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# Low Carb High Protein Diets as Management Tool of Insulin Resistance in Patients with Obesity and/or Type 2 Diabetes Mellitus

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## Abstract

**Introduction and Rationale:** Low carbohydrate high protein diets have been prescribed from as early as 1797 and are taken seriously by many researchers, although in main stream dietetics and medicine the diet can still be received with skepticism. Insulin resistance (IR) is the result of a cascade of physiological events, starting with hyperphagia leading to a positive energy balance and weight gain. Patients with IR gain weight easily and have trouble losing weight on diets with normal carbohydrate content, because of the highly elevated insulin levels. A diet for patients with IR must therefore tackle this problem to make weight loss possible. In this review the evidence on the diet short and long-term, effects on comorbidities and difference with Mediterranean diet are discussed.

**Methods:** A search was carried out in Pubmed for articles of obesity management, IR, low carb/high protein diets and weight loss combined with comorbidities, several nutrients and the Mediterranean diet between 1995 and July 2017. Outcomes were compared to patient observations from dietary practice in weight loss management.

**Management:** Diagnosis can easily be made by measuring waist circumference. The diet should be low carb/high protein but not provoking ketosis; energy and macro nutrient requirements should be individually assessed. Fat is not low but also not ad libitum, focusing on unsaturated fats. The intake of vitamin D, iodine and magnesium needs to be optimal. Alcohol consumption is not part of first phase of the diet. Exercise (endurance and resistance) is an essential part of the therapy. For patients with type 2 diabetes medication, diet and glucose values need to be meticulously observed.

**Conclusion:** Low carbohydrate/high protein diets should be considered as a serious treatment option for all obese patients with and without comorbidities. They should be administered by specialised dietitians working in a multi-disciplinary team.

**Keywords:** Low carbohydrate/high protein diet; Insulin resistance; Obesity; T2dm; Cvd; Nafld; Dietitian

## Introduction

Low carbohydrate high protein diets have been prescribed from as early as 1797, when Rollo started to treat patients with diabetes that way. Almost a century later, in 1886, Banting, a British undertaker, introduced the diet for weight loss. It became immensely popular at that time, when following a weight loss diet was even called 'banting'. In 1972 Atkins, among others, reintroduced the diet. A totally revised, evidence based version appeared in 2010 [1]. Although low carb diets are taken seriously by many researchers, in main stream dietetics and medicine the diet can still be received with skepticism. Arguments to doubt the diet are: weight loss is achieved by energy restriction, not by carbohydrate restriction; how can a low carb diet differ greatly in macro nutrient content from national guidelines and still be healthy. Furthermore: the amount of saturated fat in the diet; possible deficiencies in micronutrients, and the sustainability long term. In this article I shall focus on the importance of the diet in the world wide battle against obesity and its comorbidities and the composition of the diet, to answer the question if this diet is healthy and good for weight loss. Low carb/high protein diet will be compared to the Mediterranean diet. Finally I will discuss sustainability.

## Methods

A search was carried out in PubMed (Pubmed.gov) from 1995 to July 2017 with the search terms: insulin resistance; insulin resistance syndrome; obesity; obesity management and weight loss were combined with search terms: low carbohydrate diets; low carbohydrate/high protein diets; low carbohydrate/high fat diets ; type 2 diabetes mellitus; cardio vascular disease; comorbidities; thyroid gland function; non-alcoholic fatty liver disease; Mediterranean diet; and vitamin D 25-hydroxyvitamin D; iodine; magnesium; fiber and alcohol. The outcomes were compared to literature I used for previous articles, and to patients observations from dietitians connected to the Dutch Knowledge Centre for Dietitians specialized in Overweight and Obesity (KDOO). Preliminary results have been presented and discussed with peers at the EASO conference (European Association for the Study of Obesity) in Porto, May 19, 2017.

## The Rationale

Insulin resistance (IR) is the result of a cascade of physiological events, starting with hyperphagia (an abundant intake of carbohydrates and saturated fats) that leads to a positive energy balance and weight gain. In this way subcutaneous adipose tissues get overfilled, adipose cells enlarge. Continuous weight gain in individuals leads to fat storage outside fatty tissues into the abdomen (visceral fat), the muscles and liver. The fat stored in these locations has a different metabolism which is characterized by hypoxia, an impaired blood flow through the adipose tissue; metaflammation; an infiltration of macrophages. Leading to a rise in leptin, causing constant appetite; a rise in angiotensin, causing hypertension.

On the other hand drop in adiponectin, influencing hyperlipidemia and insulin resistance; and elevated insulin-sensitizing and anti-inflammatory adipokines. The rise in pro-inflammatory cytokines like TNF-α interferes with insulin receptor signalling, and among many others, IL-6, involved in glucose and lipid metabolism [2-4]. IR is a pathological condition in which cells fail to respond normally to the hormone insulin. When the body produces insulin under conditions of IR, the cells are unable to use insulin effectively, leading to prolonged high blood sugar values and further weight gain. Beta cells in the pancreas subsequently increase their production of insulin, further contributing to a high blood insulin level. This often remains undetected and leads to impaired glucose tolerance and eventually to type 2 diabetes [5,6]. Patients with IR gain weight easily and have trouble losing weight on diets with a normal carbohydrate content, because of the highly elevated insulin levels. A diet for patients with IR must therefore tackle this problem to make weight loss possible [7-9].

