Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

# Assessment of very low calorie diets

## Opinion of the Panel on nutrition, dietetic products, novel food and allergy of the Norwegian Scientific Committee for Food Safety 14.05.09

ISBN 978-82-8082-305-2

**VKM Report 2009: 21**

# Assessment of very low calorie diets

Margaretha Haugen
Eline Birkeland
Jak Jervell
Mette Svendsen

## CONTRIBUTORS

Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

**Acknowledgements**

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has appointed an *ad hoc* group consisting of both VKM members and external experts to answer the request from the Norwegian Food Safety Authority. The members of the *ad hoc* group are acknowledged for their valuable work on this opinion. VKM also wishes to thank Wenche Frølich (Professor Food and Nutrition Sciences) and Halvor Holm (Professor Emeritus) for their valuable contribution on fibre and proteins respectively to this opinion.

The members of the *ad hoc* group are:

*VKM members*

Margaretha Haugen, Professor RD PhD (Chair), Panel of nutrition, dietetic products, novel food and allergy

*External experts:*

Eline Birkeland, RD, MSc in Clinical Nutrition, Oslo University Hospital, Aker, Department of Clinical Nutrition

Jak Jervell, Professor Emeritus MD PhD

Mette Svendsen, RD, MSc in Clinical Nutrition, Oslo University Hospital, Ullevaal, Department of Preventive Cardiology

**Assessed by**

The report from the *ad hoc* group has been evaluated and approved by Panel of nutrition, dietetic products, novel food and allergy of VKM.

Lene Frost Andersen, Wenche Frølich, Livar Frøyland, Ragnhild Halvorsen, Margaretha Haugen (chair), Helle Margrete Meltzer, Judith Narvhus and Jan Erik Paulsen.

Scientific coordinator from the secretariat: Bente Mangschou

## SUMMARY

Very low calorie diets (VLCD products) are formulated products with 450 – 800 kcal per day intended to replace the whole diet. Regulation of VLCD is not harmonised in the EU, and there is no specific national Norwegian legislation for these products. The Norwegian Food Safety Authority has requested VKM to propose minimum and maximum limits for the content of fat/ fatty acids, protein, carbohydrates, vitamins and minerals in VLCD products based on acknowledged scientific documentation. VKM is also asked to evaluate if VLCD products are suitable in the treatment of obese subjects with type 2 diabetes, and possible contraindications for use of VLCD.

This assessment is based upon the SCOOP-report "*Collection of data on products intended for use in very-low-calorie-diets*" (SCOOP, 2002) and new literature mainly after 2002.

Based on the available scientific literature, the VKM Panel on nutrition, dietetic products novel food and allergy has concluded that, on a daily basis, VLCD products should provide minimum 55 g carbohydrates, 10 g fibres, 50 g high quality protein and 7 g fat, including 3 g from linoleic acid and 0.5 g from α-linolenic acid. The amino acid scoring pattern should be in accordance with the protein-digestibility-corrected amino acid score.

VLCD products should provide minimum 10 µg vitamin D per day, and the minimum recommended daily intake for the other vitamins and minerals.

No maximum limits are suggested for carbohydrates, protein or fat, as the energy will be the limiting factor. The fibre content should not exceed 30 g per day, and the VKM Panel recommends that the maximum limits for vitamins, minerals and trace elements should equal two times the recommended daily intake.

VLCD will give short-term weight loss and improvement in blood pressure, serum lipids and glycemia in obese subjects with type 2 diabetes, and no serious adverse effects have been reported. VLCD may impede the educational process needed in the treatment of diabetes, and should therefore only be used as part of an educational program in obese subjects with type 2 diabetes, and only under medical supervision.

VLCD is contraindicated in children, adolescents, pregnant and lactating women, elderly (above 65 years old) and in subjects with heart failure, cerebrovascular disease, gallstone disease, kidney- and liver diseases, psychiatric disorders, and in subjects with BMI $\leq 30$ kg/m$^2$. In addition one should be aware of the reducing effect of VLCD on blood pressure and the effect on hyperglycaemia which may cause problems if pharmacological therapies for these conditions are given. Medical supervision is recommended if VLCD treatment exceeds 3 weeks.

To prepare this report, VKM established an *ad hoc* group (members listed above). The VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy has discussed and adopted this opinion.

## SAMMENDRAG

Very low calorie diets (VLCD-produkter) er bearbeidede produkter som inneholder 450 – 800 kcal per dag, og som skal erstatte hele kosten. Det finnes ikke harmonisert regelverk for disse produktene i EU, og heller ingen særskilte bestemmelser i Norge. Mattilsynet har bedt VKM basert på vitenskapelig dokumentasjon, om å utrede forslag til minimums- og maksimumsgrenser for innhold av fett/fettsyrer, karbohydrater, vitaminer og mineraler i

VLCD-produkter. Videre er VKM bedt om å vurdere hvorvidt VLCD-produkter er egnet til behandling av overvektige med diabetes type 2 samt redegjøre for mulige kontraindikasjoner.

Denne vurderingen er basert på SCOOP-rapporten "Collection of data on products intended for use in very-low-calorie-diets" (SCOOP, 2002) og nyere litteratur, hovedsakelig etter 2002.

Basert på tilgjengelige vitenskapelige litteratur, har VKMs faggruppe for ernæring, dietetiske produkter, ny mat og allergi konkludert med at VLCD-produkter bør inneholde minimum 55 g karbohydrater, 10 g fiber, 50 g protein av høy kvalitet og 7 g fett per døgndose, herunder 3 g linolsyre og 0,5 g α-linolensyre. Aminosyrekvaliteten bør være i samsvar med protein-digestibility-corrected amino acid score.

VLCD-produkter bør inneholde minimum 10 µg vitamin D per dag, og minimum anbefalt daglig inntak av de andre vitaminene og mineralene.

Det er ikke gitt noen forslag til maksimumsgrenser for innhold av karbohydrater, fett eller proteiner i denne vurderingen, ettersom energiinnholdet uansett vil være den begrensende faktor. Innhold av fiber bør ikke overstige 30 g per dag, og Faggruppen for ernæring, dietetiske produkter, ny mat og allergi anbefaler at maksimumsgrense for innhold av vitaminer og mineraler settes til to ganger anbefalt daglig inntak.

Bruk av VLCD-produkter vil på kort sikt føre til vektreduksjon og bedring av blodtrykk samt blodlipid- og blodglukosenivåer hos overvektige personer med diabetes type 2. Det har ikke vært rapportert om alvorlige bivirkninger ved bruk av VLCD for denne pasientgruppen, men VLCD-produkter kan føre til at nødvendige endringer i livsstil forsinkes. VLCD-produkter bør derfor bare inngå som del av et mer helhetlig program for overvektige med diabetes type 2, og kun i samråd med medisinsk personell.

Barn, ungdom, gravide og ammende, eldre (over 65 år), personer med hjertefeil, cerebrovaskulære sykdommer, gallesten, nyre- eller leversykdommer, psykiske forstyrrelser eller BMI $\leq$ 30 kg/m$^2$ bør ikke bruker VLCD-produkter. Bruk av VLCD-produkter fører til reduksjon i blodtrykk og blodglukose. Dette kan medføre problemer hos individer som får medisinsk behandling for disse tilstandene. Bruk av VLCD-produkter utover 3 uker bør kun gjøres i samråd med medisinsk personell.

VKM har nedsatt en *ad hoc*-gruppe (liste over medlemmer gitt ovenfor) som har utarbeidet denne rapporten. Rapporten fra *ad hoc*-gruppen er vurdert og godkjent av VKMs faggruppe for ernæring, dietetiske produkter, ny mat og allergi.

## BACKGROUND

Very low calorie diets (VLCD products) are formulated products with highly restricted energy content intended to replace the whole diet with the exception of non-caloric fluids. In this assessment very low energy diets (VLED products) are included in the term VLCD. In relation to the System International the term "calorie" is not accepted anymore, so the term VLED is preferred. However, the term "very low calorie diet" is generally accepted and will be used in this report. VLCD shall provide recommended amounts of all essential macro and micro nutrients.

Regulation of these products is not harmonised in the EU, and there is no specific national Norwegian legislation for VLCD products. According to the general Norwegian food regulation, all fortified foods must have authorisation from the Norwegian Food Safety Authority before they can be placed on the Norwegian market. Several guidelines for energy restricted diets (e.g. maximum and minimum levels for the macro and micro nutrients) used in the authorisation process are of an earlier date, and are not based on scientific rationale and they do not take into account potential special nutritional needs in the obese population. The Norwegian Food Safety Authority has therefore requested a scientific assessment of maximum and minimum limits for macro and micronutrients in VLCD products.

In 2002, the report "*Collection of data on products intended for use in very-low-calorie-diets*" was published in the EU (SCOOP, 2002). This VKM assessment is based upon the SCOOP-report, and literature search has mainly been limited to after 2002. In addition, the Commission directive 96/8 on foods intended for use in energy restricted diets for weight reduction (regulating low caloric diets i.e. energy restricted products with 800 – 1200 kcal/day) (EU, 1996), the Codex Standard for Formula Foods for Use in Very Low Energy Diets for Weight Reduction (Codex, 1995), the Nordic report on Dietetic Products (The Nordic Council of Ministers, 1993) and relevant European and national regulations have been valuable background documents.

To prepare this report, VKM established an *ad hoc* group (members listed above). The VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy has discussed and adopted this opinion.

## TERMS OF REFERENCE

The Norwegian Food Safety Authority has requested VKM to evaluate VLCD products based on acknowledged scientific documentation.

The assessment shall include the following issues:

1. Proposals for minimum limits for the content of fat/ fatty acids, protein, carbohydrates, vitamins, minerals and trace elements in VLCD products, cf. the list of nutrients in annex 1.
2. Proposals for maximum limits for the content of fat/ fatty acids, protein, carbohydrates, vitamins, minerals and trace elements in VLCD products, cf. the list of nutrients in annex 1.
3. Are VLCD products suitable in the treatment of obese subjects with type 2 diabetes?
4. Are there conditions or situations in which VLCD products are contraindicated?

# INTRODUCTION

## VLCD products – description and definition

In Norway, only products providing 450-800 kcal per day can be marketed as VLCD. They shall provide recommended amounts of all essential macro and micronutrients. Most products have a high protein content and are designed to accomplish rapid weight loss, while preventing loss of excessive lean body mass. VLCD are usually formulated as a drink or soup intended to replace all meals. Five drinks/soups a day represent approximately 1 L liquid per day. An additional daily intake of non-caloric beverages in a volume of 1.5 - 2 L/day is usually recommended (No authors listed, 1993).

The Codex Alimentarius definition of VLCD products is: "*A formula food for use in very low energy diets is a food specially prepared to supply a minimum amount of carbohydrates and the daily requirements of the essential nutrients in 450-800 kcal which represents the sole source of energy intake*" (Codex, 1995).

