low in those foods (SP diet: 15% of energy as protein [~60 g/day], 55% as CHO, and 30% as fat) during 12 wks of ER (6-6.3 MJ/day) and 4 wk of EB (~8.2 MJ/day). Fifty-seven overweight volunteers with fasting insulin concentrations >12 mU/L completed the study. The FA profiles for each diet were matched (8% of energy as saturated FAs, 12% as MUFA, and 5% as PUFA). The key foods supplied to both diet groups were preweighed meat and poultry, shortbread biscuits, canola margarine (Canola Lite; Meadow Lea Foods Ltd, Mascot, Australia), and high-oleic acid sunflower oil (Sunola; Meadow Lea Foods Ltd). The HP diet group also received low-fat (3% fat) cheese (Kraft Free; Kraft Foods Ltd, Melbourne, Australia) and skim milk powder, whereas the SP diet group received rice and rice noodles. Forty-five percent of the protein in the HP diet came from dairy foods and 45% came from meat and poultry, whereas in the SP diet, only 18% of the protein came from dairy foods and 42% came from meat and poultry. BW and fasting plasma glucose concentrations were significantly greater in the men than in the women at screening. There was no effect of sex on any of the other variables. The results are shown in Table XVIII.

The Authors conclude that replacing some dietary CHO with protein during ER does not enhance weight or fat mass loss or have any deleterious effects on bone turnover or BP in subjects with insulin resistance, at least over the short term. Protein intakes from meat, poultry, and dairy foods do reduce postload glucose and fasting triacylglycerol concentrations.

Galletly *et al.*[114] designed a study, involving 25 overweight women with PCOS, to assess the psychological effects of two energy restricted diets (6 000 kJ/day). They were matched for age, weight, and whether they were trying to conceive. Subjects were independently randomized to one of two diets for 12 wks: 1) HPLC (30% protein, 40% CHO, 30% fat) or 2) LPHC (15% protein, 55% CHO, 30% fat). A weight maintenance diet, with the same dietary composition, was followed for the final four wks. All participants attended a weekly exercise, group support and educational program. The Hospital Anxiety and Depression Scale and the Rosenberg Self Esteem Scale were administered at the beginning and end of the study. Twenty-eight subjects began the study. They were randomized into two groups with 14 women in each group. The mean age of the subjects was 33±1.2 yrs in the HPLC group and 32±1.2 yrs in the LPHC group. Three women dropped

TABLE XIX.—*Galletly* et al. *Study results.*[114]

Weight loss	Their mean weight loss over 16 wks was 6.9±0.8 kg, and they had a mean BMI of 34.5±5.7 at the end of the study. At baseline the LPHC group had a mean weight of 98.6±4.6 kg and a mean BMI of 37.2±6.9. After 16 wks, their mean weight loss was 8.5±1.1 kg, and they had a mean BMI of 34.5±6.3. There were no significant differences between groups in weight loss or reduction in BMI.
Psychological well-being	In the HPLC group, there was significant improvement in depression: t(13) =3.894, P=0.002; and self-esteem: t(12) =-2.350, p=0.037. There was no significant change in any psychological measure in the LPHC group.

out due to pregnancy (two in the HPLC group and one in the LPHC group). There were no significant differences between groups in mean age or baseline weight, BMI, depression, anxiety and self-esteem ratings. At baseline the HPLC group had a mean weight of 104.2±5.3 kg and a mean BMI of 37.6±6.4. The results are shown in Table XIX.

The Authors conclude that, due to enhanced feelings of well-being, it is possible that HPLC diets may be associated with better compliance and hence be more successful in the long term treatment of obesity.

Gardner *et al.*[115] compared four weight-loss diets in a 12-month randomized trial among 311 free-living, overweight/ obese (BMI: 27-40 kg/m^2) non-diabetic, premenopausal women. Participants were randomly assigned to follow the Atkins' (very low in CHO; N.=77), Zone (low in CHO; N.=79), LEARN (Lifestyle, Exercise, Attitudes, Relationships and Nutrition; LF, high in CHO, based on national guidelines; N.=79), or Ornish (very high in CHO; N.=76) diets and received weekly instructions for two months and after that an additional 10-month follow-up. Weight loss at 12 months was the primary outcome. Secondary outcomes included lipid profile (LDL, HDL, and non HDL-C, and TG levels), percentage of body fat, W/H, fasting insulin and glucose levels, and BP. Outcomes were assessed at months 0, 2, 6, and 12. The results are shown in Table XX.

In this study the Atkins' diet shows more weight loss and more favorable outcomes for metabolic effects at one year than the other three diets. Atkins's diet related adverse effects are not substantiated within the 12-month study period.

Gately *et al.*[116] evaluated the effect of a HP diet on anthropometry, body composition, subjective appetite, and mood sensations in overweight and obese children attending a residential weight-loss camp. Children (N.=120; BMI: 33.1±5.5 kg/m^2; age: 14.2±1.9 yrs) were randomly assigned to either a SP or HP diet group (15% *vs.* 22.5% protein, respectively). The results are shown in Table XXI.

This study supports the observation that prolonged negative EB is associated with an increase in hunger motivation. However, randomizing children to a HP diet do not seem to facilitate weight loss or suppress hunger.

Johnstone *et al.*[117] compared the acute, energy-cost of meal-induced thermogenesis on a HP/LF diet *versus* a HC/LF diet. Two experimental diets were tested: the control HC diet (providing 50% of energy as complex CHO, 10% as simple sugar, 15% as protein and 25% as fat) and the HP diet (30% of energy as complex CHO, 10% as simple sugar, 30% as protein and 30% as fat). BWs did not differ on the mornings of the HP and HC test days. Ten healthy, normal weight, non-smoking female volunteers, aged 19-22 yrs, were recruited from a campus population. Using a randomized, cross-over design, subjects consumed the HP and the HC diets for one day each, and testing was separated by a 28- or 56-day interval. Control diets were consumed for two days prior to each test day. On the test day, the REE, the non-protein RQ and body temperature were measured following a 10-hour fast and at 2.5-hour post breakfast, lunch and dinner. Fasting blood samples were collected on the day of the test and the next morning, and complete 24-hour urine samples were collected the day of testing. The results are shown in Table XXII.

TABLE XX.—*Gardner* et al. *Study results.*[115]

Dietary intake and energy expenditure	Total energy intake was not different among diet groups at baseline or any subsequent time point (P>0.40 for all). At baseline, there was a significant mean decrease in reported energy intake at all post randomization time points (P<0.001): -497 (SD, 496), -387 (SD, 498), and -351 (SD, 576) kcal/d at 2, 6, and 12 months, respectively, for all groups combined. There were no significant group differences at baseline in percentage of energy from CHO, fat, or protein or in grams of saturated fat or fiber, except for a borderline significant difference in percentage of energy from fat between Atkins and LEARN (P=0.05). At subsequent time points the diets were statistically different in CHO content, progressing from low to high across the Atkins, Zone, LEARN, and Ornish groups. This same pattern was observed for fiber intake. The reverse pattern, higher to lower intakes, was statistically significant for protein, fat, and saturated fat at all time points. Between-group differences in patterns of nutrient intake were largest at 2 months. At 12 months, the patterns of nutrient differences between groups were still present, but the magnitude of differences was diminished. TEE was slightly higher for the Ornish group vs the other 3 groups at baseline but was not significantly different among groups at any subsequent time point. There was a modest and significant mean increase (P<05) in energy expenditure at all time points for all groups combined: +0.5 (SD, 2.8), +0.4 (SD, 2.7), and +1.0 (SD, 3.0) kcal/kg per day at 2, 6, and 12 months, respectively.
Weight and anthropometric outcomes	Mean 12-month weight change was -4.7 kg (95% confidence interval [CI],-6.3 to -3.1 kg) for Atkins, -1.6 kg (95% CI, -2.8 to -0.4 kg) for Zone, -2.2 kg (95% CI, -3.6 to -0.8 kg) for LEARN, and -2.6 kg (95% CI, -3.8 to -1.3 kg) for Ornish and was significantly different for Atkins vs. Zone. At the 2- and 6-month intermediate time points, the weight change for the Atkins group was significantly greater than for all other groups (P<0.05). Weight change among the Zone, LEARN, and Ornish groups did not differ significantly at any time point. The pattern of changes in BMI, percentage of body fat, and W/H among groups paralleled the changes in weight, although the between-group differences at 12 months did not achieve statistical significance for percentage of body fat (P=0.07) or W/H (P=.10).
Lipid outcomes	Results generated by 84% of the study population (N.=262) with baseline blood samples (Atkins, N.=70; Zone, N.=65; LEARN, N.=63; and Ornish, N.=64) were available for testing. At all time points, the statistically significant findings for HDL-C and triglycerides concentrations favored the Atkins group. Changes in LDL-C concentrations at 2 months favored the LEARN and Ornish diets over the Atkins diet; however, these differences diminished and were no longer significant at 6 and 12 months. Non-HDL-C differences among groups were not significant at any time point.
Insulin, glucose, and blood pressure outcomes	Insulin and glucose measurements were obtained from the same aforementioned 84% of the total sample for lipids. Neither the overall trajectory (i.e., across all time points) nor the 12-month differences were significantly different among groups for either fasting insulin or fasting glucose concentrations. Parallel to the group changes in weight, the decrease in mean BP levels was largest in the Atkins group at all time points. At 12 months, the decrease in systolic BP was significantly greater for the Atkins group than for any other group. For diastolic BP, the only significant pairwise difference at 12 months favored the Atkins over the Ornish group.

This study shows that the increased thermogenesis of a HP diet may contribute to its efficacy.

Sargrad *et al.*[118] evaluated the effects of less extreme changes in CHO or protein diets on weight, insulin sensitivity, glycemic control, CVD factors (BP, lipid levels), and renal function in obese inner-city patients with

TABLE XXI.—*Gately* et al. *Study results.*[116]

Subjective Hunger and Mood	Children had a BMI SDS of 3.0, and 42% of their BW was fat. There was a significant main effect of time on all of the outcome measures apart from height (P <0.05). However, there was no main effect of diet group or any time-by-diet group interaction (P>0.05). Combining all children from both diet groups, there were significant weight loss (5.3±2.8 kg; P<0.001); reductions in BMI SDS (0.27 ±0.1; P<0.001), BF% (2.0±6.3%; P<0.001), FM (3.8±5.4 kg; P<0.001), FFM (1.5±5.3 kg; P<0.05), WC (6.2±2.6 cm; P<0.001), and BP (systolic, 5.4±8.2 mmHg, P<0.001; diastolic, 5.7±8.6 mmHg, P<0.001); and improvement in all blood lipid measures (P <0.01). It should be noted, however, that, although not significant, there was a 4-fold difference of FFM loss between the SP and HP diet groups (2.4 and 0.6 kg, respectively).
Subjective Hunger and Mood	Children who completed ratings of hunger and mood did not differ from the rest of the sample in weight or body composition at baseline. ANOVA showed a significant increase in AUC hunger at the end compared with the start of the camp in both diet groups (P>0.001). However, neither fullness nor any of the mood ratings differed significantly over the course of the study (P>0.05). There was no main effect of diet group or group-by-time interaction on the subjective sensations (P>0.05). Children rated hunger at the end of camp significantly higher at breakfast, midmorning, and after lunch (P<0.05). There were no differences observed from dinner time into the evening. There was no significant time-by-diet interaction in palatability of the two diets as indicated by the perceived tastiness ratings (P=0.33) (55.7±18.5, start camp; 61.2±14.8, end camp; 55.7± 18.5, start camp; 58.6±14.8, end camp for SP and HP diets, respectively). In general, both diets were relatively palatable.

type 2 diabetes. Six patients with type 2 diabetes (five women and one man) were randomly assigned to the HP diet (40% CHO, 30% protein, 30% fat) and six patients (4 women and 2 men) to the HC diet (55% CHO, 15% protein, 30% fat). Patients in the HP group were instructed to select more protein (chicken, fish, eggs, LF milk, cheeses, and nuts) and less CHO (breads, cereals, pasta, and starchy vegetables). Patients in the HC group were instructed to select less protein and more CHO. Twelve study patients selected either the HP or HC diet and were followed for eight wks. The main outcome measures were: insulin sensitivity, hemoglobin A1c, weight, and BP were measured. The results are shown in Table XXIII.

This study reports that the HC diet was superior to the HP diet in terms of improving glycemic control and insulin resistance. Rather modest modification in the dietary behavior of obese inner-city patients with type 2 diabetes can achieve weight loss comparable to that obtained with very-LC diets and improve glycemic control.

Skov *et al.*[119] studied the long-term effect of dietary protein on bone mineralization. Sixty-five overweight (BMI: 25 to 29.9 kg/m^2) or obese (≥30 kg/m^2) subjects were enrolled in a randomized, placebo-controlled, six-month dietary-intervention study comparing two controlled ad libitum diets with matched fat contents: HP or LP. At baseline bone mineral content (BMC), total BMD and regional (lumbar) BMD were similar in all three groups. Baseline values of BMC as indexed by fat mass were also similar in the three groups. Dietary calcium and vitamin D intake were equal in the three groups. In a cross-sectional analysis, BW was the major determinant of BMC (r=0.69; P<0.001) together with FM (r=0.22; P<0.05). Fat mass and FFM were major determinants, explaining ~55% of the variability in BMC (P<0.001). None of the variation in the bone mineral variable could be explained by total energy intake, dietary calcium, or vitamin D intake. A total of 60 subjects completed the trial (92%), 23 in each intervention group and 14 in the control group. Dietary-protein intake increased in the HP group from a baseline value of 91.4 (81.0 to 101.82) g/day to a six-month intervention mean of 107.8 (102.2 to 112.1) g/day (P<0.05), whereas a decrease from 91.1 (82.5

TABLE XXII.—*Johnstone* et al. *Study results.*[117]

Fasting and postprandial REE	Fasting REE was similar prior to the diet intervention, 1 396±53 and 1 359±59 kcal/24 hours for HC and HP, respectively. Postprandial REE was 8 kcal/hour higher at 2.5 hours following the breakfast meal (P<0.05) and 8kcals/hour higher at 2.5 hours following the lunch meal on the HP diet vs. the HC diet. At 2.5 hours after the dinner meal, postprandial REE was 14 kcal/hour higher on the HP diet compared to the HC diet (P<0.05).
Body temperature	Body temperature rose steadily throughout the day on both diets. The change in body temperature from the fasting baseline value was +0.1 and +0.4 °F at 2.5 hours after the breakfast meal and +0.4 and +0.6° F at 2.5 hours after the lunch meal for the HC and HP diets respectively (P>0.05). At 2.5 hours after the dinner meal, the change in body temperature for the HP diet was nearly 40% higher than that for the HC diet (+0.8 and +0.5 °F respectively, P=0.08). Body temperature was related to REE in the HP group only (HP: r=0.66, P<0.05; HC: r=0.29, P>0.05).
Non-protein respiratory quotient and plasma insulin	The fasting non-protein RQ, an indicator of substrate oxidation, was similar prior to diet intervention (0.81±0.01 and 0.79±0.02 for HC and HP, respectively), and the change in post-meal non-protein RQ did not differ by diet. Fasting plasma insulin concentrations before and after the diet intervention did not vary by diet (20.8±2.7 and 19.8±2.2 µU/mL prior to and 22.1±2.7 and 22.7±3.7 µU/mL at 24 hours post-intervention, HC and HP respectively).
Fasting plasma urea nitrogen , GFR and nitrogen balance	Fasting plasma urea nitrogen concentrations were similar prior to diet intervention, 11.2±0.8 and 11.0±0.8 mg/dL for HC and HP, respectively. At 24 hours post-intervention, fasting plasma urea nitrogen concentrations were raised (P< 0.05) on the HP diet vs. the HC diet, 13.9±0.9 and 11.2±1.0 mg/dL, respectively. GFR did not vary by diet treatment (131.6±15.2 and 129.9±19.5 mL/min, HC and HP, respectively, and urinary urea nitrogen values post intervention were also similar between groups. Apparent nitrogen balance was greater for the HP diet than the HC diet, +7.6±0.9 and -0.4±0.5 gN/day, respectively.

to 99.7) g/day to 70.4 (64.8 to 76.0) g/day (P<0.05) was attained in the LP group (group difference, P<0.0002). This fact corresponded to a mean daily protein intake of 1.6 g/kg in the HP group and 1.0 g/kg in the LP group (group difference, 0.6 [0.5 to 0.8] g/kg; P<0.001). Dietary-protein intake did not change in the control group during the intervention period. Dietary calcium decreased in the LP group, whereas it increased in the HP group (group difference, 317 [62 to 572] mg/day; P<0.05). Daily vitamin D intake remained stable in the HP group, whereas it decreased by 88 IU/day in the LP group (P<0.05), although there was no group difference. The results are shown in Table XXIV.