## Prevalence

The prevalence of IR in the obese and overweight population is larger than is usually estimated and IR is in primary practice often not considered as the leading health problem which causes comorbidities. As shown in the CARDIA study IR is present in 7.7% of Caucasian and 11.9% of black individuals with a BMI lower than 25/kg/m$^2$ [10]. In obese subjects, these figures are 33.6% and 41.3% respectively. The majority of individuals with obesity develop IR, and may have dyslipidemia, gout, hypertension, cardiovascular disease or type 2 diabetes, PCOS or other fertility problems. An estimated 10-25% of obese individuals are the so-called metabolically healthy. They have still, for unknown reasons, preserved their insulin sensitivity [11]. When in obese subjects besides hypertension, dyslipidemia, IGT and type 2 diabetes non-traditional cardio metabolic factors like VAT, LM, RMR, RER, TC, LDL, HOMA-IR were considered the number of comorbidities rose from 13 to 80%. There were no significant differences between overweight and obese in %fat; VAT; lipids/GLUC; insulin; leptin; or cortisol. The obese had higher FM, LM, RMR, and estradiol; males had greater LM, RMR, and TRG ($p<0.01$); females had greater %fat, and leptin ($p<0.001$). No significant sex differences were found in RER, estradiol, insulin, or cortisol levels($p>0.05$) [12,13]. To establish what actual insulin levels in a non- study population are, a family physician in the Netherlands invited her patients randomly to come to the practice in a fasting state. She measured the insulin levels at fasting, after a breakfast of 60 grams of carbohydrates; 2.5 hours after breakfast and after a lunch with the same amount of carbohydrates. Her data show that even in young people insulin levels can stay elevated for 2.5 hours after a meal. In obese and diabetic subjects the levels were even higher (Table 1) [14]. The levels measured were much higher than published in several studies [15,16]. Even adolescents can already be insulin resistant [17].

## Risk of IR related to Lifestyle and Nutrition

IR is promoted by smoking and a sedentary lifestyle [18-22]. Food substances that have been linked to the risk of developing IR are: high carbohydrate diets [23,24]; high content of saturated fat [23]; high intake of free fatty acids and triglycerides [25]; a low fibre content [26]; diets with a high glycaemic load [27]; take away meals [28,29]; starch, rich in amylopectin [30]; a low vitamin D status [31,32]; and a high intake of fructose [33-35] (Table 2). Especially starch is a compound that needs further examination. Starch in all food products is built up of two elements: amylose and adiponectin. Products that contain more amylose are less harmful in relation to developing IR [36,37]. Ideally speaking starch contains 30% amylose. In many products this is not the case, for instance in many species of rice, with the exception of brown and basmati rice. Risotto and sushi rice and other sticky rice species, for example, have a low amylose content, and therefore eating them on a regular basis adds to the risk of developing IR. Quinoa is also low in amylose, average 12%. Many of these products have become popular through websites of foodies and restaurants. Trendy as well as traditional food styles, rich in starch with low amylose content, therefore, can lead to promotion of IR in the general population, especially when consumers have a sedentary lifestyle and stress, as is common in many in the working force. Large amounts of fructose, as consumed by many in fruit juices, and in large quantities of fruit, under the presumption that fruit is healthy and one cannot eat enough of it, are a risk too. The effects of starch and fructose make clear that foods that are quite popular among great groups of higher educated people with a western lifestyle, but also foods that have a place within the Mediterranean diet, can be harmful if consumed in large quantities on a regular basis. On the other hand the daily consumption of dairy products prevents IR. Pereira found that dairy consumption was inversely associated with the incidence of all IRS components among overweight individuals

**Table 1:** Glucose and Insulin values in at random selected patients. Patients with normal values of glucose mmol/l; insulin mU/l

| Patient A | Fasting | ½ h. after Break fast | 2 ½ h. After Break fast | After Lunch |
|---|---|---|---|---|
| Glucose mmol/l | 4.8 | 7.0 | 4.8 | 6.2 |
| insulin mUI/l | 6.5 | 63.8 | 6.6 | 36.8 |
| Patients with normal values after 2 ½ hrs | | | | |
| **Patient B** | **Fasting** | **½ h. after Break fast** | **2 ½ h. After Break fast** | **After Lunch** |
| Glucose mmol/l | 5.0 | 7.6 | 4.8 | 5.4 |
| insulin mUI/l | 5.2 | 154 | 8 | 95 |
| Patient 17 Years. Insulin stays elevated, plus accumulating effect | | | | |
| **Patient C** | **Fasting** | **½ h. after Break fast** | **2 ½ h. After Break fast** | **After Lunch** |
| Glucose mmol/l | 4.7 | 6.3 | 5.2 | 7.6 |
| insulin mUI/l | 6.9 | 96.6 | 76.6 | 180 |
| Patient 45 years. Obese | | | | |
| **Patient D** | **Fasting** | **½ h. after Break fast** | **2 ½ h. After Break fast** | **After Lunch** |
| Glucose mmol/l | 4.9 | 7.6 | 4.8 | 7.0 |
| insulin mUI/l | 10.6 | 228.3 | 164.4 | 282.4 |
| Patient 56 years. High insulin values and high post prandial glucose (type 2 diabetes) | | | | |
| **Patient E** | **Fasting** | **½ h. after Break fast** | **2 ½ h. After Break fast** | **After Lunch** |
| Glucose mmol/l | 4.5 | 14 | 7.2 | 9.8 |
| insulin mUI/l | 24.1 | 280 | 90 | 160 |