The five identified products available on the Norwegian market (February 2009) are listed in annex 2. The different manufacturers have several VLCD products, but the nutrient content of the different products from the same manufacturer is almost equal. One of the available products, (Eurodiet), it is recommended to eat five different products per day and these products vary in nutrient contents. The daily nutrient content in the Eurodiet is therefore calculated by adding the nutrient content of a soup, a shake, a bar, an omelette and a brownie. In this diet it is also recommended to eat additional vegetables.

In obesity programs, the length of VLCD treatment is about 8 – 16 weeks and the achieved weight loss is approximately 1.5 – 2.5 kg per week (Mustajoki & Pekkarinen, 2001). The subjects may be at increased risk of developing gallstones, experience cold intolerance, hair loss, headache, fatigue, dizziness, dehydration with increased risk for electrolyte abnormalities), muscle cramps and constipation (Tsai & Wadden, 2006).

Low calorie diets (LCD-products) are similar formulated products, but with a higher energy content (800 – 1200 kcal/day).

## VLCD and weight loss outcomes – efficacy

Evaluation of weight loss outcomes and efficacy from VLCD products are outside the scope of this assessment, and therefore only a few results are presented.

Reports from different studies show that obese subjects who follow comprehensive VLCD or LCD programs (including training in lifestyle modification) may obtain weight losses at 15 – 20% of their initial weight in 3 – 6 months of treatment, and may maintain a loss of 8 – 14% one to 2.5 years after treatment (Flynn & Walsh, 1993; Anderson *et al.*, 1994).

In a review by Tsai&Wadden results from clinical trials with VLCD have been reported. They observed that in obese patients with type 2 diabetes, a VLCD group lost 15.3% of the body weight after 12 weeks intervention which also included intensive training and lifestyle modification (Tsai & Wadden, 2005).

In another review Astrup and Røssner conclude that greater initial weight losses improve long term weight losses, and that increased initial weight losses may induce enhanced long term losses if behavioural therapy is included in the weight maintenance phase (Astrup & Rossner, 2000). In line with this, the Norwegian report about prevention and treatment of overweight and obesity in the health service from 2004 stated that VLCD improved weight loss and weight maintenance compared to LCD (Sosial- og helsedirektoratet, 2004).

The objectives of the most recent meta-analyses from USA were to give an update on weight loss outcomes from VLCD and to perform a meta-analysis of randomised trials comparing weight loss outcomes from VLCD and LCD. The authors conclude that the short term effect favours VLCD, but the long term outcomes from VLCD and LCD are similar (Tsai & Wadden, 2006). It should be noted that in the meta-analyses of the VLCD, weight maintaining programs and intensive follow-up studies are included, which most likely affect the long term weight loss outcomes.

**Definition of obesity**

Body mass index (BMI, $kg/m^2$) is the measurement most commonly used for classification of body weight. Table 1 illustrates the classification of obesity and BMI in adults. The BMI classification is used as a tool to evaluate risks related to overweight and obesity.

*Table 1*. Classification of obesity in adults[1] (WHO, 2000)

| Weight classification | BMI ($kg/m^2$) |
|---|---|
| Overweight | 25-29.9 |
| Obesity, grade I | 30-34.9 |
| Obesity, grade II | 35-39.9 |
| Obesity, grade III | >40 |

[1] Age 18 - 65 years

The term morbid obesity includes subjects with a BMI>40 $kg/m^2$ or BMI>35 $kg/m^2$ with obesity related conditions associated with an increased cardiovascular disease risk such as sleep apnoea and diabetes mellitus or induce physical problems that interfere with lifestyle (i.e. joint disorders or body size problems interfering with employment, family situation, ambulation) ([Anon], 1992).

**Prevalence of obesity in Norway 1960 to 2002**

Figure 1 shows the increase of obesity prevalence in the age group 40-44 years from 1965 to 2002.

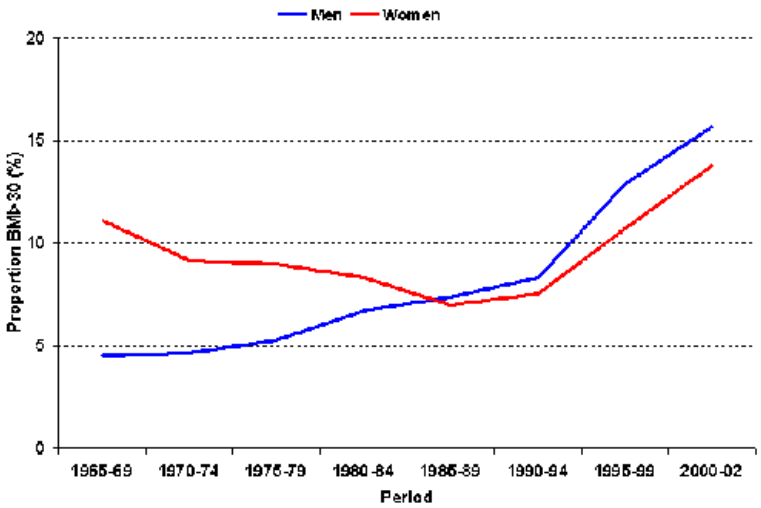


***Figure 1***: Development of obesity in the age group 40-44 years from 1965 to 2002

The figure is based on data from Skjermbildeundersøkelsene (1963-1975) and health surveys in 5 Norwegian counties (Oslo, Hedmark, Oppland, Troms and Finnmark) from 1972-73 to 2000-2002. These health surveys showed that 14-22% of the men and 13-20% of the women in the age group 40-45 had BMI above 30 kg/m$^2$.

Source: Anders Engeland, Norwegian Institute of Public Health, 2003

**Type 2 diabetes – diagnosis and prevalence**

About 90% of patients who develop type 2 diabetes mellitus are obese. Type 2 diabetes is characterized by peripheral insulin resistance and an insulin-secretory defect that varies in severity. For type 2 diabetes mellitus to develop, both defects must exist. All overweight individuals have insulin resistance, but only those with an inability to increase beta-cell production of insulin develop diabetes. An increase in the postprandial glucose levels are observed prior to diabetes type 2. Eventually, fasting hyperglycaemia develops as inhibition of hepatic gluconeogenesis declines. Patients with type 2 diabetes mellitus retain the ability to secrete some endogenous insulin, and those who are treated with insulin do not generally develop diabetic ketoacidosis if insulin therapy is stopped. They do not need insulin for short-term survival, but may need insulin for treatment of glycaemia.

People with type 2 diabetes commonly have hypertension, central (upper body) obesity, and dyslipidemia, and are at high risk of macrovascular disease. This clustering has been labelled variously as Syndrome X, the Insulin Resistance Syndrome or the Metabolic Syndrome. Alone, each component of the cluster conveys increased cardiovascular disease risk, and has an additive effect in combination. It is well documented that the symptoms of the metabolic syndrome can be present for up to 10 years before diabetes occurs, and raised blood glucose in the non-diabetic range will often be found (IGT=impaired glucose tolerance or IFG = impaired fasting glucose). Patients with type 2 diabetes mellitus can delay the need for treatment with oral glucose-lowering medication or insulin if they lose weight.

The prevalence of diabetes in Norway is unknown, but it is estimated that 90 000 – 120 000 individuals are diagnosed with diabetes. In addition it is believed that a great number of individuals have an undiagnosed type 2 diabetes. Therefore, it is likely that approximately 200 000 individuals in Norway have diabetes (Stene *et al.*, 2004).

### Ketosis

Ketosis is characterised by enhanced concentration of ketone bodies (hydroxybutyrate, acetone and acetoacetate) in blood and urine and is the metabolic adoption to starvation. Ketosis is also the metabolic response to low carbohydrate intake (<40 g per day) with sufficient energy intake. The ketone bodies are produced in the liver from fatty acid breakdown to yield energy for the gluconeogenesis process. The substrates for gluconeogenesis are amino acids and glycerol, which means that during starvation or low carbohydrate intake, body protein is lost. However, since ketone bodies can replace glucose as energy substrate in most of the body's tissues, also to a significant extent in the brain, the demand for glucose will level off and protein loss will decrease. During a semi-starvation, like with use of VLCD, ketogenesis will develop, and the degree is depending on the carbohydrate content. Ketosis have been said to suppress hunger.

## SCIENTIFIC STUDIES ON NUTRIENTS IN VLCD PRODUCTS

Possible safety concerns from use of VLCD product are mainly related to the low energy intake and to low intake of essential nutrients (protein, fat, vitamins and minerals). Loss of lean body mass is unavoidable in subjects in negative energy balance, and the loss is increasing as the energy intake decreases.

Obese individuals with type 2 diabetes will benefit from weight reduction, but concern has been raised regarding insulin/blood sugar regulation and ketosis in this population group.

### Carbohydrate

The content of carbohydrate in VLCD will have impact on development of ketosis. If the intake of carbohydrates is increased above ~ 40 g/day, the demand for glucose through gluconeogenesis is reduced and the production of ketone bodies will decrease. The total intake of both carbohydrates and proteins is important for protein sparing in weight reduction. However, a certain degradation of endogenous protein is inevitable when the energy balance is negative. After a thorough review of the available literature and extensive discussions, it was concluded in the SCOOP-report that VLCD products should contain a minimum carbohydrate level of 55 g (digestible carbohydrate) in order to reduce ketosis and reduce loss of lean body mass (SCOOP, 2002).

For this assessment we searched the MEDLINE database for new literature (after 2002, cf the SCOOP-report) and used the terms: Very low calorie diet, very low energy diet and VLCD in combination with the term carbohydrate, but few relevant studies were identified.

Ketogenic diets without energy restriction are popular for weight reduction and diets with less than 20 g of carbohydrate or less than 5% of energy from carbohydrate are usually used to achieve ketosis. This approach for weight reduction modulates hepatic metabolism by increasing gluconeogenesis and ketosis. In a small study it was recently shown that the majority of hepatic glucose production under carbohydrate restriction came from amino acid precursors, not glycerol (Browning *et al.*, 2008). However, the weight reducing effect of low carbohydrate diets does not seem to be related to the effect of ketosis, but rather to increased satiety from the high protein contents (Johnston *et al.*, 2006). Comparing a ketogenic low-carbohydrate diet (beginning with 5% of energy as carbohydrate) and a non-ketogenic low carbohydrate diet (40% of energy as carbohydrate), showed that the diets were equally effective in reducing body weight during a six week trial, but the ketogenic diet was associated with several emotional adverse effects (Johnston *et al.*, 2006). Hence this study

does not support ketosis as more efficient in weight reduction programs than non-ketogenic diets.