The present study shows that a diet providing 108 g/day of protein does not have any adverse effect on BMD compared with a diet providing only 70 g/day of protein during weight loss. Moreover a HP diet seems to preserve BMC during weight loss.

Sacks *et al.*[119] randomly assigned 811 overweight adults to one of four diets to assess the possible advantage for weight loss of a diet that emphasizes protein, fat, or CHOs. The primary outcome was the change in BW, after two yrs, in two-by-two factorial comparisons of LF *versus* HF and average protein *versus* HP and in the comparison of highest and lowest CHO content. The nutrient goals for the four diet groups were: 20% fat, 15% protein, and 65% CHOs (LF, average-protein); 20% fat, 25% protein, and 55% CHOs (LF, HP); 40% fat, 15% protein, and 45% CHOs (HF, average-protein); and 40% fat, 25% protein, and 35% CHOs (HF, HP). The four diets also allowed for a dose-response test of CHO intake that ranged from 35% to 65% of energy. Other goals for all groups were that the diets should include 8% or less of saturated fat, at least 20 g of dietary fiber per day, and 150 mg or less of cholesterol per 1 000 kcal. CHO-rich foods, with a low glycemic index,

TABLE XXIII.—*Sargrad* et al. *Study results.*[118]

Body weights and composition	Patients in both the HC and the HP groups lost weight (-2.2±0.9 and -2.5±1.6 kg, respectively, P<0.05). The difference between groups was not significant (P=0.9). In both groups, the loss of body fat (-2.2±0.7 kg in the HC group and-2.6±1.8 kg in the HP group, P<0.05), fully accounted for the loss in BW and there was no change in FFM in either group (58.9±6.6 vs. 59.0±5.9 kg in the HC group and 55.7±5.8 vs. 56.1±6.1 kg in the HP group, not significant).
Dietary intakes	The estimated caloric intakes of the two groups were not significantly different from each other (1 371±63 kcal/ day for the HC and 1 274±57 kcal/day for the HP group). As expected, there were significant differences in protein and CHO consumption. Expressed as percent of calories from CHO, protein, and fat, the HC group consumed 51%±1%, 19%±1%, and 30%±1%, respectively, while the HP group consumed 43%±2%, 27%±1%, and 30%±1%, respectively. Sodium intake was higher in the HC than in the HC group (2 484±177 vs. 1 691±133 mg/day, P<0.005), whereas there were no significant differences in potassium or calcium intakes. Fiber intake was lower in the HC group than in the HP group (15±1 vs. 18±1 g/day, P=0.02). Cholesterol intake was not significantly higher in the HP group.
REE	Initial REEs were similar in the two groups (HC 1 865±112 vs. 1 691±141 kcal/day, NS) and did not change during the study.
Fasting glucose, free fatty acids, and insulin levels.	Between the baseline and 8-wk visits, fasting plasma glucose levels decreased from 8.8±0.9 to 7.2±1.0 mmol/L (P<0.02) in the HC group and did not change in the HP group (8.3±1.2 vs. 8.3±1.5 mmol/L, NS). Basal free FA levels decreased from 714±76 to 527±60 µmol/L (P<0.04) in the HC group and remained unchanged in the HP group (735±43 vs. 726±72 µmol/L, NS). Basal serum insulin levels tended to decrease in the HC group (101±22 vs. 90±20 pmol/L, not significant) and in the HP group (94±11 vs. 75±25 pmol/L, not significant). Similar non significant changes were seen in C-peptide concentrations in the HC group (from 0.93±0.2 to 0.83±0.17 nmol/L, not significant) and in the HP group (from 0.83±0.17 to 0.80±0.17 nmol/L, not significant).
HbA1c	HbA1c decreased in the HC group (from 8.2%±0.5% to 6.9%±0.4%, P<0.03) whereas the decrease in the HP groups (from 7.6%±0.9% to 6.6%±0.5%) was not significant.
Insulin-stimulated glucose uptake	GIR increased significantly in the HC group (from 12.8±3.3 to 17.2±2.2 µmol/kg/min, P<0.03), whereas there were no significant changes in the HP group.
Insulin suppression of EGP	Basal and insulin suppressed rates of EGP were similar before and after the HC diet and the HP diet.
Blood pressure	In the HP group both the diastolic (-18±9.0 mmHg, P<0.05) and systolic (-10.5±2.3 mmHg, P<0.03) BP decreased between the baseline and the 8-wk visits (visit 1 and visit 2), whereas BP in the HC group remained unchanged.
Plasma lipids	Serum concentrations of total cholesterol, LDL, and HDL-C and triacylglycerols tended to decrease similarly in both groups, but only the small decrease in HDL (from 0.99 to 0.94 mmol/L) in the HC group, and the decrease in LDL (from 2.24 to 1.92 mmol/L) in the HP group were statistically significant.
Renal function	Serum Cr levels did not change in response to the HC diet (79.56±8.84 vs. 88.4±8.84 µmol/L, not significant) or to the HP diet (79.56 µ17.68 vs. 88.4 µ17.68 µmol/L, not significant). Blood urea nitrogen levels also did not change in response to the HC diet (4.64±0.71 vs. 6.43±1.43 mmol/L, not significant) or to the HP diet (6.78±1.43 vs. 5.71±1.07 mmol/L, not significant).

TABLE XXIV.—*Skov* et al. *Study results.*[119]

Weight loss	Weight loss after 6 months of dietary intervention was 5.1 kg in the LP group and 8.9 kg in the HP group (difference, 3.7 kg 1.3 to 6.2 kg; P<0.001), whereas weight remained stable in the control group. Fat loss was 4.3 kg in the LP group and 7.6 kg in the HP group (difference, 3.3 [1.1 to 5.5] kg; P<0.0001). No fat loss was seen in the control group. Loss of FFM was 0.9 kg in the LP group and 1.3 kg in the HP group (not significant).
Body mineral content	BMC In both intervention groups, there was a similar decline in BMC during the 6-month intervention period, independent of gender. After 3 months, BMC was reduced by 62±13 g in the LP group and by 87±13 g in the HP group (not significant), both being different from the control group (difference LP vs. control, 59 g [15 to 102 g] P<0.0001; HP vs. control, 85 g [41 to 129 g], P< 0.0001). After 6 months, BMC had declined by 85±13 g (3%) in the LP group and by 111±13 g (4%) in the HP group (not significant), again being different from the control group (difference in LP vs. control, 89 g [34 to 145 g], P<0.0001; HP vs. control, 119 g [64 to 174 g], P<0.0001). At the extreme, the subject with the largest weight loss (21 kg) lost 455 g bone mineral after 6 months. BMC did not change in the control group during the intervention. We found no significant differences between men and women in the effect of changes in BMC. There were no effects by time or group on BMD during the intervention. BMD in the lumbar region remained constant throughout the intervention in all three groups. The change in BMC after 6 months of intervention was positively associated with change in BW (r=0.63; P< 0.0001) and fat mass (r=0.83; P<0.0001). Adjusting BMC, explaining an additional 5% increase (P<0.01) together with changes in fat mass and FFM (r=0.85; P<0.001).

were recommended in each diet. Each participant's caloric prescription represented a deficit of 750 kcal per day from baseline, as calculated from the person's REE and activity level. Of 1 638 participants who were screened, 811 (50%) were randomly assigned to a diet, and 645 (80% of those assigned) completed the study (*i.e.*, provided a BW measurement at two yrs). Baseline characteristics were similar among participants assigned to the four diets and between those who were assigned to a diet and those who completed the study. The results are shown in Table XXV.

Moran *et al.*[120] compared the effects of isocaloric test meals with differing protein to fat ratios on fasting and postprandial ghrelin, insulin, glucose, appetite, and energy expenditure before and after weight loss on the respective dietary patterns. The study design was a randomized parallel design of 12 wks of weight loss (6 MJ/day) and four wks of weight maintenance (7.3 MJ/day) with meals administered at wk 0 and 16. The study was performed at an out-patient research clinic. Fifty-seven overweight (BMI: 33.8±3.5 kg/m^2) hyperinsulinemic men (N.=25) and women (N.=32) were studied. Interventions: HP/LF (34% protein/29% fat) or SP/HF (18% protein/45% fat) diets/meals were given. The main outcome measures were weight loss and fasting and postprandial ghrelin, insulin, glucose, appetite, and energy expenditure before and after weight loss. The prescribed diets were: 1) HP/LF diet (40% energy as protein 136 g/day), 30% fat (46 g/day; <10% saturated fat), (30% CHO, and 21 g fiber); 2) SP/HF diet (20% energy as protein 67 g/day), 50% fat (76 g/day; <10% saturated fat), 30% CHO, and 27 g fiber. Fifty-seven (25 men and 32 women; age: 50.3±9.9 yrs; BMI: 34.0±3.5 kg/m^2; mean weight, 97.2±14.0 kg; mean±SD) completed the intervention. Sixteen subjects dropped out of the study (work commitments, N.=2; health reasons, N.=3; personal reasons, N.=6; lost to follow-up, N.=5), five subjects before study commencement, and 11 subjects during the study. There were no differences in the characteristics of subjects in each diet group at baseline. Baseline weight (111.6±3.8 *vs.* 90.0±2.4 kg; P<0.001) and fasting glucose (107.1±7.1 *vs.* 94.6±1.8 mg/dL or 6.0±0.4 *vs.* 5.3±0.1 mmol/L; P=0.048) were higher for males than females. Both diets

TABLE XXV.—*SSacks* et al. *Study results.*[119]

Weight loss	The amount of weight loss after 2 yrs was similar in participants assigned to a diet with 25% protein and those assigned to a diet with 15% protein (3.6 and 3.0 kg, respectively; P=0.22) and among those who completed each of those diets (4.5 and 3.6 kg, respectively; P=0.11). Weight loss was the same in those assigned to a diet with 40% fat and those assigned to a diet with 20% fat (3.3 kg, P=0.94) and was similar among those who completed each of those diets (3.9 and 4.1 kg, respectively; P=0.76). There was no effect on weight loss of CHO level through the target range of 35 to 65%. The change in WC did not differ significantly among the diet groups. Most of the weight loss occurred in the first 6 months. Changes from baseline differed among the diet groups by less than 0.5 kg of BW and 0.5 cm of WC. After 12 months, all groups, on average, slowly regained BW. A total of 185 of the participants (23%) continued to lose weight from 6 months to 2 yrs; the mean (±SD) additional weight loss was 3.6±3.5 kg, for a mean total loss from baseline of 9.3±8.2 kg, with no significant differences among the diet groups. At 2 yrs, 31 to 37% of the participants had lost at least 5% of their initial BW, 14% to 15% of the participants in each diet group had lost at least 10% of their initial weight, and 2% to 4% had lost 20 kg or more (P>0.20 for the comparisons between diets).
Risk factors for cardiovascular disease and diabetes	All the diets reduced risk factors for CVD and diabetes at 6 months and 2 yrs. At 2 yrs, the two LF diets and the highest-CHO diet decreased LDL-C levels more than did the HF diets or the lowest CHO diet (LF vs. HF, 5% vs. 1% [P=0.001]; highest-CHO vs. lowest CHO, 6% vs. 1% [P=0.01]). The lowest CHO diet increased HDL-C levels more than the highest CHO diet (9% vs. 6%, P=0.02). All the diets decreased TG levels similarly, by 12% to 17%. All the diets except the one with the highest CHO content decreased fasting serum insulin levels by 6% to 12%; the decrease was larger with the HP diet than with the average-protein diet (10% vs. 4%, P=0.07). BP decreased from baseline by 1 to 2 mmHg, with no significant differences among the groups (P>0.59 for all comparisons). The metabolic syndrome was present in 32% of the participants at baseline, and the percentage was lower at 2 yrs, ranging from 19 to 22% in the four diet groups (P=0.81 for the four-way comparison).
Adherence, diet, acceptability, satiety and satisfaction	Reported energy intakes and physical activity were similar among the diet groups. The participants who completed the study had a mean weight loss of 6.5 kg at 6 months, which corresponds to a reduction in daily energy intake of approximately 225 kcal. There was a larger increase from baseline in the HDL-C level (biomarker for dietary CHO) in the lowest-CHO group than in the highest-CHO group (a difference in the change of 2 mg per dL at 2 yrs); this difference corresponds to a predicted difference in CHO intake of 6%. There was a larger decrease in urinary nitrogen excretion from baseline in the average protein group than in the HP group (a difference in the change of 1.6 g at 6 months and 0.8 g at 2 yrs); these differences correspond to a difference in dietary protein of 10 g per day and 5 g per day, respectively. The RQ was 0.84 at baseline in both the HF and LF groups, and the between-group difference in the change at 2 yrs (the value in the HF group minus the value in the LF group) was -0.02 (P=0.002). Craving, fullness, and hunger and diet-satisfaction scores were similar at 6 months and at 2 yrs among the diets.
Weight change according to attendance at group sessions and dietary adherence	Attendance at group sessions strongly predicted weight loss at 2 yrs (0.2 kg for every session attended) and was similar among the diet groups (P=0.22 for a test of difference in slopes). Adherence to the goal for protein intake was associated with more weight loss only in the HP groups, and adherence to the goal for fat intake was associated with more weight loss only in the LF groups (P<0.001). A LF intake of 25% was associated with increased weight loss in the LF groups but not in the HF groups, and a HP intake of 24 to 25% was associated with increased weight loss in the HP groups but not in the average-protein groups. Attendance at group sessions was associated with adherence to the fat and protein goals only in the HP and LF groups. Serious adverse events were reported by 57 participants (7%); there were no significant differences in the rates among diets. The ratio of urinary microalbumin to Cr was more than 30 in five participants in the average-protein group and in 5 participants in the HP group at 6 months and in seven participants, all in the average-protein groups, at 2 yrs.