**Table 2:** Clinical parameters.

| | |
|---|---|
| ▶ Hypertension | ▶ Elevated oestrogen |
| ▶ Dyslipidemia | ▶ Fertility problems |
| ▶ Low HDL | ▶ Low testosterone |
| ▶ Elevated LDL and triglycerides | ▶ Reduced thyroic gland function |
| ▶ PCOS (policystic ovarian syndrome) | ▶ Sleep apnoea |
| ▶ NAFLD (non-alcoholic fatty liver disease) | ▶ Gout |
| ▶ Impaired glucose tolerance and type 2 diabetes | ▶ Increased activity of mast cells in the duodenum |
| ▶ Osteo artritis | ▶ Vit D deficiency |
| ▶ Fatigue | ▶ Emotional instability |
| ▶ Increased risk of infections | |

(BMI ≥25 kg/m² at baseline) [10]. The change of developing IR syndrome (2 or more components) was 72% lower (odds ratio, 0.28; 95% confidence interval, 0.14-0.58) when overweight individuals consumed ≥35 times dairy per week compared to those with the lowest consumption: <10 times per week. Each daily occasion of dairy consumption was associated with a 21% lower risk of IRS (odds ratio, 0.79; 95% confidence interval, 0.70-0.88). These associations were similar for blacks and whites and for men and women. For leaner individuals (BMI <25kg/m²) these associations were not found. Other dietary factors, including macronutrients and micronutrients, could not explain the association between dairy intake and IRS.

## Diagnosis in daily practice

It is important for physicians, dietitians, nurse practitioners and other HP's to recognise IR at an early stage, because if IR is diagnosed early appropriate measures can be taken. The presence of metabolic syndrome is a solid sign of IR: high blood pressure, elevated total cholesterol or LDL cholesterol, a low HDL cholesterol, and impaired glucose tolerance are caused by IR; and are in many cases reversible if treatment is started straight away (Table 3). Less known but easy to establish IR, is the history of weight loss attempts and relapse a patient has. But, the easiest way to diagnose IR is measuring the waist circumference. For men a waist of ≥94 cm or 37 inches; and for female a waist ≥88 cm or 34 inches is a clear sign of IR [38]. Waist circumference is dominant over weight and BMI. The location of the waist measurement should be just below the lowest rib, and not halfway the lowest rib and the upper rim of the pelvis, because this location correlates better with high blood pressure, cholesterol, IR, impaired glucose tolerance and T2 DM [39], and may therefore be an easy and cheap diagnostic tool in daily practice, thus avoiding costly and in primary care impractical measurements like a fasting insulin level. Han found that even people with a BMI over 23 kg/m² already had one comorbidity related to IR [40]. Weighing and measuring the waist circumference of patients who come in with signs of metabolic syndrome, even with normal weight is therefore advisable as standard procedure. One of the pitfalls in taking BMI as diagnostic tool is that people of oriental/Asian origin have a lower BMI as normal value. For Asian populations, the suggested BMI categories are as follows: 18.5–23 kg/m² increasing but acceptable risk; 23–27.5 kg/m² increased risk; and ≥27.5 kg/m² high risk [41,42]. Cut-off points of waist circumference in Asians were set by the International Diabetes Federation for South Asians, Chinese and Japanese on >90 cm for men and >80 cm for women [43]. Because in Western countries the correct weight and waist cut-off points for patients of Asian origin are not always used obesity and IR are underestimated in this population.

## Management

The presumption is that anyone can lose weight on any diet that restricts energy intake [44]. In fact, many patients want to lose weight, but fail to reach even the point of ≥5% weight loss, similar as we found in a prospective cohort of 1546 patients (Table 4) [45,46]. This problem is well known in patients with IGT and type 2 diabetes [47]. Even though we know that greater weight loss improves long-term maintenance [48] and metabolic functions, e.g. pancreas function [49]. For years many health professionals have doubted the motivation of their patients, thus explaining the low success rates, instead of doubting the effectiveness of the treatment. But, if the treatment fails, we should attribute that not only to the patient but also to the therapy. Diet is in weight management the most significant conservative treatment option and evidence based effective [50-54], but not every diet is fit for everyone. If patients fail to lose substantial weight and suffer from relapse in many cases, the therapy, in this case the diet, could be false. Several studies have pointed out that low carb/high protein diets lead to more substantial weight loss [55-58].

## Treatment goals

Treatment goals are: firstly to improve insulin sensitivity through 10-15% weight loss (20-25% in morbid obesity) [59,60]; and loss of ≥10% waist circumference; secondly to improve comorbidities and blood parameters, including lowering or stopping medication for comorbidities; thirdly the increase of fat free mass; improvement of quality of life, sleep and physical and mental condition, and finally a weight maintenance of 5 years [45,61] (Table 5). To reach weight maintenance in insulin resistant patients, they need to understand how their body functions, what is different because of IR and how they can control that. Each kilo of weight loss will improve comorbidities [62]. A weight loss of >5% is necessary for beneficial effects on HbA1c, lipids, and blood pressure [63].