In a recent study circulating metabolites regulating hunger and satiety were measured before and after weight loss. A weight loss of 10% was achieved during eight weeks of VLCD in 12 obese men. The study showed that during ketosis the concentration of cholecystokinin, a hormone that possibly affects early satiety was not reduced. A hypothesis of an interaction between ketone bodies and cholecystokinin secretion was raised by the authors (Chearskul *et al.*, 2008).

A study examining the acid-base status of a low-carbohydrate, ketogenic diet (less than 20 g carbohydrate daily) and a low fat, energy restricted (reduced with 500 - 1000 kcal) diet in obese subjects without diabetes, showed that both groups experienced a decreased pH in arterial blood, but pH was still in the normal range (above 7.35) after 24 weeks. In the ketogenic diet group a small, transient decrease in serum bicarbonate in conjunction with a mild ketosis was seen. Serum pH was not related to serum ketone bodies and the authors pointed out that the buffering capacity of the body seems to adjust the relatively low concentrations of ketone bodies observed during carbohydrate restricted diets (Yancy *et al.*, 2007).

The mild acidosis that initially occurs during weight loss by VLCD, may be prevented by including vegetables that shift acid-base balance in the alkaline direction (Arnett, 2008). The Eurodiet recommends eating vegetables during the diet, and even with a consumption of an additional 1 kg of vegetables, the carbohydrate intake will not exceed 45 g per day.

Including additional vegetables in the VLCD period may be beneficial to preserve bone mass by shifting the acid-base balance in the alkaline direction. Mild acidosis may occur during weight loss, and it has been shown that H+ has negative impact on the skeleton (Arnett, 2008). It is possible to include about 100 kcal of vegetables (i.e. 250 g tomatoes + 300 g cucumber + 100 g salad + 100 g sweet pepper) and still achieve an energy intake less than 800 kcal. Only one of the products at the Norwegian marked recommends vegetable intake along with the VLCD. Vegetables in these amounts also contribute with 12 g carbohydrate and 8 g fibre to the total daily intake.

Further research is needed to conclude on ketosis and non-ketosis on protein sparing during VLCD treatment. The same conclusion was reached in the SCOOP-report (SCOOP, 2002). While ketosis might be effective as a satiety regulator, several negative emotional side-effects have been reported (Johnston *et al.*, 2006).

As seen in Annex 2, only one of the available VLCD products in Norway includes carbohydrate at the recommended level suggested in the SCOOP-report (55 g carbohydrate per day).

### Fibre

In the SCOOP-report from 2002 it was recommended an intake of no less than 10 g of fibre per day but not higher than 30 g in VLCD products (SCOOP, 2002). These limits were set on general knowledge of the beneficial influence of fibre on the intestinal function, and of reported reduction of gastro-intestinal distress with use of 10 g of fibre in VLCD products.

For this assessment we searched the MEDLINE database for new literature (after 2002, cf the SCOOP-report) and used the terms: Very low calorie diet, very low energy diet and VLCD in combination with the term fibre, but few relevant studies were identified

Dietary fibre is described as a class of polysaccharides that escape hydrolysis, digestion and absorption in the small intestine in humans, but with complete or partial fermentation in the large intestine.

Dietary fibre has a desirable effect on stool weight and transit time. The mechanism by which stool weight and laxation is promoted varies for different fibres. Fermentable fibres are somewhat less effective than unfermentable fibres (Stasse-Wolthuis *et al.*, 1980). The influence on fecal weight is also dependent on particle size of the fibre source, affecting the water holding capacity of the fibre matrix (Heller *et al.*, 1980).

There is little evidence that an increased intake of dietary fibre, in itself, is effective in treatment of obesity. Consumption of a diet rich in dietary fibre has, however, shown to be inversely associated with BMI (Kimm, 1995; Miller Jones, 2004). It seems that the use of fibre may be more useful in weight maintenance than in weight loss (Miller *et al.*, 1994; Kimm, 1995).

Up to recently the European Nutrition Labelling Directive did not specify a caloric factor to be used for dietary fibre, and the caloric value of dietary fibre was considered to be zero. But as some dietary fibres are partially fermented in the large intestine, fibres will give a contribution to the caloric content. Depending on the type of the dietary fibre, fibre could give 0, 1 or 2 kcal/g. In *Commission Directive 2008/100/EC on nutrition labelling for foodstuffs as regards recommended daily allowances, energy conversion factors and definitions* the caloric value of dietary fibre is set to be 2 kcal/g (EU, 2008).

According to Commission directive 96/8/EU on foods intended for use in energy-restricted diets for weight reduction, low calorie diets (LCD) must contain 10 – 30 g fibre as recommended in the SCOOP-report (EU, 1996).

As seen in annex 2, three of the five products available in Norway have a fibre content between 10 – 30 g per day.

**Protein**

The recommended dietary intake for protein is mainly based on nitrogen balance data, and is 0.8 g protein/kg body weight (bw)/day of high quality protein for both men and women (19-50 years) (IOM, 2005). A protein content above 15 E% is recommended at very low energy intakes (< 6.5 MJ) (NNR Project Group, 2004).

Nitrogen loss during weight reduction is inevitable. A desirable weight loss during dieting is 75% fat mass and 25% fat free mass (FFM) (SCOOP, 2002). VLCD will frequently provide less protein than recommended, and the question concerning optimal protein and carbohydrate content in VLCD in order to avoid excess loss of body protein is debatable.

Based on the ratio FFM loss to total weight loss, the SCOOP-report recommended a minimum level of 50 g protein per day in VLCD products with a nutritional quality equivalent to a protein-digestibility-corrected amino acid score (PDCAAS) of 1 (100%) and with a minimum of 55 g per day available carbohydrate to spare body protein (SCOOP, 2002). Only subjects with a body weight less than 63 kg will achieve the IOM recommendation at 0.8 g protein/kg bw/day with an intake of 50 g protein per day. Due to the limited energy content in VLCD, the protein recommendations from IOM 2005 cannot be met for subjects on VLCD. The recommended intake of 0.8 g/kg bw does not take account of body fat mass, and according to the SCOOP-report, it seems unnecessary to have a protein intake of 0.8 g high quality protein/kg body weight to avoid extra loss of FFM during VLCD treatment (SCOOP, 2002).

For this report we searched the MEDLINE database for new literature (after 2002) and used the terms: Very low calorie diet, very low energy diet and VLCD in combination with the terms fat free mass; lean body mass; dietary protein and nitrogen.

Only one study was identified in the time periode 2000-2008 (Zahouani *et al.*, 2003). In this study 1389 obese subjects were participating in a weight loss program using VLCD containing 600-800 kcal and 1-1.3 g protein/kg of the ideal body weight (BMI=25 kg/$m^2$). Weight loss and body composition were measured by bioimpedance and showed a mean weight loss of 12.3 kg and loss of FFM of 2.0 kg giving a ratio of FFM to total weight loss of 0.16.

This ratio is in accordance with the finding in the SCOOP-report of which an analysis of excisting data from 32 studies published between 1986 to 2000 showed a mean ratio of 0.19 (SCOOP, 2002). Moreover, in the SCCOP-report it was concluded that there was no difference in the loss of fat mass between ketogenic and non-ketogenic diets in patients with BMI levels ranging from 25 to 60 kg/$m^2$.

As seen in annex 2 all the products available on the Norwegian market contain more than 50 g protein per day. However, the protein sources and protein mixtures in these VLCD products vary. The mixture and ratio of protein sources used in the VLCD products are not known or labled. Amino acid patterns are not given. Consequently quality is unknown.

**Dietary protein quality**

Dietary protein quality is determined by its ability to provide total nitrogen and essential amino acids. Protein quality is mainly depending on two factors: its digestibility and the amino acid composition of the protein. The best method to assess protein quality is considered to be Protein Digestibility Corrected Amino Acid Score (PDCAAS) (IOM, 2005).

> PDCAAS (%) = [mg of limiting amino acid in 1 g test protein (nitrogen) / mg of same amino acid in 1 g reference protein (nitrogen) * true digestibilty (%)]

The reference protein used in the PDCAAS method is a hypothetic protein based on the protein requirements for children 1 – 3 years.

Animal protein sources generally have a digestibility of 95% and protein from plant sources a digestibility of about 80%. To assess the overall protein quality the amount of the indispensable amino acids to total nitrogen has to be known. The net protein utilization is determined by the most limiting amino acid (the essential amino acid found in the smallest quantity in the foodstuff). It is possible to have protein from different sources to enhance the protein quality. This limits the loss through deamination and increases overall net protein utilization. Annex 3 shows calculations of PDCAAS in different protein sources.

The recommended levels of indispensable amino acids in mg/g protein and in mg/g nitrogen is shown in Table 2 (reference protein). The amino acid scoring pattern suggested by the IOM is higher than previously recommended requirements for indispensible amino acids e.g. WHO. The IOM data is based on the Estimated Average Requirement for protein and indespensable amino acids for children of 1 to 3 years. Since these requirements also fullfill the requirements for young children, adolescents and adults, the requirements for 1 – 3 years old are set for all population groups.

*Table 2*: IOM Amino Acid Scoring Pattern (IOM, 2005)

| Amino acids | mg/g protein[1] | mg/g nitrogen |
|---|---|---|
| Histidine | 18 | 114 |
| Isoleucine | 25 | 156 |
| Leucine | 55 | 341 |
| Lysine | 51 | 320 |
| Methionine & Cysteine | 25 | 156 |
| Phenylalanine & Tyrosine | 47 | 291 |
| Threonine | 27 | 170 |
| Tryptophan | 7 | 43 |
| Valine | 32 | 299 |

[1] Based on Estimated Average Requirements for 1-3 year old children for both indispensable amino acids and protein

Other macronutrients such as carbohydrate and fiber may influence nitrogen balance.

**Fat and fatty acids**

In VLCD, fat intake has to be kept at a minimum to allow for a satisfactory protein intake. In the SCOOP-report from 2002 it was stated that a total intake of 7 g of fat/day would reduce the incidence of cholelithiasis (SCOOP, 2002). There was, however, no references added to this recommendation, which indicate that this might be a clinical accepted value.

Incidence of cholelithiasis is a problem in relation to energy restriction and weight loss, but obesity in itself is also a risk factor for gall stone formation. During fat intake restriction the bilary acid becomes fully saturated, and if the gall bladder is not emptied, gall-cholesterol stones can be formed. It has been shown that 10 g (Stone *et al.*, 1992) and 12.2 g fat (Festi *et al.*, 2000) maintain the gall-bladder contractions and reduces cholelithiasis in obese patients on VLCD.

The Nordic Nutritional Recommendations (NNR Project Group, 2004) state that at least 3% of the energy should be derived from poly unsaturated fatty acids (PUFA) and that at least 0.5 % of the energy should come from n-3 fatty acids. This represents 1.25 - 2.2 g as PUFA and 0.25 – 0.44 g as n-3 fatty acids in 450 kcal – 800 kcal VLCD products. In the SCOOP-report it is stated that 3 g of linoleic acid and 0.5 g of α-linolenic acid should be present in VLCD products (SCOOP, 2002), which agrees with the calculations based on NNR.

