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Research Article

Medical Nutritional Therapy Laid in Expert Hands to Strongly Suppress Insulin Resistance and to Restore Metabolic Health; a Review of the Evidence

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Abstract

Background: Very low calorie ketogenic diets, referred to as very low-carb/high-protein diets, well known for treating insulin resistance, are getting more accepted for obesity treatment. A recent review, published in Obesity Facts, presented positive results on weight loss and metabolic syndrome parameters. It has been shown that this diet reduces body weight substantially and decreases the impact of comorbidities, thus improving health. Based on available evidence, a well-formulated ketogenic diet reduces chronic low-grade inflammation through a very low-carb/high-protein diet as Medical Nutrition Therapeutic intervention. Our research question was whether Medical Nutrition Therapy (MNT) in the form of a very low-carb/high-protein diet in the hands of registered dietitians is effective and safe to suppress severe insulin resistance and its comorbidities.

Methods: We searched Pubmed, Medline and Google Scholar with the search terms: insulin resistance; obesity; overweight; weight loss; comorbidities; dietary treatment; low carb/high protein diet. And furthermore: fatty acids; omega 6-3 ratio; glycaemic index; glycaemic load and gut microbiome.

Results: Weight loss suppresses IR and chronic inflammation in obese and overweight patients through the reduction of inflammation markers like CRP, IL-6 and TNF-α; and an increase in adiponectin, IL-10 and IL-1ra. Weight loss leads to reversed postprandial inflammatory expression. The very low-carb/high-protein diet (VLCKD) that suppresses low grade inflammation is characterized by: a carbohydrate intake below 50 g/day during six months or more; a protein intake of 1 g/present weight; an omega 6/3 ratio of 4/1; ample intake of fiber; and suppletion of micronutrients including vitamin D and iodine. Treatment is long lasting, after an intensive phase of one year and carried out by registered dietitians.

Conclusion: Very low-carbohydrate/high-protein diets are effective for weight loss, to restore insulin sensitivity and reduce inflammation in patients with severe IR and comorbidities. Because of their complexity they should be administered by registered dietitians as part of Medical Nutrition Therapy.

Keywords: *Medical Nutrition Therapy (MNT); Very Low Carb/High Protein Diet; Weight Loss; Insulin Resistance; Comorbidities; Gut Microbiome; Registered Dietitian; Saturated Fatty Acids; 6x6 diet = 6x daily 6 Grams of Carbohydrates; Omega 6/3 Ratio*

Abbreviations

AA: Arachidonic Acid; ALA: Alpha-Linolenic Acid; BM: Basal Metabolism; CRP: C-Reactive Protein; CVD: Cardio Vascular Disease; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; FFM: Fat Free Mass; GI: Glycaemic Index; GL: Glycaemic Load; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-IRa: Interleukin-ira; IR: Insulin Resistance; MeDi: Mediterranean Diet; MetS: Metabolic Syndrome; MNT: Medical Nutrition Therapy; MUFA: Mono Unsaturated Fatty Acids; NCD: Non Communicable Disease; PUFA: Poly Unsaturated Fatty Acids; SFA: Saturated Fatty Acids; TNF-α: TNF Alpha; VF: Visceral Fat

Introduction

An earlier study published in 2019 provided evidence on the beneficial effects of Medical Nutrition Therapy (MNT) through a very low-carb/high-protein diet (6x6®) on patients with severe insulin resistance and comorbidities [1]. Patients with T2DM were more successful in losing weight and remission of T2DM measured by Hba1c and the use of anti-diabetic drugs on a very low carbohydrate diet than on a more liberal carbohydrate intake or an energy restricted diabetic diet. These positive health outcomes have been confirmed in other studies, as well as in a recently published review [2]. In this review we present this medical diet as a tool to restore insulin sensitivity, and to reduce weight as well as comorbidities, and we emphasize the role of the registered dietitian to provide MNT in patients with severe insulin resistance. Awareness of the health consequences of obesity is growing in health care, emphasizing the role of nutrition and lifestyle in prevention and management of the metabolic disorders, e.g. metabolic syndrome (MetS). The effects of MetS on human health are often discussed in the medical literature. However, the focus has not been yet on the suppression of insulin resistance (IR), the main driving factor of MetS but far more on medical therapies to control MetS. MNT if applied as a very low carb high protein diet aimed at weight loss and reduction of comorbidities needs our full attention to suppress IR and reverse comorbidities. MNT should be seriously considered by primary care physicians and hospital specialists when making referrals to dietitians trained to treat patients with metabolic diseases.