## Energy expenditure

The answer lies in the changed metabolism due to IR [1-4]. The high insulin production causes more fat storage and prevents weight loss. Each time a person with IR eats carbohydrates the insulin level goes up to the levels as shown in Table 1. And, because insulin not only makes it possible for glucose to enter the cells, but also promotes fat storage, patients can gain weight by eating carbohydrates in normal quantities. A low carbohydrate content of around 6 grams per meal does not create release of insulin. When the insulin levels stay low and there is an energy deficit, fat can be released from the fatty tissue. But, a low carbohydrate diet is no magical bullet. The normal law of energy expenditure stays intact: if a patient consumes a diet that is not low enough in calories, or is not close

**Table 3:** Food linked to promotion of insulin resistance.

| | |
|---|---|
| High carbohydrate diets | Diets with high glykemic load |
| High content of saturated fat | High intake of fructose |
| High intake of free fatty acids | Take away meals |
| High intake of triglycerides | Starch rich in amylopectin |
| Low fibre intake | Low vitamin D intake |

**Table 4:** Weight loss after 6 months treatment.

| **>5% weight loss** | **<3% or no weight loss** |
|---|---|
| ▶ Low energy diet 29,1% | ▶ Low energy diet 41,7% |
| ▶ RGV 34,2% | ▶ RGV 35,9% |
| ▶ Low fat diet 28,6% | ▶ Low fat diet 28,8 |
| ▶ Low carb diet 46,1% | ▶ Low carb diet 28,8% |
| **>5% loss of waist circumference** | **<3% loss of waist circumference** |
| ▶ Low energy diet 40% | ▶ Low energy diet 37,9% |
| ▶ RGV 38% | ▶ RGV 35,8% |
| ▶ Low fat diet 25% | ▶ Low fat diet 62% |
| ▶ Low carb diet 57% | ▶ Low carb diet 42,8 |

N= 1546; ref. 46; RGV: Dutch Dietary Guidelines for the Healthy population.

**Table 5:** Treatment goals.

| |
|---|
| ▶ Improvement of insulin sensitivity |
| ▶ 10-15% weight loss (20-25% in morbid obesity) |
| ▶ Loss of ≥10% of waist circumference |
| ▶ Improving comorbidities and blood parameters, including lowering or stopping medication for comorbidities |
| ▶ Increase of fat free mass |
| ▶ Improvement of quality of life and sleep |
| ▶ Improvement of physical and mental condition |
| ▶ Weight maintenance 5 years |

enough to the RMR, or less than 600 calories deficit of the usual intake, weight loss will not occur [51,60]. The energy demand should therefore be individually assessed per patient. And additionally, a diet too low in protein or fat will prevent weight loss because the diet induced energy expenditure is too low. A weight loss of 500 grams per week is good. In the first phase patients may lose much more, kilos per week, due to the loss of liquids, which always takes place when people start to eat less carbohydrates.

### Diet and exercise

Weight loss is achieved through a combination of decrease of the carbohydrate intake and increase of the protein intake (Table 6) [55]. In the first phase a strict carbohydrate restriction and high protein intake is advised for 8 weeks to 3-6 months, dependent on the progress of weight loss, loss of WC and improvement of comorbidities [55, 62-65]. Diet induced weight loss leads to better insulin sensitivity and should therefore be the most important objective in obesity management [66]. The aim is to bring the high release of insulin down. This also applies to obese patients with type 2 DM [67-70]. When weight loss results – and improvement of comorbidities - are sufficiently achieved the second phase is a less strict carb restriction, of around 50-100 grams per day, still high protein, for 3-6 months. Good results on low carbohydrate diets can be seen with an intake of 50-100 grams. An individual assessment of the carbohydrate and protein intake is necessary to determine the right content of the diet to make weight loss possible. In the maintenance phase the carbohydrate level can be elevated till weight loss stops. Sufficient protein intake stays necessary.

Exercise is an important part of the treatment. Resistance training combined with a calorie restriction leads to reduced VLDL cholesterol, triglycerides, and systolic and diastolic blood pressure [71,72]. Exercise training added to a calorie restriction leads to better physical functioning and less loss of muscle [73].

### Carbohydrates

A carbohydrate restriction does not need to be lower than 36 grams per day, spread over 6 moments. 36 grams is the absolute physiological minimum the brain and erythrocytes need to function. In this way the pancreas is not forced to produce extra insulin. Since weight loss is promoted sufficiently this way, a lower intake of carbohydrates which would also promote ketosis, is not advisable. Carbohydrate requirement should be individually calculated. The more obese the patients the better they feel on a low carbohydrate intake of around 50 grams for a long period. For example: for many patients a restriction of 75 grams is a large reduction of the daily intake in carbohydrates (Table 7) [74]. The challenge lies more in having enough variety in the diet and dealing with social events and in the workplace than in the restriction itself. Kirk and colleagues defined moderately low carb as 30-40% of energy, with the carbohydrate content depending on the energy intake [75]. However, 40% of a 1600 calorie diets 160 grams, for many women a normal daily intake. This is *de facto* not a low carb diet and it will not make a difference with an energy restricted diet. Therefore it will not have desired results in patients with IR.

One of the problems connected with obesity is carbohydrate craving. Some patients with a mild eating disorder have less craving due to a low

**Table 6:** Elements of the low carb/high protein diet.

| Nutrient | Content | Quantity |
|---|---|---|
| Energy | Individually assessed | 600 calories deficit of usual intake |
| Protein | Individually assessed; large intake of dairy; egg, fish, chicken; shell fish; moderate red meat; Pulses in phase 2 and 3 | At least 1.0 g/kg actual weight up to 1.2 g/kg actual weight, evenly spread over three meals; comparable to: 30-30-30. |
| Leucine | From protein | 3 grams per meal |
| Carbohydrates | 3 phases (Table 7); phase 2 and 3 individually assessed | Phase 1: 36 grams<br>Phase 2: 50-100 grams<br>Phase 3: 75-125 grams |
| Fat | Individually assessed | Promotion of PUFA and MUFA |
| Fibre | From vegetables, nuts, fruit, pulses; grains | Per day: vegetables large portion 2 times; 25 grams of nuts;<br>1 or 2 servings of fruit |
| Alcohol | Total restriction in phase 1; very modest in phase 2 and 3 | Phase 2 and 3: 1 glass of wine twice a week |
| Vitamin D | Suppletion | 400-800 IU (10-20 mcg/day) |
| Iodine | Suppletion can be necessary: iodine piccolinate | 150 mcg/day |
| Magnesium | Meat, fish, dairy, cheese, vegetables, pulses, potatoes and grains | 300 mg/day |
| Exersize | Combination of resistance training and fitness | 30-60 minutes per day |