TABLE XXVI.—*Moran* et al. *Study results.*[120]

Body weight, body composition, and fasting and postprandial insulin and glucose	A mean weight loss of 9.2±0.7 kg or 9.5% (P<0.001) occurred independently of diet, and weight was maintained effectively over the 4-wk EB stage (P=0.07). From wk 0–16, reductions in fat mass (13.9±1.5%; P<0.001), AbFM (17.1±2.0%; P<0.001), BLM (6.0 _ 0.6%; P <0.001), fasting glucose (3.5±1.5%; P=0.024), fasting insulin (13.8±9.3%; P=0.001), and fasting HOMA (13.3±11.7%; P=0.001) occurred with no diet or diet by gender interactions. There was a time by gender interaction, such that the men lost more weight and AbFM than the women (respectively, 10.9±1.2 vs. 7.9±0.8 kg [P=0.028] and 2.1±0.3 vs. 1.3±0.3 kg [P<0.039]). At wk 16 compared with wk 0, there were reductions in the postprandial glucose (4.1±1.6%; P=0.01) and insulin (12.3±6.9%; P<0.001) concentrations, with no effect of diet or any diet by gender interaction.
Fasting and postprandial ghrelin	At baseline, there were no differences in fasting plasma ghrelin concentrations between the diet groups. Fasting ghrelin concentrations increased from 402.5±40.0 to 557.9±35.5 pg/mL (119.1±11.7 to 165.2±10.5 pmol/L) from wk 0 to 16 (P<0.001), with no effect of diet or gender. Ghrelin concentrations decreased during the MTT at both wk 0 and There was a change in the postprandial ghrelin profile from wk 0–16 (P=0.043), such that the maximal postprandial decrease in ghrelin occurred at 120 min at wk 0 and at 60 min during wk 16 (P<0.05). The decrease in ghrelin over the first 60 min of the postprandial period was significantly greater at wk 16 than at wk 0 (-77.2±19.8 vs. -13.6±19.2 pg/mL or -22.9±5.9 vs. -4.0±5.7 pmol/L, respectively; P=0.017). There was also a trend for the postprandial nadir to be increased from wk 0 to 16 (from -70.5±10.0 to -109.5±20.7 pg/mL or -20.9±3.0 to -32.4±6.1 pmol/L; P=0.06). There was a trend for the postprandial ghrelin AUC to be improved from wk 0 to 16, such that a 5 196.3±2 993.5 pg/mL (1 538.2±886.1 pmol/L) greater reduction in AUC ghrelin concentrations occurred (P=0.087). There were no diet or diet by gender effects on changes in postprandial ghrelin. Females had a higher fasting ghrelin at wk 0 and 16 (P=0.013 and P=0.024 for effect of gender) than males, but this effect was not significant when adjusted for baseline weight.
Energy expenditure and visual analog scores (VASs)	In summary, from wk 0–16 postprandial RQ increased by 1.8% (P=0.007), and there was a trend for REE to be reduced (4.0=1.6%; P=0.055), but neither was affected by diet composition. There was a time by diet effect (P=0.015) for the thermic effect of feeding (TEF), such that it decreased by 3.6±0.7% for the SP/HF diet compared with 0.32±1% for the HP/LF diet. There was a significant reduction in the 3 h hunger response (P=0.018) and a significant increase in the fasting hunger scores (48.1±4.2 vs. 35.7±4.1 mm; P=0.026) with no diet or diet by gender interaction. There was no diet or diet by gender effect on the desire to eat responses to the MTT; however, subjects wanted less to eat after the HP/LF compared with the SP/HF MTT at both wk 0 and 16 (overall diet effect, P=0.02).

were well tolerated, with no adverse events reported, and all subjects complied with the dietary intervention based on the urinary urea/Cr ratio and reported individual macronutrient profiles. The percentage of energy derived from the macronutrients of both diets remained the same during EB as during the energy-restricted phase, but the energy content of each diet increased to achieve EB (P<0.001). Total energy intake was not different between diets during ER or EB. The results are shown in Table XXVI.

The Authors conclude that exchanging protein for fat produces similar weight loss and improvements in metabolic parameters and ghrelin homeostasis; the reduced appetite observed, with increased dietary protein, appears not to be mediated by ghrelin homeostasis; decreases in surrogate markers of insulin resistance are associated with improvements in ghrelin, suggesting a regulatory role of insulin in ghrelin homeostasis; despite a reduction in the desire to eat after an HP/LF test meal, there is no effect of

TABLE XXVII.—*Moran* et al. *Study results.*[122]

Diet and compliance	All subjects complied well with the intervention based on urinary urea/Cr and reported individual macronutrient profiles. For the PCOS subjects, exercise levels were similar between the two dietary groups. As designed, protein intake was higher and CHO intake was lower on the HP than on the SP diet during both ER (26.8 vs. 15.9%) and weight maintenance (27.0 vs. 15.6%) (P<0.001). Minor differences existed between the PCOS and non-PCOS subjects in diet composition for polyunsaturated fat acid intake in ER and fiber intake in weight maintenance (P≤0.05). When comparing the SP and HP diets, energy intake was not significantly different in either ER (6.3±0.09 MJ) or weight maintenance (7.75±0.21 MJ) between the two diets. Significant differences existed between the two diets for polyunsaturated fat acid and cholesterol in ER and weight maintenance and fiber in ER (P≤0.05).
Weight and body composition	Over the 16 wk, there was no significant difference in weight loss between the SP and HP diets (7.0±0.7 vs. 7.2±0.9 kg) or the PCOS and non-PCOS subjects (7.0±0.8 vs.7.2±0.6 kg) with a mean weight loss of 7.1±0.6 kg (7.5%) for combined subjects. Weight was maintained during EB with a total mean gain of 0.15±0.19 kg and no differences between the SP and HP diets or the PCOS and non-PCOS subjects, indicating good compliance with the weight maintenance regimen. There was no differential effect of diet composition or PCOS status on changes in body composition over the 16 wk, with an reduction in BMI (7.5%), total fat mass (13.4%), BLM (2.5%), and AbFM (13.3%) occurring for all subjects. There was no effect of diet composition or PCOS status on changes in fasting glucose, insulin, HOMA, or leptin over the study duration. There was no effect of diet composition or PCOS status on the insulin AUC after the MTTl at wk 0 or 16 or on the change in MTT insulin AUC with weight loss. The insulin response to the test meal was reduced by 25% after the 16-wk intervention. There was no effect of PCOS status on the glucose AUC after the MTT at wk 0 or 16. However, the SP meal resulted in a 2.9 times greater AUC at wk 0 (P=0.019) (69.9±16.5 vs. 25.3±8.8 mg/dlx180 min or 3.9 ±0.9 vs. 1.4±0.5 mmol/L x180 min) and a 3.4 times greater AUC at wk 16 (P=0.024) (57.8±12.1 vs. 18.4±11.2 mg/dL x180 min or 3.2±0.7 vs. 1.0±0.6 mmol/L x180 min), compared with the HP test meal. There was no change in MTT glucose AUC with weight loss.
Fasting and postprandial glucose, insulin, and HOMA	No difference in baseline fasting ghrelin between the HP and SP diets was observed. After the dietary intervention, there was no significant differential effect of diet composition on changes in fasting ghrelin between the SP and HP diets with respective increases of 67.9±26.7 (20.1±7.9) and 120.6±40.7 pg/ml (37.5±11.8 pmol/L) observed from wk 0 to wk 16 (P=0.415 for diet x time effect). However, fasting ghrelin was significantly higher by 70.4% in the non-PCOS subjects, compared with the PCOS subjects (P=0.011) (355.9±60.6 vs. 205.3±23.1 pg/mL or 103.6±17.2 vs. 60.8±6.8 pmol/L), and non-PCOS subjects had a significantly greater increase in fasting ghrelin, compared with PCOS subjects from wk 0-16 (57.5 vs. 34.0%) (161.7±56.4 vs. 55.8±17.2 pg/mL or 47.9±16.7 vs. 16.5±5.1 pmol/L) (P=0.033 for diet x PCOS status effect). Improvement in fasting ghrelin after weight loss occurred in ER. No further changes in fasting ghrelin occurred during the weight maintenance period. There was no differential effect of diet composition or PCOS status on the ghrelin response to the test meal (MTT ghrelin) at wk 0 or 16. For combined subjects at wk 0, there was no significant decrease in ghrelin after the test meal. For combined subjects at wk 16, there was a significant decrease in MTT ghrelin (-69.8±24.2 pg/mL or -21.3±5.5 pmol/L, P=0.002). There was no effect of diet on the change in MTT ghrelin from wk 0 to wk 16. However, there was a time x PCOS status interaction; the non-PCOS subjects showed a significantly greater decrease in postprandial ghrelin from wk 0 to wk 16 than the PCOS subjects (-144.1±58.4 vs. -28.9±14.2 pg/mL or -42.7±17.3 vs. -8.5±4.1 pmol/L) (P=0.02 for PCOS status_time effect).
Fasting and postprandial ghrelin VASs	There was no differential effect of diet composition or PCOS status on fasting VAS measures. There was no differential effect of diet composition on the MTT VAS measures. Data were therefore combined to assess subjects with and

(Continued)

TABLE XXVII.—*Moran* et al. *Study results.*[122]

	without PCOS. There was no significant difference between the PCOS and non-PCOS subjects with regard to changes in MTT-VAS-AUC scores over time. However, at both wk 0 and 16, the PCOS subjects were significantly more hungry (P=0.007) and less satiated (P=0.001) than the non-PCOS subjects during the MTT. This effect was apparent by 120 min (for satiety at wk 0 and 16) and 180 min (for hunger at wk 0 and 16) (P<0.05). The non-PCOS subjects had a 2.9 times higher AUC for satiety at wk 0 and a 1.66 times higher AUC for satiety at wk 16, compared with the PCOS subjects (P=0.003). For all subjects, there was a reduction in the desire to eat during the MTT from wk 0 to wk 16 with a 1.5 times higher AUC at wk 16 (P<0.001). There was no differential effect of diet composition or PCOS status on any of the fasting VAS values. However, the baseline desire to eat increased from wk 0 to wk 16 (54.8±5.0 to 72.8±4.7 mm)(P< 0.001).

macronutrient composition on changes in postprandial ghrelin before or after weight loss. The satiating effect of dietary protein is probably mediated by factors other than ghrelin.

Moran *et al.*[122] investigated the effect of diet on PCOS. Overweight women with and without PCOS were randomized to a HP (40% CHO, 30% protein; 10 PCOS, six non-PCOS) or SP diet (55% CHO, 15% protein; 10 PCOS, six non-PCOS) for 12 wks of ER and four wks of weight maintenance. The study comprised 32 subjects (weight: 94.5±2.3 kg; BMI: 35.4±0.9 kg/m^2; age: 35.7±1.1 yrs). At baseline, apart from age, there was no difference between the groups. HP PCOS had greater AbFM than HP non-PCOS subjects (P=0.024). Both diets were well tolerated with no adverse events reported. The results are shown in Table XXVII.

This study confirms that the postprandial ghrelin response is impaired in obesity and that weight loss increases fasting ghrelin levels. Moreover weight loss restores the impaired postprandial ghrelin response and subjective measures of desire to eat appear to reflect the changes in fasting and postprandial ghrelin. This study shows differences in fasting ghrelin between subjects with and without PCOS and that ghrelin homeostasis and acute measures of satiety and hunger are significantly impaired in women with PCOS both before and after weight loss.

Keogh *et al.*[123] designed a 52 wks outpatient randomized parallel-designed study involving subjects that were prescribed energy restricted (6 000 kJ) diets that were either high monounsaturated fat (HMF), 50% of energy as fat, 76 g/day and 20% of energy as protein (67 g/day) or high protein (HP), 40% of energy as protein, 136 g/day. CHO was restricted to 30% of energy (110 g/day) and saturated fat and 10% of energy in both diets. Following weight loss subjects were asked to maintain the same dietary pattern without intensive dietary counselling for the following 36 wks. The results are shown in Table XXVIII.

Subjects, although modest CHO restriction was not maintained over the course of the study, maintain a 6 kg weight loss from baseline which is associated with improvements in the CVD risk markers, namely insulin, HDL-C, triacylglycerol and CRP, at the end of 52 wks.

Luscombe *et al.*[124] determined the effect of a HP diet compared with a LP diet on weight loss REE, and the TEF in subjects with type 2 diabetes during moderate ER. In this study, 26 obese subjects with type 2 diabetes consumed a HP (28% protein, 42% CHO) or LP diet (16% protein, 55% CHO) during eight wks of ER (1 600 kcal/day) and four wks of EB. BW and composition and REE were measured, and the TEF in response to a HP or LP meal was determined for 2 hours, at wks 0 and 12. The HP diet consisted of 30% energy from protein (~110 g/day) and 40% from CHO, whereas the LP diet consisted of 15% energy from protein (~60 g/day) and 55% from CHO. Diets were matched for FA profile (8% saturated, 12% MUFA, and 5% PUFA). The diets included pre-weighed portions of beef and chicken suitable for six meals per

TABLE XXVIII.—*Keogh* et al. *Study results.*[123]

Weight loss	Weight loss from baseline for the 38 subjects who completed the study was 6,2 (SD 7,3) kg (P<0.01 for time with no diet effect, 7,6 (SD 8,1) vs. 4,8 (SD 6,6) kg HMF vs. HP, respectively). Weight regain from wk 16 to wk 52 was 3.8 (SD 4,5) kg (P<0.001 for time with no diet effect, 2.6 (SD 4·4) vs. 4,9 (SD 4.4) kg HMF vs. HP). When an intention to treat analysis was performed with baseline weight carried forward for the dropouts, weight loss was 4.1 (SD 6.7) kg (P<0.01 for time with no diet effect). To assess whether there were differences in weight loss if protein intake remained high at the end of the study, the group was divided by the median reported protein intake into two groups with an average intake of 75 (SD 12) g (19 [SD 3] %) and 111 (SD 19) g (23 [SD 4] %) protein. Weight loss was 6.4 (SD 6.7) kg in the LP reporters vs. 7.0 (SD 8.1) kg in the HP reporters (NS);macronutrient intake was confirmed by urea/Cr excretion (27·6 [SD 7.4] vs. 33.9 [SD 5.8], P<0,05).
Weight and body composition	Twenty-five subjects attended for body composition measurements, eleven HMF (three male) and fourteen HP (five male), by DEXA, at the end of the study. These subjects had a mean weight loss of 8,1 (SD 6.9) kg with a fat to lean ratio of 2.5:1 (2.1 [SD 2.7] kg LBM and 5.2 [SD 5.5] kg fat, P<0.001 for time, with no effect of diet.
Reported dietary intake and dietary compliance	Thirty-five subjects (16 HMF, 19 HP) completed 3 d weighed food records. There was no change in energy or nutrient intake with time during follow-up. As expected, men had higher energy intakes than women throughout follow-up, 9 271 (SD 2 655) vs. 6 574 (SD 1 292), 8 575 (SD 1 086) vs. 6 836 (SD 1 127) and 8 194 (SD 2 493) vs. 6 721 (SD 883) kJ, men vs. women at 28, 40 and 52 wks (P<0.001). Overall, HMF subjects reported lower energy intakes than HP at all time-points (P<0.01) but this was a function of the higher energy intake in the men on the HP diet. Reported absolute protein intake was higher in men (117 [SD 25]) vs. 93 [SD 25], 113 [SD 28] vs. 91 [SD 24] and 102 [SD 25] vs. 90 [SD 21] g/d, men vs. women at 28, 40 and 52 wks [P<0.001]) and remained higher overall in HP at all time-points (P<0.001). However, there were no differences when the protein intake was expressed as a percentage of energy. At the end of the study saturated fat intake was 11 (SD 3)% in both groups, monounsaturated fat 12 (SD 5) HMF vs. 13 (SD 3) % HP (NS) and polyunsaturated fat 5 (SD 2) % in both groups. In those subjects in the upper half of reported protein intakes, reported energy intake was also higher (8 039 [SD 2298] vs. 6 427 [SD 972] kJ, P<0.01). However, despite this, weight loss was the same in both groups at the end of the study. In a multivariate regression, model predictors of weight loss at the end of the study were sex, age and reported percentage energy from protein (R2 0.22, P<0·05 for the whole model).
Urea/creatinine ratio	Overall, there was no difference in urea/Cr ratio between the groups at baseline (34 [SD 10] vs. 42 [SD 11], HMF vs. HP) or at the end of the study (28 [SD 6] vs. 34 [SD 7], HMF vs. HP).
Markers of bone turnover	The Pyr/Cr ratio was decreased at the end of the study with no difference between groups (94.00 [SD 38.08] vs. 61.45 [SD 18.84] nmol/mmol, baseline vs. 52 wks, P<0,01). The Dpr/Cr ratio was also decreased (26.39 [SD 10.24] vs. 16.48 [SD 6.87], P<0.01 for time, no effect of diet). The 24 h calcium excretion was not different at the end of the study (3.62 [SD 3.01] vs. 3.80 [SD 2.74] mmol/L) with no differences between groups.
Blood pressure and urinary sodium	There was a trend for a reduction in systolic BP at the end of the study (130 [SD 14] vs. 127 [SD 13] mmHg, baseline vs. 52 wks, P=0.08 for time, no effect of diet) but diastolic BP was not different (73 [SD 10] vs. 74 [SD 10] mmHg). There was no difference in 24 h sodium excretion between the groups at baseline or 52 wks (153 [SD 80] vs. 177 [SD 59] mmol/24 h, baseline vs. 52 wks). Fasting plasma insulin was reduced at the end of the study (P<0.01 for time, no effect of diet, 13.9 (SD 4.6) vs. 10.2 (SD 5.2) mIU/L, baseline vs. 52 wks. Fasting plasma glucose was not different. NEFA were not different at the end of the study