A study was published in 2001 where VLCD was supplemented with medium chain triglycerides (MCT) (Krotkiewski, 2001). The rationale for the MCT supplementation study was to evaluate if the breakdown of FFM could be reduced by reaching a ketonic state faster, sparing protein conversion to glucose. Twenty two patients were randomly assigned to a control group (Adinax®) (3.0 g LCT (long chain triglycerides), 43,6 g carbohydrate, 28.7 g protein), 22 patients to an LCT group (8.8 g LCT, 30,3g carbohydrate, 28.9 g protein) and 22 patients to an MCT group (9.9 g MCT, 30.3 g carbohydrate, 28.9 g protein) for 4 weeks. A significantly higher weight loss and less loss of FFM were seen in the MCT group during the first two weeks compared to the two other groups. The concentration of ketone bodies in plasma was higher and urinary nitrogen excretion was lower in the MCT group. The

differences faded off the next two weeks and after 4 weeks the three groups had the same weight and FFM loss in the groups, which indicate that the effect of MCT was transient.

For this report we searched the MEDLINE database for new literature (after 2002) and used the terms: Very low calorie diet, very low energy diet and VLCD in combination with the terms dietary fat and fatty acid.

In a study published in 2006 the effect of supplementation of VLCD with 2.8 g eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in ratio 2:1 was evaluated (Kunesova *et al.*, 2006). The rationale for this study was that polyunsaturated fatty acids of the n-3 series have been shown to increase basal fat oxidation in humans (Delarue *et al.*, 1996). Eleven patients were randomly assigned to the n-3 group and 9 patients to the control group. Both groups had an intake of 524 kcal from Redita® (40 g protein, 70 g carbohydrates, 9 g fat per day) for three weeks. The n-3 group was supplemented with 2.8 of long chain (LC) n-3 fatty acids, while the control group got salina solution in placebo capsules. BMI and hip circumference was significantly reduced in the n-3 group compared to the placebo group. A significant higher increase in beta-hydroxybutyrate was found in the n-3 group showing higher ketogenesis (Kunesova *et al.*, 2006). This study has contributed to interest in increasing PUFAs of n-3 in VLCD products.

According to NNR, no more than 1.5 E% should come from the n-3 fatty acids EPA and DHA (NNR Project Group, 2004). The upper intake level has been put forward because of increased tendency of bleeding time with higher intake (Clarke *et al.*, 1990; Emsley *et al.*, 2008). An intake of 2 g EPA per day showed a significant increase in bleeding time in patients with schizophrenia (Emsley *et al.*, 2008). In the study to Kunesova *et al*. the energy intake from EPA and DHA contributed with 4.6% of the energy intake. With the energy restriction of VLCD it is difficult to pursue the Nordic upper level and at the same time reach therapeutic doses of long chain n-3 PUFA (Breslow, 2006). However, the studies reporting adverse health effects of EPA and DHA are using total amounts in gram and not E%, and it might not be correct to do in VLCD products. In the study to Kunsenova *et al*. no adverse health effects was reported, but the study was not designed for risk evaluation. Until further documentation is present, the VKM Panel suggests that EPA content in VLCD products should not exceed 2 g per day.

### Vitamins, Minerals and trace elements

In the SCOOP report it is concluded that VLCD products should contain vitamins and minerals in similar values as stated in Commission Directive 96/8/EC with manganese (1 mg) and chromium (33 µg) (SCOOP, 2002). The directive only includes minimum limits. To our knowledge these limits are based upon requirement of vitamins and minerals in the general adult population, and do not take into account potential special needs in overweight or obese subjects.

### Nutritional status overweight – obese patients

For this report we searched the MEDLINE database for new literature (after 2002) and used the terms: Nutritional status, vitamin status and mineral status in combination with the terms very low calorie diets and very low energy diets and VLCD.

In recent years there has been an increased focus on the prevalence of vitamin and mineral deficiency in overweight and obese subjects compared to subjects with normal weight. Scientists speculate in whether this is due to a lower intake, lower absorption, more excretion,

changed metabolism, changed storage and/or changed distribution. It has also been suggested that the low biochemical blood levels not necessarily reflect actual deficiencies (Kimmons *et al.*, 2006).

Kimmons *et al*. studied the association between BMI and micronutrient level among a national representative sample of US adults (Kimmons *et al.*, 2006). Obesity in women was related to low levels of vitamin E, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene, total carotenoids, vitamin C, selenium (premenopausal), vitamin D and folate. Obesity in men aged 19.0 - 64.9 years was associated with low levels of alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, total carotenoids, vitamin C, selenium and folate. The authors suggest that the observed low levels of serum folate but adequate levels of folate in erythrocytes may imply sufficient stores but inability to mobilize and circulate the stored folate.

In a community based cohort made in subjects from The Framingham Heart Study, Keaney *et al*. examined the clinical conditions associated with systemic oxidative stress (Keaney *et al.*, 2003). They concluded that BMI, smoking and diabetes are strong and independent precursors of oxidative stress.

Several scientists have suggested that low levels of antioxidants found in the obese might be caused by adipose tissue-specific oxidative stress. This may further contribute to some of the co-morbidities associated with overweight. The low concentration levels of vitamin C, vitamin E, selenium, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein,/zeaxanthin and total carotenoids seen in obese subjects support this theory (Kimmons *et al.*, 2006; Ernst *et al.*, 2008; Aasheim & Bøhmer, 2008; Pereira *et al.*, 2008).

Ernst *et al*. made an assessment of micronutrient status among morbidly obese subjects who had been referred for evaluation for bariatric surgery (Ernst *et al.*, 2008). Low concentration values were found in 25% of the patients for 25-hydroxyvitamin D, 25% for zinc, 18% for vitamin $B_{12}$, 13% for albumin, 8% for phosphate, 7% for ferritin, 7% for hemoglobin, 5% for magnesium and 3% for folate compared to non-obese. Thirty-seven per cent of the patients had secondary hyperparathyroidism. Additional assessments were made in a subsample and one third had low selenium concentration values and 5% or fewer had low concentration values for niacin, vitamin $B_6$, vitamin E, respectively. Normal concentration values were found for copper, vitamin $B_1$ or vitamin A in this study.

Micronutrient status in 110 morbidly obese patients referred for bariatric surgery in Norway were compared with the micronutrient status in 58 healthy non-obese controls in a cross-sectional study (Aasheim & Bøhmer, 2008). The obese patients had significant lower levels of 25- hydroxyvitamin D, vitamin $B_6$, vitamin C and lipid-standardised vitamin E compared to the non-obese.

The association between obesity and vitamin D deficiency and secondary hyperparathyroidism is demonstrated in several studies (Wortsman *et al.*, 2003; Parikh *et al.*, 2004; Kimmons *et al.*, 2006; DiGiorgi *et al.*, 2008; Goldner *et al.*, 2008; Ernst *et al.*, 2008; Aasheim & Bøhmer, 2008). The reason seems to be multifactorial and one postulated theory is that the fat soluble vitamin D is sequestered in the adipose tissue in the obese and becomes less available. This is supported by DiGiorgi *et al*. who found a positive linear relationship between percent of excess weight loss and vitamin D levels in gastric bypass patients 1 and 2 years after surgery. As the weight decreased, the concentration levels of 25-hydroxyvitamin D increased, which might suggest that vitamin D is released from the fat depots during weight loss (DiGiorgi *et al.*, 2008).

Another common assumption is that obese subjects are likely to expose less skin to the sun and therefore may synthesise less vitamin D compared to normal weight subjects. Wortsman *et al*. demonstrated in a clinical trial that the obese participants did not increase their serum vitamin D levels as efficiently as the non-obese participants when exposed to the same dose of UVB radiation (Wortsman *et al.*, 2003). However, skin biopsies obtained from a subsample in the same study showed that the capacity of the skin to produce vitamin D did not differ between the two groups. The theory of vitamin D being sequestered in the adipose tissue and thereby becomes trapped, is supported by the decreased bioavailability of cutanously produced vitamin $D_3$ found in the obese group.

Yet another aspect of consideration is variations in cut-off values in the studies. There is no common definition of optimal vitamin D status. This is also reflected in the studies of vitamin D status among the obese where the cut-off values for deficiency show some variety. In a Norwegian report from 2006, vitamin D sufficiency is defined as serum levels of 25(OH) vitamin D > 50 nmol/L. Insufficiency, deficiency and severe deficiency is defined as < 50 nmol/L, < 25 nmol/L and < 12,5 nmol/L respectively (Nasjonalt råd for ernæring, 2006). Bischoff-Ferrari *et al*. carried out a meta-analysis to determine the optimal serum 25-hydroxyvitamin levels for several end-points including bone health, and found that the most advantageous serum level appeared to be at least 75 nmol/L. (Bischoff-Ferrari, 2008). In the National Institutes of Health conference "Vitamin D and Health in the 21st Century: an Update" which was held in September 2007, scientists concluded that more research is necessary to determine the threshold 25(OH) vitamin D concentration associated with optimal functional outcomes (Brannon *et al.*, 2008).

Levels of dietary vitamin D intake required to maintain serum 25-hydroxyvitamin D status at different cut-off values were studied in a recent well designed intervention trial conducted in more than 200 men and women aged 20 - 40 years with a mean BMI of 26 kg/m$^2$, living in United Kingdom (latitude: 51 ºN and 55 ºN). The subjects were randomized to take one of four different doses of vitamin D (0, 5, 10, and 15 µg/day) during 22 weeks from October to March. A clear dose-related increment in serum 25-hydroxyvitamin D was found with increasing supplemental doses and a slope of the relationship between vitamin D intake and serum 25-hydroxyvitamin D was calculated. Based on that calculation it was estimated that an intake of 28 µg vitamin D was required to maintain serum concentrations of 25-hydroxyvitamin D above 50 nmol/L in 97.5% of the population during late winter time (Cashman *et al.*, 2008). To our knowledge no intervention trials have been performed to assess levels of dietary intake of vitamin D required to maintain serum concentrations of 25-hydroxyvitamin D during periods of weight loss with VLCD among obese subjects

It might be argued that some of the studies have only measured the micronutrient status among obese, without comparing them to subjects with normal weight or non-obese (DiGiorgi *et al.*, 2008; Ernst *et al.*, 2008) and thereby not taking into consideration that a certain prevalence of deficiencies also will exist in a population with normal weight. In some studies, however, the concentration levels of vitamins and minerals in the obese are compared to the levels in normal weight and overweight subjects (BMI 20.0-29.5 kg/m$^2$) (Parikh *et al.*, 2004; Goldner *et al.*, 2008; Aasheim & Bøhmer, 2008) and in other studies the levels in the obese are compared to levels in subjects with normal weight (BMI 20.0-24.5 kg/m$^2$) (Wortsman *et al.*, 2003).