**Table 7:** Levels of carbohydrate restriction.

| |
|---|
| Phase 1<br>Weight loss; improvement of comorbidities<br>Very strong carbohydrate restriction 36 grams; 3 meals & 3 snacks of 6 grams carbohydrates<br>Minimum duration 8 weeks, or more if IR is severe, up to 6 months. |
| Phase 2*<br>Weight loss; improvement of comorbidities<br>Strong carbohydrate restriction 50-100 grams; 3 meals & 3 snacks 8-16 grams carbohydrates<br>Duration 6 months to 2 years, dependent on desired weight loss. |
| Phase 3*<br>Maintenance phase; stable phase of comorbidities<br>Moderate carbohydrate restriction 75-125 grams; 3 meals & 3 snacks 8-20 grams carbohydrates. Elevate carbohydrate intake till weight loss stops.<br>Amount of carbohydrates dependent on weight maintenance. |

*carbohydrate content of the diet needs to be assessed individually for each patient

carbohydrate diet, because insulin promotes craving. They feel more relaxed and less hungry, and experience more control over their eating behaviour. An estimate of 30% of obese patients seeking help has a mild or more severe eating disorder (BED, DSM-5), compared to 2-3% in the normal population [76]. For patients with severe eating disorders a carbohydrate restricted diet lower than 100 grams is not a treatment option. These patients need to get cognitive behavioural therapy (CBT) first. Some of the medication used in the therapy enhances weight loss, although most therapies for BED do not lead to weight loss [77,78].

### Low carb diets for patients with type 2 DM

Low carbohydrate diets are effective to reduce fasting glucose and HBA1C levels in patients with type 2 diabetes mellitus [79] as well as to reduce visceral fat [80]. It should be the first option in patients with *de novo* T2DM. Especially in patients that have high glucose values and HBA1C, or patients that face insulin therapy, and have trouble losing weight a low carbohydrate/high protein diet works very well. Finally weight loss is possible and the amount of medication can be lowered. Oral glucose lowering medication like metformin does not lead to hypoglycaemia and can be taken in the same amount, till HBA1C and fasting glucose have diminished to normal values. In many cases patients can stop to take insulin and sulfonium derivates. These medicine can cause hypoglycemia, when not decreased as soon as the patient starts with the diet. It is suggested to stop or lower 24 hour working insulin first, and adjust short working insulin to the amount of carbohydrates in the meal. After 3-4 weeks insulin dosage can be lowered further in small steps per 4 units, similar to the way insulin was started. For better results in terms of weight loss the basal level of the insulin pump needs to be lowered more than rapid insulin dosage. Rapid insulin and medium lasting insulin need to be stopped last and for a short period higher fasting glucose values should be accepted, because they will diminish when weight loss occurs. Patient should record three times a week fasting glucose, before lunch, before dinner and before going to bed. HbA1c should be checked after two months to verify insulin need. High glucose values without fever usually mean that the insulin dosage is too high [81].

### Protein

The diet should have 1.2-1.5 grams protein per kg present body weight. Krieger calculated the cut-off point for ideal protein intake during weight loss at 1.05 grams per kilo present body weight, although if the diet was prolonged for more than 12 weeks, this figure rose to 1.2 grams/kilo [82]. The protein requirement needs to be individually assessed. Protein should be evenly spread over three meals preferably 30-30-30 grams per day [83,84]. A high protein diet leads to more satiation and sustains muscle mass [85]. Each meal should contain 3 grams of the essential amino acid leucine. Leucine is present in animal protein, dairy products, nuts, seeds and pulses. Wey protein and casein are in combination with leucine essential for building and maintaining muscle tissue [86]. Leucine prevents decrease of muscle and liver tissue; and it is a part of haemoglobin. Leucine containing products, e.g. dairy, eggs, meat, fish and pulses are therefore an essential part of the diet. The effect of protein rich foods is that they enhance thermogenesis. This effect is bigger in animal protein than in proteins from plants. However, a large intake of meats is not encouraged, preferably the increase in protein intake comes from dairy, fish, poultry, eggs, nuts, seeds and pulses. A high protein diet leads to significantly higher decrease of fat mass after a year; and better weight maintenance [87]. This study also looked into genetic predisposition and found that carriers of the AA genotype (67% of the population) benefit from a high protein diet. A rise of 5% in protein intake and a decrease of 4% in glycaemic index helped maintain weight loss, and promoted even further weight loss and improvement of biomarkers. Even children of the DiOGenes study population benefitted from the changed food behaviour of their parents: their biomarkers also improved [88].

The diet of elderly can be low in protein [89], with an average intake of 0.8 gram/kg, which prevents weight loss and is a risk for sarcopenia, a risk for patients older than 60 years that need to lose weight. For these patients 1.0-1.2 grams of protein per kilo present body weight, evenly spread over the day, combined with a moderate calorie restriction and resistance training is advised [90,91].