(Continued)

TABLE XXVIII.—*Keogh* et al. *Study results.*[123]

Insulin glucose and non-esterified fatty acids (NEFA)	(332 [SD 136] vs. 291 SD 122] mmol/L, baseline vs. 52 wks). The calculated homeostasis Model Assessment Index (fasting insulin concentration [m U/mL] x fasting glucose concentration [mmol/L]/22.5) was 3.62 (SD 1.97) at baseline and fell to 2.52 (SD 1.34) at the end of the study (P<0.01) with no difference between diets.
Lipids	At the end of the study HDL-C was higher overall with no effect of diet (1.04 [SD 0.29] vs. 1.19 [SD 0.26] mmol/L, P<0.001 for time). Triacylglycerol was reduced at the end of the study (2.22 [SD 1.15] vs. 1.85 [SD 1.23] mmol/L, P<0.05 for time with no effect of diet), however, neither total cholesterol nor LDL-C were different after 52 wks.
C-reactive protein	There was a reduction in CRP at the end of the study with no difference between diets (3.97 [SD 2.84] vs. 2.43 [SD 2.29] mg/L, P<0.01).

wk, shortbread biscuits, Canola Lite margarine, and Sunola oilplus (MeadowLea Foods), Kraft Free cheese (3% fat; Kraft Foods), skim milk powder, and diet yogurt for the HP diet and sultanas and rice for the LP diet. The energy content of the HP and LP diets was statistically the same during ER, whereas the percent of energy derived from protein, CHO, and fat was different (P<0.01). The results are shown in Table XXIX.

This study shows that short-term replacement of some dietary CHO with protein, under energy restrictive conditions, does not blunt the diet-induced fall in REE or increase the TEF to a level that is large enough to facilitate weight loss in patients with type 2 diabetes. The Authors conclude that the reduction in calories appears to be the most important determinant of weight loss in this population, at least in the short term and that ad-libitum HP diets may lead to greater weight loss in the longer term because subjects are better able to comply with the diet, possibly as a result of increased satiety.

Svendsen *et al.*[125] investigated the effect of an energy-restrictive, HP diet with or without exercise on muscle morphology and biochemistry in moderately overweight postmenopausal women (age: 49-58 yrs; BMI: 25-42 kg/m^2) who were randomly assigned to three groups for 12 wks of intervention; namely, a control group, a group on a 4.2 MJ/day diet, and a group on 4.2 MJ/day diet combined with aerobic and anaerobic exercise. Muscle morphology and biochemistry analysis were performed in 69 and 58 women, respectively. The abdominal-to-total-body fat tissue mass (FTM) tended to be positively correlated with the diffusion index (muscle area per capillary) of muscle fiber type I, IIA, and IIB (r=0.2-0.3) at baseline. However, there were no statistically significant correlations between BW, BMI, FTM and lean tissue mass (LTM), the W/H or the abdominal-to-total-body FTM, and muscle morphology or biochemistry at baseline. The VO_{2max}/kg BW was positively correlated to the number of capillaries per fiber type I, IIA, and IIB (r=0.3-0.4, P<0.01) but not to the fiber area or composition. The VO_{2max} was, furthermore, positively correlated with the activities of citrate synthase (CS) and glycogen synthase (both V_{max} and FV) (r=0.3-0.4). The RER (respiratory exchange ratio=indicator of CHO and fat oxidation) at the submaximal workload (30 W) was not correlated with muscle morphology or biochemistry, except by a negative correlation with glycogen synthase (V_{max} and FV, r about -0.3). There were no statistically significant correlations between RER and weight, BMI, FTM and LTM, the W/H or the abdominal-to-total-body FTM. There were no significant associations between changes in RER, BMI, VO_{2max}, body composition, or fat distribution parameters and changes in muscle morphology or biochemistry parameters. There were no statistically significant differences between groups in baseline values. At baseline, the women had a very high proportion of type IIB muscle fibers, nearly double as many as type IIA fibers. The muscle fibers and capil-

TABLE XXIX.—*Luscombe* et al. *Study results.*[124]

Urea/creatinine ratio	The urea/Cr ratio was significantly different between diets (P=0.003). An increase from baseline of 13.2±5% and 24.5±7% at wks 8 and 12, respectively, was observed on the HP diet and a decrease from baseline of 7.7±5% and 2.9±5% at wks 8 and 12, respectively, was observed on the LP diet. The 24-h activity recalls revealed no significant differences for the previous day's activity level at wk 0 as compared with wk 12.
Weight and body composition	After 8 wks of ER and 4 wks of EB, the mean weight loss was 4.6 kg (P<0.001), but the magnitude of change was not dependent on diet composition (–4.9±0.4 vs. -4.3±0.7 kg on the HP and LP diets, respectively; P=0.6). Percent body fat and total fat mass were reduced 3±0.04% and 4.5±0.04 kg (11.9%), respectively, at wk 12 (P<0.05). There was a small not significant decrease in BLM (0.3±0.4 kg) (P=0.4).Diet composition had no effect on the change in any of the body composition variables. There was no effect of gender or diet-by-gender interaction on the decrease in percent body fat or total fat mass. At wk 0, there was no difference between men and women for AbFM (10.02±1.0 vs. 10.07±0.6 kg, respectively; P=0.9). After 12 wks, however, AbFM had decreased more in men than in women (-1.5±0.2 vs. -0.96±0.2 kg, respectively; P<0.001).
Resting energy expenditure, respiratory quotient, and the thermic effect of feeding	There was no effect of diet composition on REE (P=0.3). However, there was an effect of gender on REE. When expressed per kilogram of BLM, REE was greater in women than in men (38 ±0.7 vs. 34±0.9 kcal/day, respectively; P=0.013), whereas when expressed as an absolute value, REE was greater in men than women (2 084±93 vs. 1 697±44 kcal/day, respectively; P<0.001). At wk 12, after stabilization at a reduced weight, REE was reduced 4.1% as compared with baseline (from 1 900±65 to 1 822±58 kcal/day; P=0.023). The decrease in REE was not related to diet composition (P=0.2) or gender (P=0.5). Fasting RQ was not affected by diet composition (P=0.6) or gender (P=0.5). Postprandial RQ increased more after the LP meal than after the HP meal (overall diet effect, P<0.001). There was NS difference in postprandial RQ from wk 0 to wk 12 (P=0.3). The energy intake during the HP test meal was 573 kcal, whereas for the LP meal it was 656 kcal; therefore, TEF was expressed as kilocalorie of energy produced above the resting metabolic rate per kilocalorie of energy consumed. TEF per kilocalorie of energy consumed was greater (28%) after the HP meal than after the LP meal (0.064 vs. 0.050 kcal x $kcal^{-1}$ energy consumed x2 h^{-1}, respectively; overall diet effect, P=0.003). There was also an overall effect of gender on TEF (P=0.03); TEF was 12.6% greater for men than women (0.062±0.004 vs. 0.055±0.004 kcalxkcal-1 energy consumed x2 h^{-1}, respectively). After 12 wks, TEF was reduced (P<0.001), but there was no effect of diet composition (P=0.8) or gender (P=0.06) on the decrease. A time-by diet- by-gender effect (regardless of whether TEF was expressed as an absolute value or as kilocalorie of energy consumed), with women on the HP diet experiencing an increase in TEF of 0.0002±0.003 kcal xkcal-1 energy consumed x2 h-1 after 12 wks, compared with women on the LP diet, who experienced a decrease of 0.013±0.006 kcal x kcal-1 energy consumed x2 h^{-1}.

laries tended to change, although not statistically significant, in the control group. The results are shown in Table XXX.

This study shows that, in overweight postmenopausal women with a relatively narrow range of body fat, there is no association between muscle morphology or biochemistry and fatness, except that the diffusion distance, *i.e.*, muscle area supplied by one capillary, had increased with increasing abdominal fatness. Weight loss induced by an energy-restrictive HP diet does not cause any changes in muscle morphology, capillarization, glycogen content, or enzyme activities, whereas the addition of exercise causes hypertrophy of muscle fiber type I and IIA, increases the number of capillaries per muscle fiber type I, and increases the oxidative capacity of muscles as judged from the increased enzyme activities.

TABLE XXX.—*Svendsen* et al. *Study results.*[125]

Muscle fiber area and number of capillaries per muscle fiber I	The diet-plus exercise group did significantly increase the area of muscle fiber type I and IIA by ~20-25%, and the number of capillaries per muscle fiber I by ~20%. There were no significant changes in the diet-only group compared with the control group.
Hexokinase (HK) and citrate synthase (CS)	On the other hand, the diet-plus-exercise group did significantly increase the activity of CS by -35% and of HK by ~20% compared with the diet-only group.
Respiratory exchange ratio	The RER (baseline: 0.86±0.06) was significantly decreased in the diet-plus-exercise (-0.039±0.06) and the diet-only groups (-0.017±0.09), compared with the control group (+0.042±0.07) (P<0.002) but with no difference between the two intervention groups.

Parker *et al.*[126] determined the effect of a HP weight loss diet compared with a LP diet on fat and lean tissue and fasting and postprandial glucose and insulin concentrations. The Authors compared an HP diet with an LP diet in 54 obese men and women with type 2 diabetes during eight wks of ER (1 600 kcal) and four wks of EB. The HP diet consisted of 30% energy from protein and 40% energy from CHO and the LP diet consisted of 15% energy from protein and 60% energy from CHO. Diets were matched for FA profile (8% saturated FAs, 12% MUFA, 5% PUFA). These included pre-weighed portions of beef and chicken suitable for 6 meals per wk and shortbread biscuits plus LF cheese (3% fat), diet yogurt, and skim milk powder for the HP diet and rice for the LP diet. The other differences between the diet lay in the amount of meat and chicken (200 *vs.* 100 g), fruit (200 *vs.* 300 g), and whole-meal bread (3 *vs.* 4 slices). Alcohol was not permitted, and a list of free choice vegetables and salad (maximum 2.5 cups) was provided. During the stable weight phase, caloric intake was increased by ~30%, with a further 7 g protein in the LP diet and 21 g in the HP diet. Subjects were matched for BMI, age, sex, FPG, and medication. There were no significant differences between the two groups for weight or BP. Energy intake in the eight-wk ER phase and the four-wk EB phase was not different between the two diets. As planned, protein intake was higher and CHO intake lower in the HP diet than in the LP diet both in ER and EB (P<0.001) with no differences between phases. Saturated fat intake was not different between the diets or the phases, but dietary fiber and dietary cholesterol were significantly different between the diets in both phases. The results are shown in Table XXXI.

The Authors conclude that both dietary patterns resulted in improvements in the CVD risk profile as a consequence of weight loss. The greater reductions in total and AbFM in women and greater LDL-C reduction, observed in both sexes on the HP diet, suggest that it is a valid diet choice for reducing CVD risk in type 2 diabetes.

Haulrik *et al.*[127] investigated the effects of HP and LP and methionine intakes on homocysteine (an independent risk factor for CVD) in 65 overweight subjects. They were randomly assigned to a 6-month intervention with a LP, low-methionine diet (LP: 12% of total energy, 1.4 g methionine/day; N.=25); a HP, high-methionine diet (HP: 22% of total energy, 2.7 g methionine/day; N.=25), both of which had similar fat contents (30% of total energy); or a control diet with an intermediate protein content (N.=15). Protein intake was increased in the HP group mainly through lean meat and LF dairy products. The group differences remained throughout the intervention and were parallel to the changes in protein intake. The results are shown in Table XXXII.

The Author concludes that a diet rich in protein from lean meat and LF dairy products does not increase plasma homocysteine concentrations over six months.

Park *et al.*[128] compared the effects of two wks of supplementation with different classes of macronutrients on gastric function, satiation, and appetite in healthy and overweight subjects. The Authors designed a parallel-group, double-blind study involving

TABLE XXXI.—*Parker* et al. *Study results.*[126]

Urinary urea and urinary albumin excretion	Urine urea fell from 450 to 420 mmol/day on the HP diet and from 428 to 301 mmol/day on the LP diet (P<0.001 for difference) during the weight loss phase and rose to 461 and 344 mmol/day, respectively, in the weight maintenance phase diet (P<0.001 for difference). Urinary urea/Cr ratio was significantly different between diets by repeated-measures ANOVA (P<0.001). Urinary albumin excretion did not change with weight loss on either diet: 24.2 to 19.8 mg/L in the 12 subjects with microalbuminuria on the HP diet and 4.3 to 3.5 mg/L in the 7 subjects on the LP diet.
Weight and body composition	Both men and women lost weight on both diets; however, there was a weak sex by diet interaction (P=0.04), such that men lost more weight on the LP diet (5.8 vs 4.7 kg), whereas women lost more weight on the HP diet (6 vs 4.2 kg). Similarly for total fat mass, men lost more on the LP diet (5.1 vs. 3.8 kg), whereas women lost more on the HP diet (5.3 vs. 2.8 kg), as reflected by a significant sex by diet interaction (P=0.01). A significant sex by diet effect was also observed in the change in AbFM (P<0.02), such that men lost more fat on the LP diet (1.7 vs.1.4 kg), whereas women lost more on the HP diet (1.3 vs. 0.7 kg). Total BLM was reduced significantly with both diets (1.35 kg on the LP diet and 0.52 kg on the HP diet) with NS difference between them.
Glycemic control	Fasting and 1-, 2-, and 3-h plasma glucose concentrations were reduced by both dietary interventions (P < 0.001); however, no significant effects of diet or sex were observed. Fasting and 2-h insulin concentrations were reduced at wks 8 and 12 (both P <0.001). The insulin-glucose product was reduced by 42% at 3 h at wk 12. HbA1c decreased by 9.4% between baseline and wk 12 (P<0.001). There were no significant differences observed for diet or sex.
Continuous low-dose insulin and glucose infusion	SSPG (steady-state plasma glucose) concentrations were significantly reduced (P=0.01) from baseline to wk 12 (12.1 to 10.7 mmol/L) with no difference between diets. Weight loss was the same in both groups. SSPI (steady-state plasma insulin) concentrations decreased significantly (P=0.003) from 523 to 428 pmol/L with no effect of diet or sex. Total cholesterol concentrations decreased more on the HP diet than on the LP diet, as reflected by a diet by time interaction of P=0.009. For all subjects, triacylglycerol concentrations decreased at wk 12 (P<0.001), and there was no diet or sex effect. There was no effect of time or diet for HDL-C concentrations. A significant time by diet effect was observed in the reduction of LDL-C (P=0.009), with a greater decrease in LDL-C Concentrations on the HP diet than on the LP diet.
Blood pressure	Systolic BP fell significantly by 8 mmHg and diastolic BP by 4 mmHg at wk 8 (P <0.001) with no differential effect of diet. During the weight stabilization period between wks 8 and 12, systolic BP rose by 3 mmHg and diastolic BP by 1 mmHg (P<0.001). This was also not affected by diet composition.