Obesity is associated with hyperparathyroidism (Wortsman *et al.*, 2003; Parikh *et al.*, 2004; Kimmons *et al.*, 2006; DiGiorgi *et al.*, 2008; Goldner *et al.*, 2008; Ernst *et al.*, 2008; Aasheim & Bøhmer, 2008). The authors found that 37 per cent of the morbidly obese patients referred for bariatric surgery had secondary hyperparathyroidism (Ernst *et al.*, 2008). A moderate loss

of bone mineral content may occur during VLCD (SCOOP, 2002). This may be due to use of bone minerals for buffering purpose during acidosis (Arnett, 2008). Positive calcium balance has been reported during VLCD providing an average intake of 1200 mg calcium per day (Davie *et al.*, 1986).

No new literature (after 2002) was found on calcium or hyperparathyroidism during VLCD treatment.

## SPECIAL GROUPS AND CONTRAINDICATIONS

### Type 2 diabetes and VLCD

The SCOOP-report discusses the use of VLCD in obese subjects with diabetes type 2, but gives no concluding recommendations. Weight loss is considered as beneficial, as it improves many of the concomitant metabolic abnormalities predisposing to the complications of diabetes, and adjustment of medication is discussed (SCOOP, 2002).

During the last decennium a large number of studies on the use of VLCD in obese subjects with type 2 diabetes have been published. Several of these are short-term use of VLCD, from a few days to 10 weeks (Gumbiner *et al.*, 1996; Willi *et al.*, 2004; Skrha *et al.*, 2005; Jazet *et al.*, 2005a; Jazet *et al.*, 2005b; Lara-Castro *et al.*, 2008).

Most obese individuals with type 2 diabetes on VLCD have a marked improvement in hyperglycemia. Blood glucose concentrations fall within the first one to two weeks, and remain lower as long as the diet is continued. Patients taking insulin and/or oral hypoglycemic drugs may have to discontinue or reduce the intensity of the therapy (Bray, 2008; Delahanty & McCulloch, 2008). Subjects adhering to VLCD usually have a fall in blood pressure, especially during the first week. Antihypertensive drugs, especially calcium channel blockers and diuretics, may have to be reduced or discontinued when a VLCD treatment is begun (Henry & Gumbiner, 1991).

A recent Nordic study demonstrates that 8 weeks of VLCD (Nutrilett) gives a 10-15% weight loss in most patients with metabolic risk factors such as dyslipidemia, impaired fasting glucose, and diet-regulated type 2 diabetes. A long term, intensive follow-up shows that half of this weight loss and the positive effects on other CVD risk factors can be maintained for three years. The use of Orlistat in the follow up period lead to better maintenance of the weight loss and some of the risk factors (Richelsen *et al.*, 2007).

A meta analysis (Norris *et al.*, 2004) of 22 studies of weight loss interventions (a total of 4659 participants) with follow-up of 1 to 5 years conclude: “Weight loss strategies involving dietary, physical activity, or behavioural interventions were associated with small between-group improvements in weight. These results were minimized by weight loss in the comparison group, however, and examination of individual study arms revealed that multicomponent interventions, including very low-calorie diets or low-calorie diets, may hold promise for achieving weight loss in obese adults with type 2 diabetes.” A Cochrane study (Norris *et al.*, 2005) came to the same conclusion.

Very few complications have been reported with short-term use of VLCD also within obese subjects with type 2 diabetes.

On the other hand, the management of persons with hyperglycaemia and other features of the metabolic syndrome should focus not only on blood glucose control but also include strategies for reduction of the other CVD risk factors. A combination of life style changes (nutrition, physical activity, weight loss and smoking cessation) and medication is necessary (WHO, 2008).

### Contraindications

Contraindications for the use of VLCD products are discussed in the SCOOP-report chapter 9.3 (SCOOP, 2002). Newer scientific literature has not been found. The VKM Panel supports the contraindications mentioned in the SCOOP-report chapter 9.3; and outlined as follows: Porphyria, liver or kidney disease, type 1 diabetes mellitus, haemopathy, cancer, electrolyte disorders, orthostatic hypotension, cardiovascular or cerebrovascular disease (including cerebral arteriopathy), hereditary metabolic diseases, e.g. phenylketonuria, abnormal psychological states of more than a minor degree including schizophrenia, behavioural disorders involving eating (bulimia or anorexia), alcoholism or drug addiction, major surgery or serious accident within the last 3 months, gout, gallstones, renal lithiasis or acute ischaemic cardiopathies

In addition, VLCD is unsuitable for use in children and adolescents, pregnant and lactating women and elderly (above 65 years). The SCOOP Panel did not find any differences in loss of FFM in subjects with BMI ranging from 25 to 60 kg/m$^2$. Despite this, the SCOOP-report did not recommend the use of VLCD in subjects with BMI < 30 kg/m$^2$ (SCOOP, 2002). The VKM Panel supports this conclusion.

## EXPOSURE

Most VLCD products are marketed as suitable for use for 8 – 16 weeks (Mustajoki & Pekkarinen, 2001), and VLCD products are commonly used as the only source of nutrients. It might be assumed that some individuals on VLCD also take food supplements. It is therefore important that VLCD products contain an appropriate amount of all essential nutrients, but in amounts preventing excessive intake of vitamins and minerals in cases of additional exposure from food supplements.

## RISK CHARACTERIZATION/CONCLUSION

The VLCD diets are designed to produce rapid weight loss for individuals with BMI ≥30 kg/m$^2$. The method is considered safe and effective when used under careful medical supervision and included in a treatment program for lifestyle modification. The method may be used in patients in need for rapid weight loss before surgery or in subjects that have difficulty to comply with other energy deficient diets for weight loss purposes. Being the only source of nutrients, it is important that VLCDs contain nutrients in appropriate amounts, and include all essential nutrients. In the SCOOP-report, medical supervision is recommended if VLCD treatment exceeds 3 weeks (SCOOP, 2002).

Side-effects of ketogenic diets need more studying. The advantage of suppressed hunger and increased satiety could make the diet more tolerable and enhance the compliance, hereby counterbalancing the disadvantage of an insignificant extra protein loss and emotional side-effects. Allowing for ketogenic VLCDs prescribed to patients under medical supervision (i.e. during clinical trials), is a quite different matter compared to when sold over the counter. Literature search has not provided any further documentation for minimum intake level of carbohydrate during VLCD treatment.

Until further scientific proof is present, the VKM Panel agrees with the conclusion in the SCOOP-report and recommends minimum 55 g carbohydrate per day. Additional intake of vegetables during VLCD can be recommended to prevent acidosis.

The SCOOP-report concludes that VLCD products should contain minimum 10 g of fibre to reduce gastro-intestinal distress and constipation. An upper limit of 30 g of fibre was

suggested because higher intake might give rise to gastro-intestinal problems. Literature search has not provided any further documentation for minimum and maximum intake levels of fibre during VLCD treatment, and hence the same minimum and maximum amounts as given in the SCOOP-report is recommended. There are no specific recommendations for insoluble and soluble fibres, but because of their different physiological quality, the VKM Panel recommends that both types are present in VLCD products.

The SCOOP-report concludes that the minimum level of protein should be 50 g per day of high quality protein to reduce loss of lean body mass and spare body protein. Both the total protein and the protein quality are essential. Literature search has not provided any further documentation for minimum intake level of protein during VLCD treatment, and hence the VKM Panel recommends minimum 50 g high quality protein per day in VLCD products. If the PDCAAS in a VLCD is less than approximately 100% , the amount of total protein has to be increased. The VKM Panel suggests that the amount of protein in the VLCD products should be based on analyses of both nitrogen content (total protein) and the amino acid pattern. The recommended amino acid pattern is given in table 2.

According to the SCOOP-report, the content of fat should be 7 g/day to prevent incidence of cholelithiasis (SCOOP, 2002). Incidence of cholelithiasis is a problem in relation to energy restriction and weight loss. An intake of 10 g (Stone *et al.*, 1992) and 12.2 g fat (Festi *et al.*, 2000) has been shown to maintain the gall-bladder contractions in obese patients on VLCD. However, no studies have been performed to evaluate a lower intake limit of fat to maintain a normal gall-bladder function. The conclusion in the SCOOP-report was based on clinical experience of reduced incidences of cholelithiasis at an intake of 7 g fat per day. No documentation as of today to increase or reduce this recommendation is available. Hence the VKM Panel suggests maintaining 7g of fat per day as a minimum content in VLCD products (i.e. 14 E% in 450 kcal VLCD products and 8 E% in 800 Kcal VLCD products).

In the SCOOP-report it is stated that VLCD products should contain 3 g of linoleic acid (which represents 6 - 3 E% in 450 - 800 kcal diets), and 0.5 g of α-linolenic acid (i.e. 1 - 0.5 E% in 450 - 800 kcal diets). Since no new information on fatty acid requirements in VLCD products was found, and since these recommendations are within the limits given in NNR (NNR Project Group, 2004), the VKM Panel suggests that the values recommended in the SCOOP report are followed.

The lowest recommended amounts of carbohydrate, protein, fat and fibre in VLCD products will give an energy intake of no less than 500 kcal/day, i.e. 220 kcal (55 g) from carbohydrates, 200 kcal (50 g) from protein and 20 kcal (10g) from fibre, and 63 kcal (7g) from fat.

In the SCOOP-report it is suggested that the minimum content of vitamins and minerals should have similar values as stated in Commission Directive 96/8/EC with manganese (1 mg) and chromium (33 µg). The minimum limits in Directive 96/8/EC are generally lower than the Norwegian recommendations for intake of nutrients. Considering the studies indicating reduced nutritional status in obese subjects, it might seem reasonable to recommend minimum limits of micronutrients in VLCD products above the general recommendations for micronutrients, but further research is needed before this can be considered sufficiently documented for most of the vitamins, minerals and trace elements. Further research is needed to elaborate on the reasons why obese subjects present with low concentration values of several micronutrients. The clinical significance of the observed deficiencies needs to be established and new recommendations for optimal doses to ensure sufficiency should be made for the overweight and obese population.

The VKM Panel recommends that the minimum limits of the micronutrients listed in Annex 1 (except for vitamin D, see below) should at least equal the recommended levels in the general population. In case of different recommendations for men and women, the VKM Panel has suggested the highest recommended level in the Norwegian recommendations. Exception should be made for folic acid. Women in reproductive age are recommended an intake at 400 mcg per day, and the rest of the adult population is recommended an intake at 300 mcg. The VKM Panel suggests 300 mcg as minimum limit in VLCD products. There are no recommendations for intake of vitamin K, sodium or molybdenum, for these nutrients the VKM Panel therefore suggests to establish minimum limits based upon the minimum limits from Directive 1279 on foods for medical purposes and calculated from an energy intake of 2000 kcal. For fluoride and chloride there are no recommendations for intake as they are not considered essential nutrients, and the VKM Panel suggests that there should be no minimum limits.