### Fat

In a low carb/high protein diet the intake of fat is not restricted, although there is no argument for ad libitum consumption. Diets for weight loss will always be calorie restricted and fat has the highest amount of calories per gram. So controlled intake of fat is always necessary and fat needs to be individually calculated. The diet is not low fat however. Lately the discussion about which kind of fat has been enhanced by several publications showing evidence that saturated fat may not be the main cause of CVD [92-95], and may even be beneficial for type 2 diabetes [92,96-99]. A systematic review and meta-analysis by Pimpin et al. [100] suggests relatively small or neutral overall associations of butter with mortality, CVD, and diabetes. A 14 grams consumption of butter would give a 4% risk reduction. Related to the glucose-insulin homeostasis, Imamura et al. [101] found in a meta-analysis that replacing carbohydrates with PUFA (poli-unsaturated fatty acids) leads to significant lowering of glucose, HBA1C, C peptide, and HOMA-IR. PUFA also significantly improved insulin secretion capacity when replacing carbohydrate, saturated fats or mono-unsaturated fatty acids. The study has limitations due to the small number of trials for some outcomes and the heterogeneity. Industrial trans-fat was associated with all-cause mortality of CVD; ruminant trans-palmoleic fat was inversely associated with type 2 diabetes [92].

Omega-3 fatty acids have positive effects on non-alcoholic fatty liver disease (NAFLD), which is a disease resulting from abdominal obesity. DHA (docosahexaenoic acid (22:6 ω -3)) was superior to EPA (eicosapentaenoic acid (20:5 ω -3)) at attenuating changes in plasma lipids and hepatic injury as a result of Western diet in mice. It reversed dietary effects on hepatic metabolism, oxidative stress, and fibrosis [102]. A systematic review showed omega-3 fatty acids can reduce waist circumference, but have no effect on BMI [103]. Patients with type 2 diabetes who received 520 mg of DHA and EPA had a beneficial effect on waist circumference, glucose, Hb1Ac, leptin, leptin/adiponectin ratio, and lipid profile compared to placebo. In both groups no changes in adiponectin were found; whereas resistin, insulin, and HOMA-IR increased in both groups [104].

To summarise: fat does not need to be restricted but can also not be taken at libitum. Unsaturated fats are preferable over saturated fats for all patients. Omega-3 fatty acids may have positive effects and should be part of the diet, consumed as fatty fish or supplements with fish oil. In a low carb diet there is very little room for products like cookies and biscuits, cake, pie, ice-cream, milkshake and chocolate. This means that a low carb diet automatically is lower in saturated and industrial trans-fat, the latter being defined as a serious risk factor for CVD [92].

### Vitamins and Minerals

If vitamin D is deficient in the diet and from sunlight, supplementation is advisable with 400 or 800 IU (10-20 mcg). The relationship between vitamin D 25-hydroxyvitamin D (25[OH]D) and IR, and its comorbidities is still unclear. Because vitamin D plays a role in lipid and glucose metabolism, it is to be expected that a good vitamin D status could be beneficial. Renzaho found evidence that in ethnic groups links between vitamin D deficiency and obesity-related chronic diseases exist, reporting a statistically significant result with a measurement of obesity, T2DM, CVDs, and the metabolic syndrome. However, the strength of the association varied across ethnic groups [105]. Patients with NAFLD

who received a 25 µg vitamin D supplement or placebo combined with a hypo caloric diet had reductions in triglycerides, AST, ALT, insulin and HOMA-IR compared to the placebo group, which meant they had improvements in lipids, liver enzymes and insulin sensitivity [106]. It is also not clear whether low vitamin D status is a cause or an effect of IR and obesity. Therefore supplementation for all obese might not be the ultimate solution for the cure of comorbidities and IR [107,108]. Pannu carried out a systematic review on vitamin D status, where 18 of 23 trials that met the criteria reported an increase in vitamin D status with weight loss, although the increase in 25OHD was smaller than would be expected from a direct mobilization of stores into the circulation [109]. Mallard found no evidence for a dose-response effect of weight loss on the change in serum 25-hydroxyvitamin D [110].

A contributing problem in the assessment of vitamin D studies is, that in different parts of the world synthesis of the vitamin in the human body is absent during half of the year, between October and March e.g. in de the moderate climate of Middle and Northern European countries, including Belgium, Germany, Poland, the United Kingdom, the Netherlands, Scandinavia and so on. Latent vitamin D deficiency is very common is these regions and is in many cases not actively diagnosed.

The diet should contain sufficient magnesium. Since magnesium rich foods are meat, fish, dairy, cheese, vegetables, pulses, potatoes and grains, a deficiency in a low carb/high protein diet is not to be expected. Magnesium has a major role in the regulation of blood pressure. Although not all data are consistent, there is an inverse relationship between magnesium intake and blood pressure, especially when obtained from food rather than that obtained *via* supplements. Moreover magnesium seems to have a positive role in the prevention of diabetes mellitus, obesity, and metabolic syndrome [111].

Iodine is a crucial element in thyroid function. Thyroid hormones are involved in the regulation of metabolism, thermogenesis, food intake, and fat oxidation. Iodine can be obtained by eating sea fish and shellfish, meats, eggs, dairy, seaweed and iodine containing salt. Obesity and thyroid function are closely related. In a group of morbidly obese patients, serum TSH concentration was associated with fasting serum insulin levels and insulin resistance but not with serum leptin levels, body mass index (BMI), fat mass, and lean body mass. The prevalence of overt and subclinical hypothyroidism was high (19.5%). They had higher levels of T3, FT3, T4, and TSH than healthy controls, probably the result of the reset of their central thyrostat at higher level [112]. De Pergola found that progressive accumulation of abdominal fat is associated with an increase in both FT3 and TSH serum levels, independently of insulin sensitivity, metabolic parameters and blood pressure, suggesting that progressive central fat accumulation is associated with a parallel increase in FT3 levels, possibly as an adaptive thermogenic phenomenon [113]. At the same time the control of TSH secretion by free thyroid hormones is possibly impaired in obesity. Knudsen found a positive association between BMI and category of serum TSH ($P<0.001$) and a negative association between BMI and category of serum free T4 ($P<0.001$) but not to serum free T3 levels. There was an association between obesity (BMI>30 kg/m(2)) and serum TSH levels ($P=0.001$) [114]. The role of leptin as a cross-talk between the thyroid gland and the fat cells, and it's role in the genesis of auto immune thyroid failure is still unclear. Fact is that sufficient iodine intake is a point of concern for many.