52 (14 men, 38 women) healthy normal-weight, overweight, and obese participants (BMI: 19.4-47.0 kg/m^2) aged 18–64 yrs who were randomly assigned to consume different isocaloric diets (N.=13 per diet group) adjusted for BMI and activity level. The standard diet provided 20% of energy as protein, 30% as fat, and 50% as CHO. The HP, HF, and HC diets contained 500 additional kcal in each nutrient class. Demographic characteristics and baseline measurements of satiation from a liquid-nutrient test drink showed no significant differences between the diet groups. The results are shown in Table XXXIII.

The Authors conclude that a HF diet may facilitate adaptive changes that contribute to the development of obesity through reduced postprandial satiation in people with a high baseline MTV. Given the lack of significant changes in the gastric motor functions studied, the data are consistent with the hypothesis that a HF intake influences the central control of appetite and behavioural choices in food intake. An additional effect that may contribute to obesity is adaptation in absorp-

TABLE XXXII.—*Haulrich* et al. *Study results.*[127]

Urinary nitrogen	Analyses of 24-h urinary nitrogen excretion showed subjects' compliance to be high. Twenty–four hour urinary nitrogen increased in the HP group and decreased in the LP group (P=0.0001), with NS changes in the control group.
Weight loss	Weight loss in the HP group was larger than that in the LP group (9.4 compared with 5.9 kg; P=0.0003).
Protein and vitamins intake	No group differences in dietary intake of B vitamins or protein were observed at baseline. After 3 and 6 mo, there were differences between all the groups in protein intake as a percentage of total energy: at 3 months, LP vs. HP and HP vs. control, P=0.0003, LP vs. control, P=0.006; at 6 months, HP vs. LP vs. control, P=0.0003. Methionine intake after 3 months increased in the HP group (55%; P=0.0003), tended to decrease in the LP group (~24%; P=0.06), and remained unchanged in the control group. After 3 months, the HP group had a higher intake of methionine than did the LP and control groups (P=0.0003), whereas no significant differences were observed between the control and LP groups. Methionine intake in the HP group increased further from 3 to 6 months (14%; P=0.03). Group differences remained at 6 months (HP vs. LP and control, P=0.0003). Folate intake increased after 3 months of the intervention in both the HP (60%; P=0.0003) and LP (92%; P=0.0003) groups and remained unchanged in the control group. After 3 mo, the HP and LP groups both had higher intakes of folate than did the control group (P=0.006 and P=0.0003, respectively), whereas no significant differences were observed between the LP and HP groups. There were no changes in folate intake in any of the groups from 3 to 6 months of the intervention. However, differences between all the groups were observed after 6 mo (HP and LP vs. control, P=0.0003; HP vs. LP, P=0.02). Vitamin B-12 intake decreased in the LP group (-49%; P=0.0003) and increased in the HP group (84%; P=0.0003) after 3 mo of the intervention. After 3 months, there were group differences between the LP and HP groups and between the HP and control groups (P=0.0003 and P=0.0009, respectively). There were no significant changes in vitamin B-12 intake in any of the groups from 3 to 6 months. Group differences remained at 6 mo (LP vs. HP and HP vs. control, P=0.0003). No significant differences in vitamin B-6 intake were seen between the HP and LP groups after 3 and 6 months, but the control group had a lower intake than did the 2 intervention groups (P=0.0002). Vitamin B-6 intake increased from baseline to month 3 in the HP (77%; P=0.0002) and LP (73%; P=0.0002) groups. NS changes were seen in any of the groups from 3 to 6 months of the intervention.
Plasma homocysteine	A nonsignificant decrease in total plasma homocysteine (~25%) was observed in the HP group after 3 and 6 months of the intervention. No significant changes were observed in the LP or the control groups, and there were no significant differences between the groups. No diet-by-time interaction (P=0.233) was observed. The homocysteine concentration after 3 months of the intervention showed a significant positive association with baseline homocysteine and an inverse relation with vitamin B-12 and weight change. The plasma homocysteine concentration after 6 months was associated with baseline homocysteine only (P<0.001).

tive function as suggested by fat-induced changes in villus height and nutrient absorption.

Noakes *et al.*[129] evaluated the effects of a diet with a high ratio of protein to CHO during weight loss on body composition, CVD risk, nutritional status, and markers of bone turnover and renal function in overweight women. The subjects were randomly assigned to 1 of 2 isocaloric 5 600-kJ dietary interventions for 12 wks according to a parallel design: 1) a HP, low-saturated-fat dietary pattern (HP group; 34% of energy from protein, 20% from fat [<10% from saturated fat] and 46% from CHO) and 2) a HC, low-saturated-fat dietary pattern (HC group; 17% of energy from protein, 20% from fat [<10% from saturated fat], and 64% from CHO). There were no significant differences in total energy, alcohol and dietary fiber intakes between the diet groups. Total, saturated, and monounsaturated fat intakes were significantly lower in the HC group as the dietary cholesterol intake was. Intakes of the

TABLE XXXIII.—*Park* et al. *Study results.*[128]

Effects on the gastric emptying of solids	The effects of individual classes of macronutrients in excess of caloric requirements on the gastric emptying half-time (GEt1/2) of solids were not significant; standard diet (median: 103 min; interquartile range [IQR]: 88-125 min), HP diet (median: 114 min; IQR: 100-137 min), HC diet (median: 119 min; IQR: 105-125 min), and HF diet (median: 118 min; IQR: 97-128 min).
Effects on maximum tolerated volume and postprandial symptoms	There was an interaction between treatment group and baseline maximum tolerated volume (MTV) ($P < 0.01$). An effect of fat was detected in subjects with high baseline MTV values ($P<0.05$). For example, in those subjects with high baseline MTV values (above the median value for the entire group) who consumed the HF diet, MTV values 2 wk after the HF diet were higher than MTV values in other diet groups. The individual symptoms did not differ significantly between the diet groups.
Effects on gastric volumes	Fasting gastric volumes did not differ significantly between the 4 diet groups. Relative to the other diet groups, the fasting gastric volume in the HF diet group was numerically, although not statistically, greater (P=0.11; Figure 4, left panel). The HF and HP diets contained the same amounts of CHO and reciprocal amounts of fat and protein. The comparison between fasting gastric volumes in these 2 groups was not significant in a post hoc 2-group comparison (P=0.09). The changes in postprandial volume relative to fasting were not significantly different between the groups.
Effects on food intake at an ad libitum meal	Total calories, total weight of the food, and the distribution of macronutrients consumed at a standard ad libitum meal were not significantly different between the diet groups. A significant association was found between BMI and the amounts of CHO (Spearman r=0.44, P=0.002) and protein (Spearman r=0.30, P=0.037) consumed at the ad libitum meal offered in the study, particularly CHO.
Gastric functions in different BMI groups across all diets and assessment of study power	No significant differences between normal-weight or overweight and obese persons in the GEt1/2 of solids, MTV, aggregate symptom score, or fasting and postprandial gastric volumes were observed after ingestion of each preload meal. The overall observed variation with no imputation in the primary endpoints was very similar to the estimates that were used before the study to assess the chosen sample sizes, e.g., for GEt1/2 the observed CV was 21%, whereas the pre-study estimate was 31%. Similarly, for fasting gastric volume, the observed CV was 25%, and the pre-study estimate was 31%. The postprandial gastric volume CV was 10%, and the pre-study estimate was15%. Only the MTV had an observed CV of 34% greater than the pre-study estimate of 25%. The proposed sample sizes provided 80% power to detect differences between any 2 diet groups (N.=13 per group) of 17-36% on the basis of the pre-study estimates. In fact, smaller effect sizes in gastric emptying and gastric volumes would have been detectable with the smaller CV that we actually observed.

micronutrients thiamine, riboflavin, niacin equivalents, calcium and iron were significantly higher in the HP group. The results are shown in Table XXXIV.

The Authors conclude that both the HP and HC result in significant improvements in markers of CVD risk, although the HP diet resulted in a greater reduction in triacylglycerol concentrations and improvements in hemoglobin and vitamin B-12 status. An energy restricted diet high in protein from lean red meat and LF dairy products seems to provide a weight loss advantage in subjects with elevated triacylglycerol concentrations, a marker of the metabolic syndrome. There is no evidence of adverse effects on bone or renal metabolism with either diet over the 12-wk study.

Johnston *et al.*[130] compared the hunger, appetite, and weight loss responses to a HP, LC (ketogenic) and those ones to a HP, medium-CHO (MC; non-ketogenic) diet in 17 obese men feeding ad libitum. Subjects were offered 2 HP (30% of energy) ad libitum diets, each for a 4-wk period, an LC (4% CHO) ketogenic diet and an MC(35% CHO) diet. They were randomized in a crossover design trial. The meals and snacks

TABLE XXXIV.—*Noakes* et al. *Study results.*[129]

Weight and fat loss	The subjects who completed the 12-wk trial (N.=100) had a mean weight loss of 7.6±0.4 kg with the HP diet (N.=52) and 6.9±0.5 kg with the HC diet (N.=48); these values were not significantly different from each other (P=0.29). There were 84 subjects with weight losses >4 kg. However, there was no statistically significant difference in weight loss or in the number of subjects achieving >4 kg weight loss by diet. There was a significant interaction with diet and weight loss according to triacylglycerol status (P=0.032). Triacylglycerol status was categorized about the median of 1.5 mmol/L. Weight loss was ~25% greater with the HP diet in subjects with a triacylglycerol concentration >1.5 mmol/L (P=0.005), whereas there was no differential effect of diet in women with a low triacylglycerol concentration. The DXA data showed no overall effect of diet composition on total fat loss (P=0.16), but a significant interaction was observed with diet and triacylglycerol status on total (P=0.019) and midriff (P=0.03) fat. In women with high triacylglycerol concentrations, the total fat loss was 6.4 ±0.7 kg in the HP group and 3.4=0.7 kg in the HC group (P=0.035 for diet difference). The amount of weight lost specifically from the midriff area in the HP group was twice that in the HC group, but the difference was not statistically significant by post hoc analysis across the 4 groups (1.0±0.2 kg compared with 0.5±0.1 kg; P=0.12).
Serum and urinary urea, creatinine, and creatinine clearance	The urea-Cr ratio in urine as well as serum urea were both significantly different by diet (P=0.003 and P <0.001, respectively). Cr clearance decreased with weight loss, from 82±3.3 75±3.0 mL/min (8%; P=0.002), with NS difference between the diets (P=0.346). There was no significant change in serum Cr (74.0±0.9 µmol/L at baseline compared with 75.4±0.8 µmol/L at wk 12); therefore, the difference was due to the amount of Cr excreted in the urine from 8.9±0.32 to 8.1±0.21 mmol/d. There was no correlation between weight loss and change in Cr clearance or Cr excretion. Adjustment for the change in weight rendered the change in clearance insignificant (P=0.621), i.e, the change in calculated Cr clearance was due to the weight change and not to a change in renal function.
Lipids	There was no significant effect of diet composition on LDL-C, HDL-C, and glucose concentrations. LDL-C decreased by 6%, HDL-C decreased by 7%, and glucose concentrations decreased by 4% with both diets. Diet composition affected the decrease in triacylglycerols, which decreased by 8% with the HC diet and by 22% with the HP diet (P=0.007). Because subjects with high triacylglycerol concentrations may be more responsive to factors that alter triacylglycerols, we reanalyzed the data according to triacylglycerols status (above or below the median of 1.5 mmol/L). There was a diet x triacylglycerol status interaction for triacylglycerol (P=0.023). In the women with a high triacylglycerol concentration, the HP diet lowered triacylglycerols significantly, by 28% compared with only 10% with the HC diet. In the low-triacylglycerol group, there was no significant effect of diet composition on triacylglycerol. Fasting glucose, insulin, and free FA concentrations all decreased significantly with weight loss, with no differential effect of diet composition. CRP decreased significantly overall, by 19% (P <0.001), with no significant effect of diet (P=0.447). The change in CRP in the low-triacylglycerol group was 0.74±0.27 mg/L, and the change in the high- triacylglycerol group was 1.90±0.41 mg/L (P=0.03 for the difference). This difference was enhanced (P=0.018) after adjustment for weight loss.
Iron status	There was a small but non-significant 2% increase in hemoglobin with the HP diet (P=0.116) but no change with the HC diet. Transferrin decreased by 9-12% with both diets. There were no significant changes in iron status. Ferritin concentrations were outside the normal range of 150 µg/L in 17 subjects, which suggested that iron stores were likely to be replete and nonresponsive to dietary changes. When these subjects were excluded from the analysis, there was a significant 41% increase in serum ferritin in the HP group but no change in this marker of iron stores in the HC group (P=0.004 for diet effect).Ferritin was positively correlated with serum homocysteine concentrations at baseline (r=0.209, P=0.037).
Vitamins B-12 and B-6, homocysteine, and folate	Vitamin B-12 rose significantly (by 9%) with the HP diet, whereas it decreased (by 13%) with the HC diet. The difference between diets was significant (P<0.0001). Vitamin B-6 increased with both diets, with no significant difference between them, whereas homocysteine did not change significantly over the intervention. Serum folate increased marginally with time (P=0.045), with no effect of diet composition (P=0.234 for diet).

(Continued)

TABLE XXXIV.—*Noakes* et al. *Study results.*[129]

Markers of bone turnover	Osteocalcin increased by 23%, with no significant difference between dietary interventions. There was no correlation between the amount of weight lost and changes in urinary crosslinks or the calcium-Cr ratio. The urinary crosslinks and the calcium-Cr ratio, however, were inversely related (r=0.36 for Pyr and r=0.28 for Dpr), i.e, the greater the decrease in calcium excretion, the smaller the increase in crosslink excretion. Changes in crosslinks or osteocalcin were unrelated to menopausal or triacylglycerol status. Osteocalcin at wk 12 was correlated with the urinary crosslinks at wk 12 (P<0.01) after the adjustment for baseline osteocalcin, but was not related to weight changes (P=0.723). However, the urinary crosslinks at wk 12 were both correlated with the change in weight (P <0.01) and in osteocalcin (P <0.05) after the adjustment for baseline values.

of the LC diet contained 30%, 4%, and 66% of energy as protein, CHO, and fat, respectively; the meals and snacks of the MC diet contained 30%, 35%, and 35% of energy as protein, CHO, and fat, respectively. All meals within both diets had a fixed energy density of 5.5 MJ/kg. The LC meals contained 38.8 g (660 kJ) protein, 39.2 g (1 450 kJ) fat, 5.5 g (88 kJ) CHO, and 2198 kJ energy. The MC meals contained 38.8 g (660 kJ) protein, 20.8 g (770 kJ) fat, 48.0 g (767 kJ) CHO, and 2 197 kJ energy. Only 17 volunteers completed the study. Volunteers consumed significantly (P<0.020) more energy (0.7 MJ/day) when following the MC non ketogenic diet than when following the LC ketogenic diet. The diets were isoenergetic, which meant that the subjects consumed significantly more food, including more protein (12 g/day; P<0.022) and CHO (148 g/day; P<0.001), but significantly less fat (51 g/day; P<0.001) with the MC non ketogenic diet than with the LC ketogenic diet. The subjects' average consumption of beverages did not differ between the LC and MC diets (1.655±1.05 and 1.662±1.12 kg, respectively). These beverages were free of both calories and caffeine, and thus the difference in energy intake was due to weight of food eaten, rather than fluid intake. The total weight of food intake was 1.25±0.56 and 1.46±0.43 kg with the LC and the MC diet, respectively. The results are shown in Table XXXV.

In summary this study shows that in the short term, HP, LC ketogenic diets reduce hunger and lower food intake significantly more than HP, MC non ketogenic diets do.