Obesity is clearly associated with vitamin D deficiency (Wortsman *et al.*, 2003; Parikh *et al.*, 2004; Kimmons *et al.*, 2006; DiGiorgi *et al.*, 2008; Goldner *et al.*, 2008; Ernst *et al.*, 2008; Aasheim & Bøhmer, 2008), even though the cut-off values for vitamin D deficiency show some variety in the different studies. In a Norwegian report from 2006, vitamin D sufficiency is defined as serum levels of 25(OH) vitamin D > 50 nmol/L (Nasjonalt råd for ernæring, 2006). Because of the observed vitamin D deficiency among the overweight and obese, the VKM Panel recommends minimum 10 µg vitamin D per day in VLCD products. This is higher than the recommendations at 7.5 µg for adults (NNR Project Group, 2004), but lower than the 28 µg vitamin D suggested by Cashman *et al*. (Cashman *et al.*, 2008).

Recommended intake for calcium is 800 mg/day for adults (NNR Project Group, 2004). The reported secondary hyperparathyroidism in obese patients is not considered as sufficient documentation for recommending a higher intake of calcium during VLCD treatment. The calcium balance in obese subjects and during VLCD needs further investigation.

As seen in Annex 2, vitamin D is lower than recommended in all the VLCD products in Norway. In addition some of the products also have lower contents of vitamin A, thiamin, niacin, vitamin $B_{12}$, folic acid, vitamin C, magnesium and potassium than the minimum limits suggested by the VKM Panel.

There are no conclusions regarding the maximum limits for vitamins or minerals in the SCOOP-report. There is no science based support for setting maximum limits for vitamins, minerals and trace elements in VLCD products. Maximum limits for vitamins and minerals listed in annex 1 should equal two times the recommended daily intake in the general population to avoid excessive intake. VLCD products should be labelled with a warning to avoid additional food supplements with vitamins and minerals during VLCD treatment.

As seen in Annex 2 four products contain copper, sodium and molybdenum at or above the suggested maximum limits, and two products contain chromium above the suggested limit.

As a part of the beneficial effect from weight loss, most obese individuals with type 2 diabetes have a marked improvement in hyperglycemia, blood glucose levels, blood lipids and blood pressure, especially during the first weeks on VLCD (Henry & Gumbiner, 1991; Gumbiner *et al.*, 1996; Jazet *et al.*, 2003; Willi *et al.*, 2004; Skrha *et al.*, 2005; Jazet *et al.*, 2005a; Bray, 2008; Delahanty & McCulloch, 2008; Lara-Castro *et al.*, 2008). However, these effects will not last unless long term lifestyle modifications are adopted.

Weight loss is usually a part of the life-style intervention included in the treatment of obese subjects with type 2 diabetes. However, it has to be mentioned that a beneficial effect on so called hard endpoints (morbidity and mortality) of weight loss programs in type 2 diabetes

have not been demonstrated. The effects of intended weight loss of cardiovascular morbidity and mortality is now investigated in an on-going major controlled trial in the United States (Brancati *et al.*, 2003). In this study other weight reduction regimes than VLCD are used. The study are planned to have a follow up time of 12 years. So far, beneficial effects on risk factors have been shown after one year (Espeland *et al.*, 2007).

Neither the Norwegian Collage of General Practitioners (NSAM) guidelines for diabetes management (Claudi *et al.*, 2005) or the new Norwegian "Clinical Guidelines for Diabetes" mention the use of VLCD (Helsedirektoratet, 2009).

The American Diabetes Association in their position statement writes: "Very-low-calorie diets provide ≤800 calories daily and produce substantial weight loss and rapid improvements in glycemia and lipemia in individuals with type 2 diabetes. When very-low-calorie diets are stopped and self-selected meals are reintroduced, weight regain is common. Thus, very-low-calorie diets appear to have limited utility in the treatment of type 2 diabetes and should only be considered in conjunction with a structured weight loss program" ([Anon], 2008).

VLCD is contraindicated in children, adolescents, pregnant and lactating women, subjects in the age above 65 years or in subjects with porphyria, liver or kidney disease, type 1 diabetes mellitus, haemopathy, cancer, electrolyte disorders, orthostatic hypotension, cardiovascular or cerebrovascular disease (including cerebral arteriopathy), hereditary metabolic diseases, e.g. phenylketonuria, abnormal psychological states of more than a minor degree including schizophrenia, behavioural disorders involving eating (bulimia or anorexia), alcoholism or drug addiction, major surgery or serious accident within the last 3 months, gout, gallstones, renal lithiasis or acute ischaemic cardiopathies. In addition one should be aware of the effect of VLCD on blood pressure and hyperglycaemia which may cause problems if therapies for these conditions are given.

VLCD products should be labelled with a recommendation to drink 1.5 – 2.0 litres of fluid in addition to VLCD (No authors listed, 1993). In line with the SCOOP-report, the VKM Panel will not recommend the use of VLCD in subjects with BMI < 30 kg/m$^2$.

## DATA GAPS

At present the impact of ketogenic diets are unclear. Protein sparing effect in weight reduction regimens are found with intake of a certain amount of carbohydrates which reduces ketosis. Further studies are needed to clarify the role of ketosis with use of VLCD. Loss of energy through ketonuri is said to increase weight loss. Clinical studies so far do not support these theories.

The calcium balance in obese subjects and during VLCD needs further investigation, and further research is needed to elaborate on the reasons why obese subjects present with low concentration values of several micronutrients.

## ANSWER TO THE TERMS OF REFERENCE

*Proposals for minimum limits for the content of fat/ fatty acids, protein, carbohydrates, vitamins, minerals and trace elements in VLCD products:*

VLCD products should provide minimum 55 g carbohydrates, 10 g fibres, 50 g high quality protein and 7 g fat per day including 3 g from linoleic acid and 0.5 g from α-linolenic acid. The amino acid scoring pattern should be as listed in table 2. If the protein source has reduced

protein quality, the amount of protein should be increased or mixed with another protein source in order to obtain this amino acid scoring pattern.

VLCD products should provide minimum 10 µg vitamin D per day, and minimum recommended daily intake for the other vitamins, minerals and trace elements, see Annex 1

*Proposals for maximum limits for the content of fat/ fatty acids, protein, carbohydrates, vitamins, minerals and trace elements in VLCD products.*

No maximum limits are suggested for carbohydrates, protein or fat, as the energy will be the limiting factor. However, it is suggested that the long chain fatty acid EPA should not exceed 2 g per day. The fibre content should not exceed 30 g per day.

There is no documentation in the scientific literature for setting maximum limits of vitamins, minerals or trace elements in VLCD products. The VKM Panel recommends that the maximum limits for vitamins, minerals and trace elements should equal two times the recommended daily intake.

*Are VLCD products suitable in treatment of obese subjects with type 2 diabetes?*
Type 2 diabetes is a chronic disease, and treatment includes long-term life style changes and specific medication to prevent complications due to the increased risk of cardiovascular diseases and the specific diabetic microvascular complications. VLCD will give short-term weight loss and improvement in blood pressure, serum lipids and glycemia, and no serious adverse effects have been reported. On the other hand, VLCD may impede the educational process, which should lead to necessary modifications in life style. VLCD should only be used as part of an educational program in obese subjects with type 2 diabetes, and only under medical supervision.

*Are there conditions or situations in which VLCD products are contraindicated?*

VLCD is contraindicated in subjects with BMI $\leq$ 30 kg/m$^2$, in children, adolescents, pregnant and lactating women, elderly (above 65 years old) or in subjects with porphyria, liver or kidney disease, type 1 diabetes mellitus, haemopathy, cancer, electrolyte disorders, orthostatic hypotension, cardiovascular or cerebrovascular disease (including cerebral arteriopathy), hereditary metabolic diseases, e.g. phenylketonuria, abnormal psychological states of more than a minor degree including schizophrenia, behavioural disorders involving eating (bulimia or anorexia), alcoholism or drug addiction, major surgery or serious accident within the last 3 months, gout, gallstones, renal lithiasis or acute ischaemic cardiopathies. In addition one should be aware of the effect of VLCD on blood pressure and hyperglycaemia which may cause problems if therapies for these conditions are given.

## ANNEX 1

Recommended minimum and maximum limits per day in VLCD products

| | Minimum per day | Maximum per day |
|---|---|---|
| Energy, kcal | 500 | 800 |
| Protein, g | 50 | |
| Carbohydrate, g | 55 | |
| Fibre, g | 10 | 30 |
| Fat, g | 7 | |
| Linoleic acid, g | 3 | |
| α-linolenic acid, g | 0.5 | |
| | | |
| **Vitamins** | | |
| Vitamin A, µg | 900[1] | 1800 |
| Vitamin D, µg | 10[2] | 20 |
| Vitamin E, mg | 10[1] | 20 |
| Vitamin C, mg | 75[1] | 150 |
| Thiamin, mg | 1.5[1] | 3.0 |
| Riboflavin, mg | 1.7[1] | 3.4 |
| Niacin, mg | 20[1] | 40 |
| Vitamin $B_6$, mg | 1.6[1] | 3.2 |
| Vitamin $B_{12}$, µg | 2.0[1] | 4.0 |
| Folic acid, µg | 300[1] | 600 |
| Biotin, µg | 30[1] | 60 |
| Pantothenic acid, mg | 5[1] | 10 |
| Vitamin K, µg | 70[3] | 140 |

[1] Based on the Norwegian recommendations for nutrient intake adults 18-74 years old

[2] Based on new scientific evidence

[3] Based on the minimum limits from the Commission Directive 1999/21/EC on Dietary Foods for Special Medical Purposes and an assumed energy intake of 2000 kcal

| | Minimum per day | Maximum per day |
|---|---|---|
| | | |
| **Minerals/electrolytes** | | |
| Calcium, mg | 800[1] | 1600 |
| Phosphorus, mg | 600[1] | 1200 |
| Iron, mg | 15[1] | 30 |
| Iodine, µg | 150[1] | 300 |
| Magnesium, mg | 350[1] | 700 |
| Copper, mg | 0.9[1] | 1.8 |
| Zink, mg | 9[1] | 18 |
| Potassium, g | 3.5[1] | 7.0 |
| Sodium, g | 0.6[3] | 1.2 |
| Selenium, µg | 50[1] | 100 |
| Manganese, µg | 2.3[1] | 4.6 |
| Chloride, g | 0 | 0 |
| Molybdenum, µg | 70[3] | 140 |
| Chromium, µg | 35[1] | 70 |
| Fluoride, mg | 0 | 0 |

[1] Based on the Norwegian recommendations for nutrient intake adults 18-74 years old