## Fiber and Resistant Starch

Fiber is an important element in any diet. In the low carb/high protein diet fiber may not come from bread, or potatoes, the fiber content of the diet is usually that high that patients seldom complain about intestinal problems. Patients on a Western diet often have a low vegetable consumption. On a low carb/high protein diet they need to eat vegetables twice a day, and fruit once a day. Plus the advice is to take a small serving of nuts, eat pulses once a week and to drink 2 litres per day. When patients consumed beforehand lots of white bread, white pasta and white rice, cookies, sweets and fruit juices, all low in fiber, their intake in fiber has increased through the diet.

Resistant starch is a carbohydrate that is not digested in the small intestine. Resistant starch (RS) is a natural compound of foods but can also be added as manufactured resistant starch. RS1- is in digestible resistant starch in seeds or legumes and unprocessed whole grains. RS1 from seeds and legumes/pulses has a place within a low carb/high protein diet. It is even advisable to give patients daily portions of seeds and nuts because of the low carbohydrate content, the satiety and the amount of fiber. Pulses are advised once a week in the second phase, which is more often than most patients on a Western diet are used to.

The other groups are: RS2 - indigestible due to starch conformation, as in high amylose corn starch; RS3 - is formed when starch-containing foods are cooked and cooled, such as pasta; RS4 – starch that has been chemically modified to resist digestion. RS 1, 2 and 3 are fermented by the large intestinal microbiota, producing short-chain fatty acids, promoting butyrate-producing bacteria, creating a has similar physiological effect as dietary fiber. Consuming it at high doses can lead to flatulence. When isolated resistant starch is used to substitute for flour in foods, the glycaemic response of that food is reduced [115,116]. High amylose resistant corn starch was said to be protective against type 2 diabetes mellitus. A claim first acknowledged by the FDA in the USA was almost immediately retrieved with the note ´there is limited credible scientific evidence for a qualified health claim for high-amylose maize resistant starch and reduced risk of type 2 diabetes.

## Alcoholic Beverages

Alcohol is discouraged in the first phase of a low carb/high protein diet. Alcohol provides calories which will be metabolised before any other energy source, thus preventing weight loss and lipolysis. Alcoholic beverages are a source of carbohydrates as well, especially beer and liqueurs. If patients can refrain from alcohol for several weeks or months, weight loss can be promoted. In the second phase a glass of wine a couple of times per week can be taken. Another aspect of alcohol is that daily consumption is discouraged because of its relation with breast cancer. A study found nineteen metabolites significantly associated with oestrogen receptor positive (ER+) breast cancer (418 cases): 12 alcohol-associated metabolites, including 7 androgens and α-hydroxyisovalerate (OR: 2.23; 95% CI: 1.50, 3.32); 3 vitamin E (tocopherol) derivatives (e.g., γ-CEHC; OR: 1.80; 95% CI: 1.20, 2.70); butter-associated caprate (10:0) (OR: 1.81; 95% CI: 1.23, 2.67); and fried food-associated 2-hydroxyoctanoate (OR: 1.46; 95% CI: 1.03, 2.07), meaning that prediagnostic serum concentrations of metabolites related to alcohol, vitamin E, and animal fats were moderately strongly associated with ER+ breast cancer risk. No metabolites were significantly associated with ER- breast cancer (144 cases) [117]. For colon cancer a relation with age, male sex and high BMI was found. Intakes of grains, meats, proteins, coffee, alcohol, aspirin, fibre, fruits, and vegetables were not associated with colorectal cancer mortality [118].

## Difference between Mediterranean Diet and Low Carb/ High Protein Diet

The Mediterranean Diet was introduced in 1993 by the Harvard School of Public Health and WHO Europe, based on the dietary traditions of Crete, Greece and southern Italy of around 1960. Research had revealed that the rates of chronic disease among populations in these regions were among the lowest in the world, and adult life expectancy was among the highest even though medical services were limited [119,120]. The 'poor' diet of the people of the southern Mediterranean, consisting mainly of

fruits and vegetables, beans and nuts, healthy grains, fish, olive oil, small amounts of dairy, and red wine, proved to be much more likely to lead to lifelong good health than the Western diet [121,122]. Other vital elements of the Mediterranean lifestyle are daily exercise, sharing meals with others, and appreciation for the food. The Mediterranean diet in its original form was the total opposite of 'modern' food and drink habits in industrialized countries, the latter leading to consumption of more meat and other animal products, fewer fresh fruits and vegetables, and more processed convenience foods, with large rates of heart disease, obesity, diabetes, and other chronic diseases as result. In 2008 the Mediterranean Diet was updated by the addition of herbs and spices, for reasons of both health and taste, at the same time contributing to the national identities of various Mediterranean cuisines, as well as the introduction fish and shell fish on the pyramid to be eaten at least two times per week. A central role is for plant foods (fruits, vegetables, grains, nuts, legumes, seeds, olives and olive oil), followed by fish and shellfish, higher in the pyramid are dairy products (yoghurt and cheese), eggs and chicken, whereas the top segment contains red meat and sweets. In Scandinavian countries the Mediterranean diet is interpreted as the Nordic diet; a comparable diet having local product as fatty fish, red fruit, rape seed oil and local grains as main components.