High-protein diet and obese patients undergoing surgery

Critically ill patients are characterized by alterations in CHO, lipid, amino acid and protein metabolism leading to increased energy requirement and protein catabolism and contribute to alterations of the immune system and the gastrointestinal tract.[131] The critically ill patient is also affected by alterations of hormone secretion and action (*i.e.*, increased secretion of cortisol, glucagon and the catecholamines, decreased secretion of testosterone and insulin-like growth factor-1 [IGF-1]) and resistance to the combined effects of insulin and growth hormone or growth hormone alone.[132, 133] There is evidence that obese critically ill patients are at greater risk than lean individuals for postoperative sepsis, bacteremia and clinical sepsis after acute thermal injury.[134, 135] Elamin *et al.*[136] report that acutely injured obese patients are at equal or greater risk for nutritional depletion than normal-weight patients in particular because they are likely to develop protein-energy malnutrition in response to metabolic stress leading to increased net protein oxidation and higher daily muscle mass degradation. The same Authors report that the effect of counterregulatory hormones in glucose control is one of the major metabolic derangements, particularly in obese critically ill patients: 1) with diabetes mellitus, the increase in stress-related hormones, such as cortisol and catecholamines, results in a worsening of existing insulin resistance 2) critical-illness induced hyperglycemia combined with the increase in endogenous glucose production and an impaired ability for

TABLE XXXV.—*Johnston* et al. *Study results.*[130]

Appetite	Subjects felt significantly (P<0.014) less hungry (-4.6 on the VAS) while following the LC ketogenic diet than while following the MC non ketogenic diet. There was a significant effect of day and a significant day x diet interaction (P<0.001 for both). Hunger was reduced over wk 1 to a greater extent with the LC ketogenic diet than with the MC non ketogenic diet. There was no significant diet x time interaction for any of the appetite scores. Order effect was considered by the period and period x diet interactions. There were no period x diet interactions for any of the appetite variables, but there were period effects for prospective consumption (P=0.037) and thirst (P=0.035), whereby values were higher in the first period than in the second. This suggests adaptation throughout the study duration. There were no significant differences (P>0.10) between diets for thirst, desire to eat, prospective consumption, preoccupation with thoughts of food, or fullness.
Pleasantness of the diets	Subjects had no significant preferences for either diet for pleasantness (P=0.213) or satisfaction (P=0.164). Breakfast was the most enjoyable meal of the day (P < 0.001) and dinner the least enjoyable (P < 0.001), with average meal scores of 89.7, 87.5 and 85.8 mm (SED: 1.10) for breakfast, lunch, and dinner, respectively. A diet x day interaction (P=0.021) indicated that the subjects perceived pleasantness improved with the MC diet and declined with the LC diet over the first few days. There was no correlation of the difference in pleasantness between the LC and MC diets and the difference in energy intake.
Self-reported influences on eating behavior and mood	On average, there was no significant difference in perceived anxiety or depression according to diet composition. Mean±SD scores for anxiety with the LC diet were 4.1±3.3 and 3.4±2.5 and those for depression were 2.5±2.1 and 2.8±2.2 before and after treatment, respectively. Similarly, mean scores for anxiety with the MC diet were 4.1±3.4 and 3.4±2.3 and those for depression were 3.6±2.2 and 2.9±2.6 before and after treatment, respectively. There was a period effect with anxiety: scores decreased between weight-loss periods 1 and 2 (P=0.043). There was no diet effect or diet x period effect. Influences on eating behavior showed no diet effects in restraint, disinhibition, and hunger but, when adjusted for covariate analysis (based on baseline (before treatment) levels), there were significant order effects and order diet effects, which reflected higher scores during period 1 than in period 2. Specifically, restraint increased on both diets with mean scores for LC of 5.8±4.6 to 6.7±4.8 and those for MC were 5.8±4.0 to 6.5±4.8 before and after treatment, respectively. The influence of disinhibition remained unchanged on both diets with mean values for LC of 6.7±2.4 to 6.8±3.0 and those for MC of 3.3±3.4 to 6.2±3.0 before and after treatment, respectively. Finally, hunger declined with both diets: from 6.3±1.8 to 5.8±2.3 with the LC diet and from 7.0±2.5 to 6.7±2.5 before and after weight loss, respectively.
Weight loss and body composition	Weight loss during the 4-wk period was significantly (P=0.006) greater with the LC than with the MC diet (6.34±2.24) and 4.35±2.61 kg, respectively; it was equivalent to a 5.8% and 4.0% reduction in BW (P < 0.001), respectively, expressed as a proportion of BW at the start each diet phase. There was a significantly (P=0.002; SED: 0.282) greater weight loss during wk 1 of the LC ketogenic diet than during wk 1 of the MC non ketogenic diet (2.68 and 1.62 kg, respectively). There was a significant period effect (P=0.005), in that subjects lost more weight during weight-loss period 1 than during period 2. There were no diet x order effects. The significantly (P=0.006) greater weight loss with the LC diet (1.99 kg) than with the MC diet was due, in part, to the difference in water loss with the ketogenic diet, although this difference did not reach significance (0.71 kg;P=0.158). There also tended to be greater losses of fat mass (1.05 kg; P=0.083) and FFM (0.94 kg; P=0.054) with the LC diet than with the MC diet. In the 4-compartment model used, glycogen is considered part of the FFM, and it cannot easily be directly measured. Examination of the change in protein mass indicated that there was a weight loss of 0.25 and 0.02 kg with the LC ketogenic and MC nonketogenic diets, respectively (P=0.281; SED: 0.202). When considered over the span of 4 wk, however, only 35% of the difference in total weight loss between the 2 diets was accounted for by water depletion. The remainder of the difference was accounted for mainly by fat mass and some BLM. These additional losses probably are associated with the 0.7 MJ/d lower energy intake with the LC diet than with the MC diet.
Compliance and metabolic profile	Both fasting glucose (P < 0.001) and HOMA (P < 0.001) were significantly lower than baseline with the LC diet. In contrast, these values were unchanged with the MC diet, which

TABLE XXXV.—*Johnston* et al. *Study results.*[130]

	led to significant between-diet effects (P < 0.035, and P=0.038, for glucose and HOMA, respectively). Total and LDL-C were reduced to a significantly greater extent with the MC diet than with the LC diet (P=0.002 and P=0.004, respectively), but there was no significant diet effect on HDL or triacylglycerol. There were significant diet effects for glucose (P=0.035), insulin (P=0.035), and HOMA-IR(P=0.038), which reflected the differing CHO intakes. There was a similar small increase in plasma concentration of urea with both diets, which probably reflects the elevated protein intake and which was considered an indicator of compliance. There was no difference in response between diets. Furthermore, as anticipated, fasted plasma 3-hydroxybutyrate (3-OHB) increased 6-fold (P=0.007) with the LC ketogenic diet. Daily urine testing with indicator sticks (acetoacetate) showed that all subjects became ketotic after 1–3 d of the LC diet and remained so for the duration of the dietary period. This effect was also reflected in the concentration of 3-OHB in the 24-h urine collections, which did not change significantly (P>0.05) between the end of wk 1 and the end of wk 4 (2.98 and 2.99 mmol/L (SED: 0.36) and 0.47 and 0.18 mmol/d (SED: 0.21), respectively) of the LC and MC diets, respectively. Total urine output of 3-OHB differed significantly (P < 0.001) between diets, but did not change significantly between the end of wk 1 and the end of wk 4 of each diet: 4.37 and 5.02 mmol/d (SED: 0.62), respectively, with the LC diet and 0.30 and 0.51 mmol/d (SED: 0.29), respectively, with the MC diet. The decrease in BP did not differ significantly between diets, so these improvements were probably a response to the weight loss. Similarly, changes in waist and gluteal circumferences did not differ significantly (P>0.01) between the 2 diets.
Efficacy of the 3-d maintenance diet	The 3-d maintenance diet was designed to 1) neutralize the ketogenic state and replete liver CHO stores and 2) to return hunger to baseline levels equivalent to the maintenance period 1, before ad libitum feeding recognizing that a carryover effect from the weight-loss phase existed. This design is particularly relevant for the subjects who were given the LC ketogenic diet first and then the MC non-ketogenic diet. The plasma data would support that the 2 goals above were achieved, in that fasted plasma 3-OHB concentrations did not differ significantly (P>0.05) between the 2 phases for the maintenance periods 1 and 2. In addition, glucose concentration did not differ significantly between diets (P>0.05) for maintenance period 1 or period 2. Moreover, comparison of fasted plasma 3-OHB concentrations at maintenance period 2 and at the end of the MC non-ketogenic diet showed no significant difference between the 2 phases. The data from all 3 maintenance periods indicated that hunger had returned to baseline or below within 3 d.

its oxidation is associated with an increased incidence of postoperative infections and a worse prognosis after stroke and head injuries. The various obesity-associated conditions are responsive to the challenging and complex issues in medical and surgical intensive care units (ICUs) in the treatment of obese patients. Several studies report that these patients have a more adverse outcome in a medical ICU compared with non-obese ones.[137] Moreover obese patients may have protein depletion as evidenced by decrease serum protein concentrations or decreased muscle mass and they are more susceptible to develop postoperative complications such as wound complications, nosocomial infections, increased mortality post-trauma, increased medical-surgical ICU mortality respiratory complications, and delayed cardiac recuperation.[138-141] It is not easy to provide these patients with an appropriate feeding because it is really difficult to calculate accurately their real energy expenditure.[142] Moreover the iatrogenic malnutrition of neurosurgical patients in ICU is an underestimated problem. It may cause a decrease in plasma albumin and oncotic pressure, leading to an increase in the amount of water entering the brain and an increased intracranial pressure.[143] Harris Benedict's equation is commonly used to determine the metabolic needs in these patients but it has not been fully understood if the weight to be used in this formula should be the actual BW or the ideal BW. Ireton-Jones *et al.*[144] in their study of obese surgical and non-surgical patients with a mean age of 52 yrs, suggested that the actual BW should be used in crit-

TABLE XXXVI.—*Dickerson* et al. *Study results.*[141]

Serum prealbumin and albumin levels	Blood samples for serum levels of prealbumin and albumin were drawn after the initiation of nutrition support on mean days 2, 9, 16, and 23 of feeding. Univariate repeated measures ANOVA did not demonstrate an overall difference in serial prealbumin and albumin concentrations between groups (P=not significant). Initial serum prealbumin concentrations were low in both groups; but the concentrations increased over time in both groups. Serum albumin did not change significantly over the observation period for either group.
Nitrogen balance	Nitrogen balances were done on mean days 6 (N.=12 and 25 for the eucaloric and hypocaloric groups, respectively) and 14 (N.=10 and 11, respectively) of feeding. Protein intakes at the time of the first nitrogen balance determination were 1.81±0.46 and 1.58±0.52 g/kg of ideal BW per day (P=not significant) for the eucaloric and hypocaloric groups, respectively. Protein intakes for both groups during the second nitrogen balance were 1.95±0.40 and 1.99±0.53 g/kg of ideal BW per day (P=not significant), respectively. Both groups were near nitrogen equilibrium and no significant differences in nitrogen balance were evident between groups. Both groups had mean negative nitrogen balance for wks 1 and 2 balance studies. There were insufficient nitrogen balance determinations thereafter for meaningful comparisons.
Serum glucose	Daily serum glucose was averaged each wk. There was no clinically or statistically significant difference in average serum glucose concentrations between the eucaloric and hypocaloric groups for wks 1 (143±22 vs. 147±32 mg/dL, P=not significant, respectively), 2 (156±38 vs. 141±32 mg/dL, P=not significant, respectively), 3 (142±27 vs. 139±30 mg/dL, P=not significant, respectively), and 4 (142±32 vs. 133±24 mg/dL, P=not significant, respectively).
Clinical outcomes	The hypocaloric group had a significantly reduced ICU stay by 10 d ($P \leq 0.03$) and decreased duration of antibiotic therapy by 10 d ($P \leq 0.03$). A statistically insignificant trend toward a decreasing duration of mechanical ventilation by 8 d was also evident in the hypocaloric group ($P < 0.09$). The number of episodes of infectious complications, such as pneumonia, presence of intra-abdominal abscess or empyema, or sepsis, did not differ between groups.

ically ill obese patients demonstrating that age, sex, ventilator status and the actual BW are significantly correlated with basic metabolic needs. Furthermore Green *et al*. assessed the energy expenditure of 65 hospitalized and non-hospitalized obese patients, using indirect calorimetry and conclude that actual BW is a better predictor of energy expenditure in these patients. The current standard of nutrition therapy for obese ICU patients includes enteral tube feedings, based on a diet containing nutrient mixtures, characterized by a low-calorie to nitrogen ratio with a HP provision which can reach up to 2 g per kg of ideal BW per day.[137, 145]

Obesity is associated with a low-grade inflammation of white adipose tissue (WAT), resulting from chronic activation of the innate immune system, which can subsequently lead to insulin resistance, impaired glucose tolerance and even diabetes.[146] WAT is not in fact a simple storage of lipids but an endocrine organ, participating in several physiological and pathophysiological processes, which is able to secrete adipokines such as adiponectin, resistin, leptin which play a key role in this low grade inflammation and are also involved in obesity associated complications, such as insulin resistance, endothelial dysfunction, arterial hypertension, and atherosclerosis.[147, 148] These considerations led Cave *et al*.[137] to suppose that this pre-existing state of inflammation, resulting from obesity, may fulfill the classic 1-hit-2-hit pattern of immune stimulation (this phenomenon is clinically evident when the pre-existing disorder [obesity] leads to an exaggerated immune response with the secondary

TABLE XXXVII.—*Swenson* et al. *Study results.*[154]

Pre-operative	No demographic or clinical preoperative variables, including preoperative BMI, showed statistical differences between the two groups.
Post-operative	Both groups showed significant yet similar weight loss both by reduction in BMI (at 12 months, LF diet, -14.0±5.5% vs. LC, -17.0 ±4.5%; P=0.15) and excess BW lost (at 12 months, LF diet, -60.3 ±15.3% vs. LC, -59.6± 13.0%; P=0.96).

injury [surgery, trauma, sepsis etc.] leading obese subjects to be more likely to report obesity associated pathologies than lean patients). The same Authors propose that: 1) the regimen should promote "safe" weight loss by optimizing FA oxidation and preventing FA accumulation in the liver as the patient loses weight; 2) in patients awaiting for bariatric surgery it might be important delaying the surgery to decrease the systemic inflammatory response syndrome response, improve insulin sensitivity, and remove fat from the liver preoperatively.

Rubio *et al.*[149] described the several steps, composing the restrictive diet required after bariatric surgery (gastric bypass and restrictive procedures), due to anatomical change in the anatomy of the gastrointestinal tract. It requires modification of dietary patterns that have to be adapted to new physiological conditions, either related to the volume of intakes or the characteristics of the macro- and micronutrients to be administered. The first phase after surgery consists in the administration of clear liquids for two-three days, followed by completely low-fat and high-protein content (>50-60 g/day) liquid diet for two-four weeks, normally by means of formula-diets. Soft or grinded diet including very soft protein-rich foods, such as egg, low-calories cheese, and lean meats such as chicken, cow, pork, or fish (red meats are not so well tolerated) is recommended two-four weeks after hospital discharge. Normal diet may start within eight weeks from surgery or even later. It is important to incorporate hyperproteic foods with each meal, such as egg whites, lean meats, cheese or milk. The supervision of an expert nutritionist who always advises the patients and adapts the diet to some special situations (nausea/vomiting, constipation, diarrhea, dumping syndrome, dehydration, food intolerances, overfeeding, etc.) plays a key role. The most frequent vitamin and mineral deficiencies in the different types of surgeries are reviewed, with a special focus on iron, vitamin B12, calcium, and vitamin D metabolism. The Authors underline that the aim of obesity surgery is to make the patient lose weight and thus post-surgery diet must be designed to achieve that goal without forgetting the essential role that nutritional education has on the learning of new dietary habits contributing to maintain that weight loss over time.