[2] Based on new scientific evidence

[3] Based on the minimum limits from the Commission Directive 1999/21/EC on Dietary Foods for Special Medical Purposes and an assumed energy intake of 2000 kcal

**ANNEX 2**

Nutrient content in some VLCD products available in Norway

| Product name | Allévo[4] | Cambridge[5] | Eurodiett[6] | Mincur[7] | Nutrilett[8] |
|---|---|---|---|---|---|
| Energy, kcal | 594 | 490 | 631 | 471 | 580 |
| Protein, g | 63 | 50.6 | 78.1 | 50 | 63 |
| Carbohydrate, g | 71 | 50.2 | 28.3 | 50 | 53 |
| Fibre, g | 21 | 3.5 | 19.7 | 2.5 | 14.4 |
| Fat, g | 13 | 9.6 | 17.0 | 7.6 | 12.9 |
| Linoleic acid, g | 3.0 | 3.7 | 5.0 | 3.4 | 6.4 |
| α-linolenic acid, g | 0.4 | 0.5 | 0.7 | 0.5 | 0.5 |
| **Vitamins** | | | | | |
| Vitamin A, µg | 1000 | 1080 | 889 | 1034 | 1010 |
| Vitamin D, µg | 5 | 5.3 | 6.5 | 5.1 | 6.8 |
| Vitamin E, mg | 10 | 11.7 | 12.5 | 10.3 | 14.5 |
| Vitamin C, mg | 60 | 60.1 | 57.5 | 61.1 | 85 |
| Thiamin, mg | 1.4 | 1.6 | 1.4 | 1.4 | 1.8 |
| Riboflavin, mg | 2.3 | 2.2 | 2 | 1.8 | 2 |
| Niacin, mg | 18 | 19.6 | 22.5 | 18.3 | 18 |
| Vitamin $B_6$, mg | 2.1 | 2.6 | 2.1 | 2.1 | 2.8 |
| Vitamin $B_{12}$, µg | 3 | 3.1 | 1.9 | 3.1 | 3.3 |
| Folic acid, µg | 300 | 205.2 | 254 | 254.6 | 264 |
| Biotin, µg | 150 | 151.2 | 19.0 | 101.8 | 102 |
| Pantothenic acid, mg | 6 | 6.2 | 4 | 6.0 | 7 |
| Vitamin K, µg | 70 | 71.6 | | 71.3 | 123 |
| **Minerals/electrolytes** | | | | | |
| Calcium, mg | 900 | 1080 | 1147 | 865.1 | 1040 |
| Phosphorus, mg | 800 | 904.5 | 1130 | 941.2 | 908 |
| Iron, mg | 16 | 16.2 | 22 | 21 | 20 |
| Iodine, µg | 150 | 151.2 | 167.2 | 155.8 | 215 |

[4] Chocolate drink

[5] Soups

[6] Average content in bar, omelette, shake, soup and brownie

[7] Chocolate drink

[8] Creamy Chicken Soup

| Product name | Allévo[4] | Cambridge[5] | Eurodiett[6] | Mincur[7] | Nutrilett[8] |
|---|---|---|---|---|---|
| Magnesium, mg | 350 | 360.5 | 204.9 | 427.9 | 411 |
| Copper, mg | 2 | 2.1 | 1.5 | 2.3 | 3 |
| Zink, mg | 15 | 15.1 | 12.6 | 12.8 | 15 |
| Potassium, g | 1.9 | 3.2 | 3.7 | 3.3 | 2.3 |
| Sodium, g | 1.2 | 1.9 | 1 | 1.6 | 3.2 |
| Selenium, µg | 55 | 81 | 69.9 | 56 | 96 |
| Manganese, µg | 2.5 | 2.6 | 1.4 | 2.5 | 4 |
| Chloride, g | 1.7 | 3.6 | | 2.5 | 4.5 |
| Molybdenum, µg | 150 | 256.5 | | 152.8 | 264 |
| Chromium, µg | 50 | 62.1 | | 84.5 | 95 |

[4] Chocolate drink

[5] Soups

[6] Average content in bar, omelette, shake, soup and brownie

[7] Chocolate drink

[8] Creamy Chicken Soup

## ANNEX 3 PDCAAS IN SOYA, WHEAT, MILK POWDER AND FISH FLOOR AND A MIXTURE OF SOYA AND MILK POWDER

Table 1 PDCAAS in soya, wheat (60/70[9]), milk powder and fish floor

| Protein source | Protein, % | N, % | Digestibility,% | Isoleu. | Leu | Lys | S-Aa | A-Aa | Thr | Trp | Val | His | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Soya** | **38** | **6.65** | **86** | **284** | **486** | **399** | **162** | **505** | **241** | **80** | **300** | **158** | **(mg/g N)** |
| | | Digestibility corrected | | **244** | **418** | **343** | **139** | **434** | **207** | **69** | **258** | **136** | **(mg/g N)** |
| | | Reference amino acid pattern | | **156** | **341** | **320** | **156** | **291** | **170** | **43** | **299** | **114** | **(mg/g N)** |
| | | Amino acid score, % | | **157** | **123** | **107** | **89** | **149** | **122** | **160** | **86** | **119** | |
| | | | **PDCAAS, %** | | | | **89** | | | | | | |
| **Wheat** | **9.2** | **1.61** | **95** | **217** | **400** | **113** | **229** | **423** | **153** | **58** | **240** | **121** | **(mg/g N)** |
| | | Digestibility corrected | | **206** | **380** | **107** | **218** | **402** | **145** | **55** | **228** | **115** | **(mg/g N)** |
| | | Reference amino acid pattern | | **156** | **341** | **320** | **156** | **291** | **170** | **43** | **299** | **114** | **(mg/g N)** |
| | | Amino acid score, % | | **132** | **111** | **34** | **139** | **138** | **86** | **128** | **76** | **101** | |
| | | | **PDCAAS, %** | | | **34** | | | | | | | |
| **Milk powder** | **26** | **4.08** | **95** | **330** | **619** | **453** | **220** | **614** | **263** | **89** | **402** | **179** | **(mg/g N)** |
| | | Digestibility corrected | | **314** | **588** | **430** | **209** | **583** | **250** | **85** | **382** | **170** | **(mg/g N)** |
| | | Reference amino acid pattern | | **156** | **341** | **320** | **156** | **291** | **170** | **43** | **299** | **114** | **(mg/g N)** |
| | | Amino acid score, % | | **201** | **172** | **134** | **134** | **200** | **147** | **197** | **128** | **149** | |
| | | | **PDCAAS, %** | | | | | | | | **100** | | |
| **Fish floor** | **75** | **12** | **95** | **269** | **452** | **484** | **248** | **434** | **265** | **60** | **327** | **161** | **(mg/g N)** |
| | | Digestibility corrected | | **256** | **429** | **460** | **236** | **412** | **252** | **57** | **311** | **153** | **(mg/g N)** |
| | | Reference amino acid pattern | | **156** | **341** | **320** | **156** | **291** | **170** | **43** | **299** | **114** | **(mg/g N)** |
| | | Amino acid score, % | | **164** | **126** | **144** | **151** | **142** | **148** | **133** | **104** | **134** | |
| | | | PDCAAS, % | | | | | | | | **100** | | |

[9] Extraction rate

Valine and the sulfur containing amino acids are limiting amino acids in soya giving a PDCAAS of ~90. Soya is a high quality protein source, and may be used in VLCD formulas if the total amount of protein is in accordance with the recommended amount.

Wheat protein has a PDCAAS of ~30. This protein source would have to be in triple amount to give the recommended level of lysine and can not be used as single protein source in a VLCD formula.

The proteins in the milk powder and the fish floor have PDCAAS of 100. The amino acid score numbers above 100 indicates that the protein may be used in mixture with other protein sources lacking these particular amino acids.

Reference List

Aasheim ET & Bøhmer T (2008) Low preoperative vitamin levels in morbidly obese patients: a role of systemic inflammation? *Surg Obes Relat Dis* **Epub ahead of print**.

Anderson JW, Brinkmankaplan V, Hamilton CC, Logan JEB, Collins RW & Gustafson NJ (1994) Food-Containing Hypocaloric Diets Are As Effective As Liquid-Supplement Diets for Obese Individuals with Niddm. *Diabetes Care* **17**, 602-604.

Arnett TR (2008) Extracellular pH regulates bone cell function. *Journal of Nutrition* **138**, 415S-418S.

Astrup A & Rossner S (2000) Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance. *Obesity Reviews* **1**, 17-19.

Bischoff-Ferrari HA (2008) Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Sunlight, Vitamin D and Skin Cancer* **624**, 55-71.

Brancati F, Charleston J, Cheskin L*, et al.* (2003) Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Controlled Clinical Trials* **24**, 610-628.

Brannon PM, Yetley EA, Bailey RL & Picciano MF (2008) Overview of the conference "Vitamin D and Health in the 21st Century: an Update". *American Journal of Clinical Nutrition* **88**, 483S-490S.

Bray GA (2008) *Overview of therapy for obesity in adults*: UpToDate Version 16.2. May 2008.
www.uptodate.com.

Breslow JL (2006) n-3 fatty acids and cardiovascular disease. *American Journal of Clinical Nutrition* **83**, 1477S-1482S.

Browning JD, Weis B, Davis J, Satapati S, Merritt M, Malloy CR & Burgess SC (2008) Alterations in Hepatic Glucose and Energy Metabolism as a Result of Calorie and Carbohydrate Restriction. *Hepatology* **48**, 1487-1496.

Cashman KD, Hill TR, Lucey AJ*, et al.* (2008) Estimation of the dietary requirement for vitamin D in healthy adults. *American Journal of Clinical Nutrition* **88**, 1535-1542.

Chearskul S, Delbridge E, Shulkes A, Proietto J & Kriketos A (2008) Effect of weight loss and ketosis on postprandial cholecystokinin and free fatty acid concentrations. *American Journal of Clinical Nutrition* **87**, 1238-1246.

Clarke JTR, Cullendean G, Regelink E, Chan L & Rose V (1990) Increased Incidence of Epistaxis in Adolescents with Familial Hypercholesterolemia Treated with Fish Oil. *Journal of Pediatrics* **116**, 139-141.

Claudi T, Midthjell K, Cooper J, Daae C, Furuseth K & Hanssen KF (2005) NSAMs handlingsprogram for diabetes 2005. http://www.nsamdiabetes.no/.

Codex (1995) *Codex Standard for Formula Foods for Use in Very Low Energy Diets for Weight Reduction* no. 203.

Davie MW, Abraham RR, Hewins B & Wynn V (1986) Changes in bone muscle constituents during dieting for obesity. *Clin Sci* **70**, 285-293.

Delahanty LM & McCulloch DK (2008) *Nutritional considerations in type 2 diabetes mellitus*: UpToDate Version 16.2. May 2008. www.uptodate.com.