The greatest difference between low carb/high protein and Mediterranean diet lies in the abstinence from starch in the former: IR among other factors is caused by long-term consumption of refined grains in large quantities which demands a stricter approach in reducing carbohydrates. Another difference is the protein content, which is considerably higher in the low carb/high protein diet. The Mediterranean diet however, is great for weight maintenance in patients with IR or type 2 diabetes mellitus. Almost all products in the Mediterranean diet also fit in the low carb/high protein diet. By the public the Mediterranean diet is often interpreted differently than the original: replacing fibre rich potatoes by large dishes of white pasta with tomato sauce is regarded as Mediterranean and therefore healthy, as well as daily consumption of several glasses of wine. Around the Mediterranean sea part of the population has forgotten about healthy eating: in Croatia for example the old eating habits have been replaced by a more Western eating style [123]. Patino-Alanso examined factors that influenced adherence to the Mediterranean diet. Adherence was lower among individuals younger than 49 years of age. The factors associated with improved Mediterranean diet adherence were female sex, age older than 62 years, moderate alcohol consumption, and more than 17 metabolic equivalents (METs)/h/wk of physical exercise. Poorer adherence was associated with males and obesity [124]. Weight loss in both low carb/high protein and Mediterranean diets are beneficial for CVD risk factors [125].

### Long-term Effects of a Low Carb High Protein Diet

One of the problems in low carb-high protein diets is their sustainability. For how long can patients keep up with the diet. Several researchers found that low carb-high protein diets lead to significantly more weight loss short term, but differences with other energy restricted diets have disappeared after 60 months [126-128]. This was always presented as a problem and as an argument to refrain from these diets, but in fact it is not. Low carb diets are designed to help patients lose weight that otherwise would not have lost substantial amounts of weight, thus improving their health and postponing or reducing comorbidities. Grieb et al. [129] evaluated the effect of a long-term (>1 year) consumption of a low carb/high fat diet on lipid profile, glycaemic control, and cardiovascular disease risk factors in healthy subjects. Of 31 the dieters enrolled in the study (17 women and 14 men, aged 51.7 ± 16.6 years), 22 adhered to the diet for more than 3 years. The metabolic profiles of most subjects were positive for several indicators, including relatively low concentrations of triacylglycerols, high levels of high-density lipoprotein cholesterol (HDL-C), and normal ratios of low-density lipoprotein cholesterol/HDL-C and total cholesterol/HDL-C. In most subjects, plasma concentrations of glucose, insulin, glucagon, cortisol, homocysteine, glycerol, and C-reactive protein were within reference ranges. The HOMA-IR remained below the threshold for diagnosis of insulin resistance [129]. These results were confirmed in a review on short term results (more than 3 months) [130]. Nackers examined a group of obese women and found that fast, moderate and slow weight loss groups differed significantly in mean weight changes at 6 months (-13.5, -8.9, and -5.1 kg, respectively, $p<0.001$), and the fast and slow groups differed significantly at 18 months (-10.9, -7.1, and -3.7 kg, respectively, $p<0.001$). No significant group differences were found in weight regain between 6 and 18 months (2.6, 1.8, and 1.3 kg, respectively, $p<0.9$). The fast and moderate groups were 5.1 and 2.7 times more likely to achieve 10% weight losses at 18 months than the slow group, indicating short- and long-term advantages to fast initial weight loss. Fast weight losers obtained greater weight reduction and long-term maintenance, and were not more susceptible to weight regain than gradual weight losers [131]. One of the outcomes of the DiOGenes study was that a higher protein content of an ad libitum diet improves weight loss maintenance in overweight and obese adults over 12 months [132].

## Discussion

This review shows that there is a rationale for prescribing low carbohydrate/high protein diets to patients for weight loss, and for improvement of diabetes management. And, although these diets have been in the commercial domain for most of the time, they should be administered by dietitians because intake of macro nutrients and energy expenditure need to be individually assessed. Another argument for professional handling of these diets in patient care is, that most obese patients in health care have comorbidities, not seldom more than one, that also need to be taken into account. Patients that benefit from a low carbohydrate/high protein diet in many cases are vigorous carbohydrate consumers and need thorough guidance to help them along. A last argument for specialised dietetic care is that obese patients have a troubled relation between food and emotional balance, stress and nutritional knowledge. It is in this complicated field that patients benefit best from individual treatment, that, however, needs to be embedded in a multi-disciplinary setting. Montesi et al. [133] argue that a non-physician lifestyle counsellor would be an asset to an obesity team. I should advocate that we need the highest quality health professionals, because of the complex disease obesity is. I would further emphasize that we need to train dietitians, physicians, nurses, psychologists and physiotherapists in obesity management. We have a dietary approach that works and should be given to more patients, to make them able to lose weight and sustain it. We also need environmental and psychological approaches that can support patients in their lifelong dealing with this chronic disease.

## Conclusion

Low carbohydrate/high protein diets should be considered as a serious treatment option for all obese patients with and without comorbidities. They should be administered by specialised dietitians working in a multi-disciplinary team.

## Strengths and Weaknesses

A strength of this study is the thorough approach of all the evidence available on management short and long term effects of low carbohydrate high protein diets on weight loss and comorbidities, as well as the research done on different nutrients. A weakness of the study is that no meta-analysis took place to weigh the evidence.

## Conflict of Interest

The author has no conflict of interest.

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