MacLean *et al.*[150] designed a study involving 45 patients who underwent end-to-side jejunoileal bypass, with 51 cm in circuit. The patients were followed up from eight months to eight yrs (average 3.4 yrs). No early or late mortality was observed, but morbidity was considerable. In particular, inadequate weight loss or late gain in 22%, malnutrition and liver failure in 11%, severe diarrhea and electrolyte imbalance in 11%, were observed. Cholelithiasis and wound complications also occurred. Reanastomosis was necessary in 13% (six patients). The result of the bypass was good in only 20%, satisfactory in 44% and unsatisfactory in 36%. The Authors observe that the complication of malnutrition, characterized by a decline in body cell mass, an expansion of the extracellular mass and an increase in the ratio of total exchangeable sodium to total exchangeable potassium is quickly and effectively treated by intravenous administration of amino acids or protein hydrolysates. They conclude that the long-term management of protein malnutrition requires a high protein diet (100 g/day) or reanastomosis.

Shizgal *et al.*[151] performed a study involving 44 morbidly obese individuals who underwent jejunoileal bypass for weight

TABLE XXXVIII.—*Mesejo* et al. *Study results.*[155]

Lipids, reactant proteins, hormones and immunological parameters	There were no significant differences at days 1, 7 and 14 in the levels of lipids (cholesterol, triglycerides, HDL and LDL), visceral proteins (retinol-binding protein, prealbumin, albumin and transferrine), reactant proteins (C protein, alfa-1-antitripsin, ferritin and haptoglobin), hormones (glucagon and insulin) and immunological parameters (C3, C4, CD4, CD8 and lymphocytes).
Glycemic control	The study showed Improved glycemic control and lower insulin requirements in the patients receiving the study formula with significant differences. These differences persist when comparing the average of the same parameters between the two groups (plasma glucose level, capillary glucose level and insulin/day, P=0.001; insulin/g CHOs received, P=0.02; insulin/g CHOs received/kg, P=0.04). The effect of the formula on glycemic control was also analyzed including factors such as concomitant corticosteroid treatment, sepsis on admission and history of diabetes. In all cases interaction with these factors was far from being statistically significant, although the subgroup of patients with a history of diabetes had higher glycemia and greater insulin requirements than the subgroup of patients with no history of diabetes, regardless of the used formula.
Administration route and enteral feeding complications	Gastric route was first chosen for enteral nutrition in 25 cases (96.2%)in the study group and in 22 cases (91.7%) in the control group. The transpyloric route was the first option for three patients, one case (3.8%)in the study group and two cases (8.3%)in the control group. In three cases for each group (12% in the study group and 12.5% in the control group), the gastric route was changed to the transpyloric route due to intolerance shown by an increase in gastric residuals. In these cases, a dual tube was introduced for jejunal feeding and gastric decompression. There was one case of patient withdrawal of the tube in the study group and two cases in the control group. There were also two cases of tube blockage in the study group. The transpyloric tube was introduced using fluoroscopic technique. All complications in the feeding route were solved within 12 hours and did not cause the withdrawal of any patient from the study. In the study group, eight patients (30.8%) suffered at least one feed-related complication: four were increased gastric residuals, two vomiting, one abdominal distension and one diarrhea. In the control group, nine patients (37.5%)suffered at least one diet-related complication: seven were increased gastric residuals, one vomiting and one diarrhea. All feed-related complications were mild, were solved within 24 h and did not interfere with patient evolution or the conduct of the study.
Acquired infections	There were no significant differences in the infection rate between the two groups. There were 17 infections in the study group vs. 13 in the control group with 10 patients infected (38.5%) in the study group vs. eight (36%)in the control group (P=0.7). The rate per infected patient was 1.7 in the study group and 1.63 in the control, with an accumulated incidence/100 days of ICU stay of 6.05 in the study group and 4.78 in the control group (P=0.5). A quantitative and semi-quantitative colony count were done on all of the cultures and catheters, respectively. In the study group, there were 10 cases of pneumonia, three bacteriemias and four catheter-induced infections. In the control group, there were seven cases of pneumonia, three bacteriemias, two catheterinduced infections and one urine infection.
Length of stay, mechanical ventilation and mortality	There were no statistically significant differences between the group of patients receiving the study formula and those patients given the control formula in days of ICU length of stay (14.879.39 vs. 14.878.76; P=0.99), days of mechanical ventilation (8.776.18 vs. 9.475.96; P=0.71) and mortality (N.=8, 30.8% vs. N.=7, 29.2%; P=0.91). By grouping the patients into dead (N.=15) and alive (N.=35), univariate analysis of the factors which could be related to mortality, showed significant differences in most of the CHO metabolism parameters and in the presence of infection. In a multivariate logistic regression model adjusted for the presence of infection, all the variables related to the CHO metabolism showed a statistically significant association with mortality, except for plasma glucose level. These variables showed low correlation and were not statistically significant either for ICU length of stay adjusted for the presence of mortality (P=0.8) and for the number of days of mechanical ventilation (P=0.3).

TABLE XXXIX.—*Dickerson* et al. *Study results.*[156]

Serum albumin and iron	Serum albumin and total iron-binding capacity increased significantly ($P<0.01$ and $P<0.05$, respectively) over the course of hypocaloric parenteral nutrition. Two subjects demonstrated significant biochemical evidence of iron deficiency (transferrin saturation ≤10%, microcytic anemia): subjects 6 and 10 received a 2-wk course of iron dextran therapy at the midpoint of nutritional therapy with minimal overall TIBC changes (232-275 mg/dL and 258-248 mg/dL, respectively).
Total lymphocyte count and serum urea nitrogen	No significant changes were noted in the total lymphocyte count during the hypocaloric refeeding (1 899±1 049 cells/mm^3 to 1 659±522 cells/mm^3). Nitrogen balance data showed all measured patients to be in nitrogen equilibrium or positive balance after 24.0±9.7 days of hypocaloric parenteral nutrition. Only two of these patients had a significant increase in serum urea nitrogen requiring the additional computations to account for expanded total body urea in the nitrogen balance calculations.
Weight loss	These obese patients lost weight down to an average weight of 109.7±32.5 kg (180±66% ideal BW) during hypocaloric feeding over a period of 46.9 d averaging weight loss of 2.3±2.7 kg/wk. Assuming 9000 non-protein caloric deficit will result in 1 kg fat loss, most patients lost more weight than predicted from caloric deficits alone.
Respiratory quotient and resting energy expenditure	Twenty-one serial indirect calorimetry measurements in eight patients without lipid emulsion administration or oral intake revealed the expected low RQ averaging 0.80±0.06 over the 5-wk observation period. Substrate utilization studies from indirect calorimetry suggests CHO and fat oxidation accounted for ~32±19% and ~68±19% of the non-protein energy expenditure, respectively. REE decreased significantly from baseline. Initially, the mean REE was 2 205±689 kcal/d or 150±33% of basal energy expenditure at ideal BW. This declined to 1 898±498 kcal/d or 131±32% of basal energy expenditure at ideal BW after the course of hypocaloric feeding ($P<0.05$).
Healing and complications	All patients demonstrated complete tissue healing as documented by contrast studies in fistulas patients or clinical wound healing in wound dehiscence patients in an average time of 35.8±18.1 days out of a total hospital stay of 59.9±51.2 days. Patient 7 developed ketonuria during a 3-day period of total caloric and protein deprivation. Minor complications occurred in three patients. Subject 1 develop on both palms dry, scaly skin which appeared unresponsive to a water-miscible ointment. A review of the patient's regimen revealed 20 consecutive days without lipid emulsion administration and sporadic trace element supplementation throughout his nutritional therapy. The dermatologic manifestation responded within several days of daily, concomitant intravenous zinc and lipid emulsion supplementation. Subject 13 had acute renal failure secondary to aminoglycoside therapy and subsequently developed candidemia requiring amphotericin B therapy. Subject 5 was readmitted 1 month after discharge with a recurrence of anastomotic leak. She was retreated conservatively with hypocaloric HP parenteral nutrition and percutaneous drainage of her abscess with complete resolution of her anastomotic leak.

reduction. In these patients, 139.7 cm of proximal jejunum were anastomosed, end to side, to 12.7 cm of distal ileum. In 33 patients a decrease in body fat accounted for the entire postbypass weight loss, while the lean body mass remained normal in both size and composition. In these patients, at one yr, BWs had decreased by 24.4±2.1%, while the body cell masses had decreased by 2.1±7.1%. In the remaining 11 patients, the postbypass weight loss resulted from a loss of both body fat and body cell mass. Their body weights at one year had decreased by 27±3%, while the body fat and body cell mass. Their body weights at one year had decreased by 27±3%, while the body cell masses decreased by 22±6.1%. The Authors observe that their body compositions are characteristic of protein malnutrition with a contracted body cell mass and an expanded extracellular mass. Moreover six of these 11 patients have required admission to hospital on 10 occasions because of malaise, anorexia, debilitating weakness, hypokalemia, and abnormal liver function. After treatement for 14.5±1.9 days, with an intravenous infusion

of amino acids without additional non-protein calories, the body composition, initially characteristic of malnutrition, became normal; their symptoms disappeared and hepatic function returned to normal. Subsequently, a HP diet was required to prevent a recurrence of symptoms and to maintain a normal body composition.

Ackerman *et al.*[152] treated five patients who showed signs of degenerating liver function (the most useful tests for assessing the status of liver function in these patients have been serum albumin, serum bilirubin and prothrombin time) development after jejunoileal bypass with protein supplementation, either on an outpatient or inpatient basis, making use of preparations orally and intravenously. Subjective as well as objective evidence of improving liver function was obtained, and all patients have survived. The Authors underline that it is important to maintain a high protein intake postoperatively.

Heimburger *et al.*[153] designed a study involving 13 patients who underwent 30.5 cm to 15.2 cm jejunoileal bypass procedures. Hepatic fatty infiltration complicating jejunoileal bypass can be massive and may require restoration of gastrointestinal continuity. This fatty infiltration appears to be caused by protein depletion associated with adequate or HC intake. The Authors observed that three out of 13 patients developed symptomatic hepatomegaly with near total replacement of hepatocytes by massive fatty infiltration. After undergoing liver scan, liver biopsy, and liver function tests, the patients were started on a peripheral infusion of 2 L per day of a 4.25% crystalline amino acid solution, allowing for fat mobilization while preserving body protein stores. All oral intake was withheld, except for water. At the end of a 14 to 21 day infusion period, serum albumin levels increased by 1 gm in all patients. Decreases in liver volume of 83%, 45%, and 40% occurred. During the infusion period ketonuria was 4 plus in all patients indicating active lipolysis. Weight loss was impressive (17, 19, and 40 pounds). All patients showed marked symptomatic improvement, and postinfusion liver biopsy specimens showed a return to near normal architecture. Maintenance of normal liver size by a HP, LC diet was observed in a five to seven month follow-up period. The Authors conclude that the use of calorie-free amino acid solutions reverses the hepatic fatty infiltration, seen after intestinal bypass, by mobilization of fat. This fat mobilization does not occur as readily in the presence of large amounts of glucose.

Dickerson *et al.*[141] compared the nutritional and clinical efficacies of eucaloric and hypocaloric enteral feedings in 40 critically ill, obese patients admitted to the trauma or surgical ICU. They studied adult patients (18 to 69-year-old), with weights greater than 125% of ideal BW, normal renal and hepatic functions, who received at least seven days of enteral tube feeding. Patients were stratified according to feeding group: eucaloric feeding (≥20 kcal/kg of adjusted weight per day; N.=12) or hypocaloric feeding (≥20 kcal/kg of adjusted weight per day; N.=28). The goal protein intake for both groups was approximately 2 g/kg of ideal BW per day. Clinical events and nutrition data were recorded for four wks. Enteral nutrition was administered to each group as a standard HP feeding by use of Isosource VHN (Novartis Nutrition, Minneapolis, MN, USA) or a supplemental HP feeding with the addition of 20 to 25 g of a protein powder supplement (ProMod, Ross Laboratories, Columbus, OH, USA) to the standard high-protein formula. There was no difference in age, BW, BMI, Acute Physiology score, Second Acute Physiology and Chronic Health Evaluation score, Trauma score, and Injury Severity score between groups. Most patients had multiple trauma from motor vehicle accidents and several patients experienced chronic health complications associated with their obesity. The hypocaloric feeding group received significantly fewer calories than the eucaloric feeding group for the first three wks of nutrition support therapy, with a statistically insignificant trend observed by wk 4 in a limited number of subjects (seven and six patients per group by wk 4). Average daily protein intake for each wk was similar and not statistically significant between groups for three of the four wks of the study; however, a significant dif-

ference in protein intake was observed between groups during wk 2. The study results are shown in Table XXXVI.

The Authors conclude that, although it was not a randomized controlled trial, hypocaloric enteral nutrition support is as least as effective as eucaloric feeding in critically ill, obese patients.

Swenson *et al.*[154] designed a study to assess what diet should be followed, after surgery, by patients undergoing laparoscopic gastric bypass procedures for morbid obesity to maximize their weight loss. Patients were randomly assigned to either a low-fat control diet based on American Heart Association recommendations or a LC, HP diet based on the South Beach Diet. Body composition, including BMI, was recorded preoperatively and during postoperative visits at 3, 6, and 12 months. The standard University of Virginia postgastric bypass diet is a LF, "heart-healthy" diet based on AHA guidelines. Of the specified macronutrients, patients were advised to consume 50-60 g of protein each day and limit fat intake to less than 35 g per day. The LC, HP diet involved minimal CHO intake, HP intake, and moderate fat intake. The diet instructions focused on the different types of fats, discouraged intake of saturated fat, and emphasized use of mono- and polyunsaturated fats. It also promoted HP intake and low-glycemic index CHOs in small quantities. When the subjects recovered sufficiently from surgery and were able to tolerate a semisolid diet, they were asked to follow the strict phase of the diet for two wks in accordance with the South Beach Diet plan. This two-wk period is designed to eliminate CHO cravings. After completion of the strict part of the diet, CHOs were gradually added back into the diet. Thirty-two patients were included in the analysis with 13 control and 19 LC, HP subjects. The results are shown in Table XXXVII.

The Authors conclude that no weight loss advantage is observed in substituting a LC, HP diet in place of a standard LF diet in patients who have undergone laparoscopic gastric bypass surgery.

Mesejo *et al.*[155] performed a prospective, randomized, controlled, single-blind trial to determine whether a specific HP enteral formula, with a similar caloric percentage of fat and CHOs, is able to achieve greater control over glycemic levels and to reduce insulin requirements in hyperglycemic critically ill patients, when compared to a control HP enteral formula. The study involved 50 patients with diabetes mellitus or stress hyperglycemia with basal glycemia ≥160 mg/dL and indication for enteral nutrition ≥5 days. Patients with severe kidney failure, liver failure or obesity were excluded from the study. In the first 48 hours of admission, after randomization, 26 patients received the study diet and 24 patients received the control diet. The variables were monitored for 14 days. The Harris-Benedict formula with a fixed stress factor of 1.2 was used to calculate caloric needs. An intention-to-treat analysis was performed. All the patients had a medical or traumatological diagnosis. The volume ratio received by the patients was high, over 92% in both groups. There were no significant differences in total caloric supply, although there were differences in nutrient supply, due to the different composition of the formulas. However, the total amount of CHOs and fat was, within moderate limits, respectively, below 225 and 80 g/day. Formulas were first administered, whenever possible, by nasogastric tube. Gastric residuals were evaluated every 6 hours for the first two days and then every 12 hours for the remaining days, changing to a transpyloric tube if there was gastric intolerance. All the patients received 10 mg of intravenous metoclopramide every 8 hours. Fifty percent of requirements were administered during the first day and 100% during the second day of nutrition. Formulas were administered by 24 hours continuous infusion controlling the exact volume infused every day. Insulin was administered by continuous infusion. Both the enteral formulas were HP, but the control formula had slightly higher nitrogen content than the study formula. They were both isocaloric, but with different caloric distribution, since the study formula has a similar fat and CHO percentage (40%), while the control formula has a higher percentage of CHO (49%)to fat (29%). The study formula had

also more MUFA (15.4 g/500 mL)than the control formula (7.7 g/500 mL)and soluble fiber (7.5 g/50 mL of hydrolized guar gum-Benefiber®). The source of CHOs was different with starch and fructose (74% and 26%) in the study formula and maltodextrine and sucrose (78% and 22%)in the control formula. The results are shown in Table XXXVIII.