Delarue J, Couet C, Cohen R, Brechot JF, Antoine JM & Lamisse F (1996) Effects of fish oil on metabolic responses to oral fructose and glucose loads in healthy humans. *American Journal of Physiology-Endocrinology and Metabolism* **33**, E353-E362.

DiGiorgi M, Daud A, Inabnet WB, Schrope B, Urban-Skuro M, Restuccia N & Bessler M (2008) Markers of bone and calcium metabolism following gastric bypass and laparoscopic adjustable gastric banding. *Obesity Surgery* **18**, 1144-1148.

Emsley R, Niehaus DJH, Oosthuizen PP, Koen L, scott-Evans B, Chiliza B, van Rensburg SJ & Smit RM (2008) Safety of the omega-3 fatty acid, eicosapentaenoic acid (EPA) in psychiatric patients: Results from a randomized, placebo-controlled trial. *Psychiatry Research* **161**, 284-291.

Ernst B, Thurnheer M, Schmid SM & Schultes B (2008) Evidence for the Necessity to Systematically Assess Micronutrient Status Prior to Bariatric Surgery. *Obesity Surgery*.

Espeland M, Pi-Sunyer X, Blackburn G*, et al.* (2007) Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes - One-year results of the Look AHEAD trial. *Diabetes Care* **30**, 1374-1383.

EU (1996) *Commission directive 96/8/EU on foods intended for use in energy-restricted diets for weight reduction*.

EU (2008) *Commission Directive 2008/100/EC of 28 October 2008 amending Council Directive 90/496/EEC on nutrition labelling for foodstuffs as regards recommended daily allowances, energy conversion factors and definitions*.

Festi D, Colecchia A, Larocca A, Villanova N, Mazzella G, Petroni ML, Romano F & Roda E (2000) Review: low caloric intake and gall-bladder motor function. *Alimentary Pharmacology & Therapeutics* **14**, 51-53.

Flynn TJ & Walsh MF (1993) Thirty-month evaluation of a popular very-low-calorie diet program. *Arch Fam Med* **2**, 1042-8.

Goldner WS, Stoner JA, Thompson J, Taylor K, Larson L, Erickson J & McBride C (2008) Prevalence of vitamin D insufficiency and deficiency in morbidly obese patients: A comparison with non-obese controls. *Obesity Surgery* **18**, 145-150.

Gumbiner B, Wendel JA & McDermott MP (1996) Effects of diet composition and ketosis on glycemia during very-low-energy-diet therapy in obese patients with noninsulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* **63**, 110-115.

Heller SM, Hackler SR, Rivers JM, Van Soest PJ, Roe DA, Lewis BA & Robertson J (1980) Dietary fiber: the effect of particle size of wheat bran on colonic function in young adult men. *American Journal of Clinical Nutrition* **33**, 1734-44.

Helsedirektoratet (2009) Kliniske retningslinjer for diabetes.

Henry RR & Gumbiner B (1991) Benefits and Limitations of Very-Low-Calorie Diet Therapy in Obese Niddm. *Diabetes Care* **14**, 802-823.

IOM (2005) Protein and Amino Acids. In *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*, pp. 589-768 [Institute Of Medicine (IOM), editor]: The National Academies Press, Washington DC.

Jazet IM, Pijl H, Frolich M, Romijn JA & Meinders AE (2005a) Two days of a very low calorie diet reduces endogenous glucose production in obese type 2 diabetic patients despite the withdrawal of blood glucose-lowering therapies including insulin. *Metabolism-Clinical and Experimental* **54**, 705-712.

Jazet IM, Pijl H, Frolich M, Schoemaker RC & Meinders AE (2005b) Factors predicting the blood glucose lowering effect of a 30-day very low calorie diet in obese Type 2 diabetic patients. *Diabetic Medicine* **22**, 52-55.

Jazet IM, Pijl H, Schoemaker R, Frolich M & Meinders AE (2003) Remaining endogenous insulin secretion predicts the long-term hypoglycaemic effect of a very low calorie diet in obese Type 2 diabetic patients. *Diabetologia* **46**, A260.

Johnston CS, Tjonn SL, Swan PD, White A, Hutchins H & Sears B (2006) Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. *American Journal of Clinical Nutrition* **83**, 1055-1061.

Keaney JF, Larson MG, Vasan RS, Wilson PWF, Lipinska I, Corey D, Massaro JM, Sutherland P, Vita JA & Benjamin EJ (2003) Obesity and systemic oxidative stress - Clinical correlates of oxidative stress in the Framingham Study. *Arteriosclerosis Thrombosis and Vascular Biology* **23**, 434-439.

Kimm SYS (1995) The Role of Dietary Fiber in the Development and Treatment of Childhood Obesity. *Pediatrics* **96**, 1010-1014.

Kimmons JE, Blanck HM, Tohill BC, Zhang J & Khan LK (2006) Associations between body mass index and the prevalence of low micronutrient levels among US adults. *MedGenMed* **8**, 59.

Krotkiewski M (2001) Value of VLCD supplementation with medium chain triglycerides. *International Journal of Obesity* **25**, 1393-1400.

Kunesova M, Braunerova R, Hlavaty P*, et al.* (2006) The influence of n-3 polyunsaturated fatty acids and very low calorie diet during a short-term weight reducing regimen on weight loss and serum fatty acid composition in severely obese women. *Physiological Research* **55**, 63-72.

Lara-Castro C, Newcomer BR, Rowell J*, et al.* (2008) Effects of short-term very low-calorie diet on intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetic subjects. *Metabolism-Clinical and Experimental* **57**, 1-8.

Miller Jones J (2004) Dietary Fibre intake, disease prevention, and health promotion: An overview with emphasis on the evidence from epidemiology. In *Bioactive Carbohydrates for Food and Feed* [JW.Van der Kamp, editor]: Academic Publishers.

Miller WC, Niederpruem MG, Wallace JP & Lindeman AK (1994) Dietary-Fat, Sugar, and Fiber Predict Body-Fat Content. *Journal of the American Dietetic Association* **94**, 612-615.

Mustajoki P & Pekkarinen T (2001) Very low energy diets in the treatment of obesity. *Obesity Reviews* **2**, 61-72.

Nasjonalt råd for ernæring (2006) *Tiltak for å sikre en god vitamin D-status i befolkningen* no. IS-1408: Avd. for ernæring, Sosial- og helsedirektoratet.

NNR Project Group (2004) *Nordic Nutrition Recommendations 2004*, 4th ed.: Nordic Council of Ministers.

No authors listed (1993) Very low-calorie diets. National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health. *JAMA* **270**, 967-74.

Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH & Lau J (2005) Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database of Systematic Reviews*.

Norris SL, Zhang XP, Avenell A, Gregg E, Bowman B, Serdula M, Brown TJ, Schmid CH & Lau J (2004) Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: A meta-analysis. *American Journal of Medicine* **117**, 762-774.

Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J & Yanovski JA (2004) The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *Journal of Clinical Endocrinology and Metabolism* **89**, 1196-1199.

Pereira S, Saboya C, Chaves GV & Ramalho A (2008) Class III Obesity and its Relationship with the Nutritional Status of Vitamin A in Pre- and Postoperative Gastric Bypass. *Obesity Surgery* **Epub ahead of print**.

Richelsen B, Tonstad S, Rossner S, Toubro S, Niskanen L, Madsbad S, Mustajoki P & Rissanen A (2007) Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients - A 3-year randomized, placebo-controlled study. *Diabetes Care* **30**, 27-32.

SCOOP (2002) *Report on tasks for scientific cooperation. Collection of data on products intended for use in very-low-calorie-diets*: Directorate-General Health and Consumer Protection.

Skrha J, Kunesova M, Hilgertova J, Weiserova H, Krizova J & Kotrlikova E (2005) Short-term very low calory diet reduces oxidative stress in obese type 2 diabetic patients. *Physiological Research* **54**, 33-39.

Sosial- og helsedirektoratet (2004) *Forebygging og behandling av overvekt/fedme i helsetjenesten* no. 03/2004: Sosial- og helsedirektoratet.

Stasse-Wolthuis M, Ablers HFF, Van Jeveren JGC, Wil de Jong J, Hautvast JGAJ, Hermus RJJ, Katan MB, Brydon G & Eastwood MA (1980) Influence of dietary fibers from vegetables and fruits, bran or citrus pectin on serum lipids, fecal lipids and colonic function. *American Journal of Clinical Nutrition* **33**, 1745-56.

Stene L, Midthjell K, Jenum A, Skeie S, Birkeland K, Lund E, Joner G, Tell G & Schirmer H (2004) Hvor mange har diabetes mellitus i Norge? *Tidsskr Nor Lægeforen* **124**, 1511-1514.

Stone BG, Ansel HJ, Peterson FJ & Gebhard RL (1992) Gallbladder Emptying Stimuli in Obese and Normal-Weight Subjects. *Hepatology* **15**, 795-798.

The Nordic Council of Ministers (1993) *Nordic Report on Dietetic Products* no. 557.

Tsai AG & Wadden TA (2005) Systematic review: An evaluation of major commercial weight loss programs in the United States. *Annals of Internal Medicine* **142**, 56-66.

Tsai AG & Wadden TA (2006) The evolution of very-low-calorie diets: An update and meta-analysis. *Obesity* **14**, 1283-1293.

WHO (2000) *Obesity: preventing and managing the global epidemic. WHO Technical Report Series, No 894*: World Health Organization, Geneva, Switzerland.

WHO (2008) *WHO Fact sheet N°312 Diabetes*: World Health Organization, Geneva, Switzerland.

Willi SM, Martin K, Datko FM & Brant BP (2004) Treatment of type 2 diabetes in childhood using a very-low-calorie diet. *Diabetes Care* **27**, 348-353.

Wortsman J, Matsuoka LY, Chen TC, Lu Z & Holick MF (2003) Decreased bioavailability of vitamin D in obesity (vol 72, pg 690, 2000). *American Journal of Clinical Nutrition* **77**, 1342.

Yancy WS, Olsen MK, Dudley T & Westman EC (2007) Acid-base analysis of individuals following two weight loss diets. *European Journal of Clinical Nutrition* **61**, 1416-1422.

Zahouani A, Boulier A & Hespel JP (2003) Short- and long-term evolution of body composition in 1,389 obese outpatients following a very low calorie diet (Pro'gram18 VLCD). *Acta Diabetologica* **40**, S149-S150.

[Anon] (1992) Gastrointestinal Surgery for Severe Obesity - National-Institutes-Of-Health Consensus Development Conference Statement - March 25-27, 1991. *American Journal of Clinical Nutrition* **55**, S615-S619.

[Anon] (2008) Nutrition recommendations and interventions for diabetes - A position statement of the American Diabetes Association. *Diabetes Care* **31**, S61-S78.