The Authors conclude that enteral nutrition in the hyperglycemic critically ill patient, with a disease-specific HP diet and similar caloric percentage of fat and CHOs, produces a significant reduction in plasma glucose levels, capillary glucose levels and insulin requirements in comparison with a conventional HP diet. This study shows no significant differences in the rate of acquired infections, ICU length of stay, days of mechanical ventilation or mortality between the groups.

Dickerson *et al.*[156] performed a study involving thirteen obese (averaging 208% of ideal BW at 126.9±60.0 kg) patients requiring parenteral nutrition for postoperative complications (sepsis, anastomotic leaks, abscesses, enteric fistulae and/or wound dehiscence) to evaluate, prospectively, the efficacy of hypocaloric, HP parenteral feeding (hypocaloric parenteral nutrition is parenteral non-protein caloric intake less than the measured REE of the patient; HP intake is parenteral intravenous amino acids intake >1.5 g/kg ideal BW). Nutrients were provided mainly by the central venous parenteral route. Non-protein calories were provided primarily as dextrose and the protein source was crystalline amino acids. Most patients had a continuous infusion of 1-2 L of a glucose (5-35%)-amino acid (3-5%) mixture per day. Additional parenteral amino acid was intermittently piggybacked over a 4-12 hour period. Intermittent intravenous fat emulsion was infused over 4-12 hours. Daily infusions were supplemented with appropriate electrolytes and trace minerals and with a commercially available 12 vitamin preparation daily. Subcutaneous injection of 10 mg of vitamin K was administered weekly. Intravenous albumin supplementation was not provided). Hypocaloric parenteral nutrition was provided for 48.2±31.4 days. Non-protein caloric intake averaged 881 kcal/d or 5 1.5% of the patient's measured REE. Protein intake averaged 129 g/day or 2. 13 g/kg ideal BW or 1.16 g/kg of current BW. The results are shown in Table XXXIX.

The Authors conclude that in obese, protein-depleted surgical patients net protein anabolism and clinical efficacy can be achieved with hypocaloric, HP feeding.

Martin *et al.*[157] designed a study to determine whether it is practical and safe to make obese patients lose weight preoperatively. One hundred severely obese patients requesting gastric bypass surgery were asked to diet before their operations and 70 of them agreed. The diet consisted of 420 Kcal, 70 g protein liquid diet daily for at least one month. All patients underwent Rouxen-Y gastric bypass connecting a 40 cm Roux limb of jejunum to a 20-mL proximal gastric pouch using an 11 mm diameter hand-sewn gastrojejunostomy. Postoperatively, patients were maintained on the protein-sparing modified fast (PSMF: approach consisting in a diet high in protein [more than 1 g/kg per day to protect the patient's LBM] but low in CHO and fat to promote lipolysis) formula for the first six wks before beginning a transition to a regular diet. Patients were instructed to take a multivitamin daily and received 1 000 mg of vitamin B12 intramuscularly every six months. The Authors observed that 47 patients lost at least 7.5 kg (mean ± SD 17.1±0.7). The patients who successfully lost weight preoperatively (dieters group) were significantly heavier than patients (nondieters group) who did not lose weight (251±45% of ideal body weight *versus* 229±33% ideal body weight, respectively; P<0.01), had a significantly higher ratio of men to women. Postoperatively, the dieters and non-dieters had similar rates for morbidity. Dieters and non-dieters had no differences in wound healing complications and subgroups, who had collagen deposition measured experimentally, had similar amount of hydroxyproline accumulation in their wounds. The Authors conclude that a preoperative diet program appeals more to certain subgroups of severely obese patients than to others. This study shows that severely obese patients can safely lose up to 45 kg immediately preoperatively, that commercial

PSMF programs help make this amount of weight loss feasible, and that losing weight may help improve the outcome of some procedures for severely obese patients who complete a preoperative weight loss program.

Polyunsaturated fatty acids and obesity

FA are classified into two main families of PUFAs, *i.e.*, ϖ-3 FAs which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and ϖ-6 FAs which include linoleic acid (LA), arachidonic acid, and γ-linolenic acid.[155] It has been hypothesized that the increasing incidence of inflammation, related to diabetes, CVD, obesity, arthritis, asthma and the metabolic syndrome, may be linked to a lack of dietary consumption of n-3 FAs.[159] In particular ϖ-3-FAs have well-documented protective effects against these pathological conditions which are attributed not only to eicosanoid inhibition, but also to the formation of novel biologically active lipid mediators (*i.e.*, resolvins and protectins).[160, 161] Conjugated linoleic acid (CLA), DHA, and EPA have similar effects on alleviating obesity and/or preventing from obesity: 1) they influence the balance between energy intake and expenditure; 2) they reduce BW and/or fat deposition in animal models; 3) they inhibit key enzymes responsible for lipid synthesis, such as FA synthase and stearoyl-CoA desaturase-1; 4) they enhance lipid oxidation and thermogenesis; 5) they prevent free FAs from entering adipocytes for lipogenesis; 6) they exert suppressive effects on several key factors involved in adipocyte differentiation and fat storage.[162] Moreover, experimental studies in rodents fed HF diets show that fish oil (and its important long-chain n-3 PUFAs), EPA and DHA protect against insulin resistance and obesity and in humans they might also reduce insulin response to glucose.[163-165] Ramel *et al.*[166] in a eight wk dietary intervention study, involving 324 overweight participants (BMI: 27.5-32.5 kg/m^2; age: 20-40 yrs and WC of ≥94 cm and ≥80 cm for men and women respectively) randomized to one of four energy restricted diets (-30E%) of identical macronutrient composition but with different long-chain n-3 PUFAs content (control [N.=80; no seafood; single-blinded]; lean fish [N.=80; 150 g cod, three times/wk]; fatty fish [N.=84; 150 g salmon, three times/wk]; fish oil [N.=80; daily DHA/EPA acid capsules, no other seafood; single-blinded]), demonstrate the importance of long-chain n-3 PUFA consumption for improvement of insulin resistance and, possibly, for the prevention of type 2 diabetes in addition to weight lowering strategies. The mechanism, underlying the possible fish oil induced prevention of insulin resistance, is not yet understood, but several studies have shown a strong association between elevated triacylglycerol concentration (plasma and/or tissues) and insulin resistance.[167] Experimental animal models show that insulin resistance is significantly correlated with hepatic or plasma triacylglycerol content and fish oil intake has been shown to decrease plasma and liver triacylglycerol levels and VLDL-triacylglycerol secretion, and to suppress postprandial hypertriacylglycerolemia.[168-170] In healthy humans plasma n-3 PUFAs has also been correlated to circulating adiponectin which stimulates glucose utilisation and FA oxidation in muscle and decreases hepatic gluconeogenesis.[171] Intake of n-3 PUFAs has been associated with a reduced risk of coronary heart disease,[172] and n-3 PUFA-consuming populations also appear to have a relatively low prevalence of cholesterol gallstone disease,[173] which is known to be closely associated to obesity.[174, 175] A decrease biliary cholesterol saturation in the bile of patients with gallstones has been also associated with dietary n-3 PUFAs.[176] Méndez-Sánchez *et al.*[177] in a double-blind, placebo-controlled clinical trial, involving 35 obese women (BMI: 30 kg/m^2), assigned to a hypocaloric regimen (5.02 MJ [1 200 kcal]/day) and receiving 1 200 mg/day of ursodeoxycholic acid (UDCA) and 11.3 g/day of n-3 PUFA or a placebo for six wks, showed that n-3 PUFAs administered to obese subjects are associated with the maintenance of the cholesterol saturation index. They also improve the composition of the bile through maintenance of the cholesterol nucleation time. The addition of n-3 PUFAS of fish ori-

gin to a very low-calorie diet results in a greater BMI loss and hip circumference reduction in severely obese women during an inpatient short-term weight-reducing regimen.[178] This study also shows a higher increase in beta-hydroxybutyrate in the n-3 PUFA group, probably due to a higher beta-oxidation of FAs. PUFA have been reported to modulate appetite since they are a major component of synaptic endings and are closely involved in the transport of appetite-regulating molecules such as dopamine. They can interact with neuroendocrine factors that participate in brain-intestinal loop signals related to energy metabolism, such as insulin ghrelin or leptin.[179] The same Authors show that subjects who have dinner rich in long chain n-3 FA feel less hunger and fuller soon after and two hours later than their counterparts fed on the low long-chain n-3 FA diet indicating that long-chain n-3 FAs modulate hunger signals. The augmentation of the antiadipogenic effect of EPA/DHA, during the development of obesity, has been documented in mice suggesting that EPA/DHA could reduce accumulation of body fat by limiting both hypertrophy and hyperplasia of fat cells.[180] Future clinical trials in obese individuals are required to better understand PUFAs pathways to contrast the continuous spreading of obesity.

Conclusions

HP diets increase weight loss and are helpful in maintaining weight possibly because they are responsible for an increased satiety and decreased energy intake. A HP intake may also be responsible for a higher termogenesis. So the HP approach could be useful but it is important to choose protein sources low in saturated fat. Moreover, HP diets may minimize lean tissue loss during ER.[49] It is relevant to underline the importance of medical supervision. In fact, as some studies show, dieting could be fatal.[181-184] Ahmed *et al*.[185] reported that: 1) several case reports and small studies of patients, receiving starvation diets, have shown hypotension and sudden cardiac death; 2) myofibrillar damage has been documented in one case; 3) very-low-calorie diets are generally safe and well-tolerated, but reduce QRS voltage and QT interval prolongation; 4) both non-sustained ventricular arrhythmias and sudden cardiac death have been described in subjects treated with very-low-calorie diets; 5) orthostatic hypotension may complicate very-low-calorie protein diets because of sodium depletion and depressed sympathetic nervous system activity. Although there is little evidence that HP diets are able to bring serious risks to kidney function in healthy population, people, affected by renal disease, should be more careful with a HP intake. Patients with a clinical history of diabetic ketoacidosis, hypoglycemia, over the age of 60, or severely immunocompromised should avoid a hypocaloric, HP diet.[186] Long-term randomized controlled studies, comparing HP diets to LF/HC diets, are required and the impact of behavioral therapy, lifestyle and exercise on this diet plans should be evaluated in the future. The regimen for obese hospitalized patients should be able to provide sufficient nutritional support to minimize catabolic losses, avoiding at the same time the problems of overfeeding, hyperglycemia and infectious complications, but it should not be severely restrictive compromising the clinical outcome analogous to semi-starvation.[183, 188] Reviewing the literature, it seems that HP enteral and parenteral nutrition are effective as they prevent complications associated with overfeeding, and they are good for the metabolic support of critically ill obese patients. It is important to stress the timeliness of the nutritional support providing sufficient protein and calories to reduce catabolic losses favoring protein anabolism. The physician, in the course of events, must be able to modify the protein administration according to the patient's needs introducing gradually CHOs and lipids. Further randomized prospective studies, including large cohorts of critically ill obese patients fed on a HP diet, are warranted to reach a final conclusion. We have previously reported the hypothesis that n-3 PUFAs may exert

protective effects against several inflammatory conditions including obesity. In the field of surgery it has been observed that: 1) oral administration of a supplement, enriched with ϖ-3 FAs (1 L/day of impact [Japan]) for five days, before the surgical procedure, improves preoperative nutritional state and perioperative inflammatory and immune responses in cancer patients and it has been proposed, due to these beneficial effects, to be able to decrease the incidence of complications and length of hospital stay in patients who have cancer, are undergoing major surgery, and have a high risk of infection;[189] 2) PUFA administration (2 g/day), for at least five days, before elective coronary artery bypass grafting operation (CABG) and until the day of discharge from the hospital, in patients undergoing CABG, substantially reduces the incidence of postoperative AF (54.4%) and is associated with a shorter hospital stay;[190] these findings are confirmed by Heidt *et al*. who report that preoperative intravenous infusion of PUFA s (100 mg fish oil/kg BW/day) reduce the incidence of atrial fibrillation (AF) after CABG and leads to a shorter stay in the ICU and in the hospital;[191] 3) preoperative administration of oral PUFA-enriched diet (3.7 g of PUFAs preoperatively for five days) leads to increased incorporation of EPA and DHA not only in liver and gut mucosa tissue, but also in tumor tissue in patients with solid gastrointestinal tumors undergoing major gastrointestinal surgery;[192] 4) fish oil supplementation (0.2 g/kg BW/day), after major abdominal tumor surgery, improves liver and pancreas function, possibly contributing to a faster recovery of the patients;[193] 5) ω-3 PUFAs (EPA: 3 g/day; DHA: 1.3 g/day), administered preoperatively for 28 days to patients scheduled for coronary artery bypass graft surgery, are safe, enhance vascular prostacyclin production which may contribute to antithrombotic effects and potentially to other antiatherosclerotic actions and seem to have potentially beneficial effects on vascular physiology, platelet reactivity, and plasma lipid status that may combine to improve outcome in revascularization procedures.[194] In the last ten years of our clinical experience of HP-low calorie diet prescription for overweight/obese patients, undergoing surgical procedures, we have observed that, adding a moderate amount of ϖ-3 PUFAs (2-3 g/day preoperatively for 40-60 days) to the dietary regimen is safe, reliable and seems to confirm the previously described benefits of these compounds. In particular, in patients undergoing bariatric surgery a HP-low calorie diet, enriched with ϖ-3 PUFAs, seems to be effective maximizing weight loss without complications and leading to a faster physical recovery and, consequently, shortening the patient stay in the ICU.

Riassunto

Il paziente obeso: efficacia clinica di una dieta ipocalorica ad alto contenuto proteico e sua utilità nel campo della chirurgia

L'obesità è divenuta un problema di proporzioni epidemiche poiché coinvolge giovani e adulti in tutto il mondo. Nonostante la predisposizione genetica giochi un ruolo importante nel manifestarsi di questa condizione, una delle principali cause rimane il cambiamento a cui sta andando incontro la società. Tale cambiamento é associato alla mancanza di un'adeguata attività fisica e alla continua crescita del mercato alimentare, che offre una sempre più vasta scelta al consumatore. L'obesità è correlata a un gran numero di condizioni patologiche che possono influenzare la qualità della vita e persino condurre alla morte. L'Atkins Nutritional Approach è divenuto molto popolare sin dalla pubblicazione del primo libro del Dottor Atkins intitolato "Dr Atkins' Diet Revolution", nel 1972. Questo regime dietetico, molto criticato dai dietologi, è stato utilizzato come modello per molte diete ad alto contenuto proteico e a basso contenuto di carboidrati. Al giorno d'oggi è noto come il paziente obeso sia maggiormente soggetto a prognosi sfavorevole nei reparti di chirurgia e terapia intensiva, e questo ha sollevato la questione di quale sia il corretto apporto nutrizionale per questo tipo di paziente. Può un regime ad alto contenuto proteico apportare dei benefici al paziente obeso? Questo tipo di regime e legato ad effetti collaterali? Può una dieta ad alto contenuto proteico apportare benefici al paziente obeso che si deve sottoporre a intervento chirurgico? Questo articolo si propone di affrontare queste tematiche riportando vari studi clinici che coinvolgono l'utilizzo di una dieta ad alto contenuto proteico in pazienti obesi.

Parole chiave: Alimentazione - Obesità - Obesità, trattamento chirurgico.

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