IR promotes low-grade inflammation, that leads to non-communicable diseases (NCDs), that are responsible for more than 70 percent of global mortality [3]. Chronic low-grade inflammation has been associated with age and diet related NCDs, including cardiovascular disease, cancer, type 2 diabetes (T2DM), obesity, arthritis, depression, respiratory and autoimmune diseases [4,5]. Besides, a typical Western-type diet plays an important role in etiology of those diseases [6]. MNT in this form can even help to prevent NCDs. A study of nutritional trends (1990 - 2010) in 187 countries reported alarming data on rapid adverse changes in food composition, underscoring the need for global nutritional policies to reduce NCD risk [7]. Based on insights from such population studies it has become evident that we can reduce chronic low-grade inflammation by introducing MNT as a part of a lifestyle intervention. Moreover, in a review by Calder it has been shown that a change of diet can suppress the chronic inflammatory condition and improve health [8]. Our research question was whether Medical Nutrition Therapy (MNT) in the form of a very low-carb/high-protein diet in the hands of registered dietitians is effective and safe to suppress severe insulin resistance and its comorbidities. In this review we describe the evidence. Furthermore, we introduce food based guidelines for patient management to suppress IR.

Methods

We searched Pubmed, Medline and Google Scholar with the search terms: insulin resistance; obesity; overweight; weight loss; comorbidities; dietary treatment; fatty acids; EPA; DHA; ALA; AA; linolic fatty acid; linoleic fatty acid; LCHP diet; MUFAs; SFAs; omega-3 fatty acids; omega-6 fatty acids, glycaemic index, glycaemic load, intermittent fasting, gut microbiome.

Results

MNT in the battle against IR and low-grade inflammation

In general, durable suppression of IR, low grade inflammation and reduction of body weight needs a durable change of lifestyle through a holistic approach. This means imposing to reduce carbohydrate intake, better food choices, bodyweight reduction, more exercise, sleep

hygiene, stress reduction and improving the emotional balance. In this review the food related measures as part of a holistic vision to reverse disease will be discussed. We will focus on substantial weight loss by deploying an intervention with the strength of a medical treatment, Medical Nutritional Therapy (MNT), which aims at reducing nutritional acid overload, suppress IR and low-grade inflammation and switch the gut microbiome. MNT to treat IR requires three phases: two intensive phases of 6-12 months, followed by maintenance, explained in paragraph 3. MNT also requires precision nutrition since postprandial responses differ for everyone [10,11]. Registered dietitians are crucial in guiding patients in their struggle to achieve health goals [12]. They are able to provide a complete analysis of the cause of obesity and comorbidities, and identify psychological and environmental factors that have led to the current situation; consequently, they are able to operationalize IR management in the consultation room [13]. They can reach optimal results together with the patient, but not at any cost. An effective MNT is not sustainable without shared decision making between dietitian and patient.

Substantial and durable weight loss

The positive effects of weight loss to suppress IR and chronic inflammation have been described for obese [14-17] as well as for overweight patients [18]. These effects include the reduction of inflammation markers like CRP, IL-6 and TNF-α, as well as an increase in adiponectin, IL-10 and IL-1ra. Clement found that four weeks of hypo energetic diet resulted in a modification of inflammatory genes in the subcutaneous adipose tissue in obese women with a 59% decreased expression of pro-inflammatory and an 41% increased decreased expression of anti-inflammatory genes [18]. Endothelial inflammation markers improve after weight loss as well [14,19,20]. The amount of weight loss is still under debate, because even five per cent weight loss gives improvements. Ryan found that to get comorbidities in remission more weight loss is needed, for example 5-10% for CV risk factors; 10% in case of T2 diabetes and 10 - 15% for liver diseases [21]. An extra argument to promote weight loss is that obesity is an important determinant of postprandial inflammatory response [22] and correlates with the degree of IR [22]. Body weight reduction leads to reversed postprandial inflammatory expression [23,24]. Because weight loss is beneficial for restoring of one of the most important health factors, the low-grade inflammation, it is required to choose a dietary strategy that suppresses low grade inflammation. The optimal way to reach that goal is to choose any intervention which causes substantial weight loss [1,20,25,26].

Low-carbohydrate/high protein diets

The ideal low-carbohydrate/high-protein diet contains less than 50 grams of carbohydrates per day, 1 gram of protein per kilo present weight, and around 40 energy percent of fat, mainly MUFAs or PUFAs, and no alcohol and is restricted in energy. An energy restriction is a logical consequence of a carbohydrate restriction, because many food products cannot be eaten and replacement of them is limited. If IR is very severe, for instance in case of T2DM with insulin, 20 grams of carbohydrates can be advised as well. Low carb diets focus on weight loss and reduction of IR. Dietary intervention is essential to suppress IR through decreasing insulin release and ideally restoring insulin sensitivity. Because insulin promotes lipogenesis when an abundance of triglycerides (from carbohydrates, fats and alcohol) is available, it will cause fat storage and weight gain. One efficient way to reduce insulin release and restore insulin sensitivity is by a rigorously reduction of carbohydrates in the diet for a long time. This has been shown in several studies on clinical endpoints i.e. durable weight reduction as well as restoration of comorbidities, especially T2DM [26] and CVD [27]. Table 1 gives an outline of this typical form of MNT that reduces carbohydrate intake below 50 grams per day in the intensive phase, as is the case with the 6x6 diet, containing 36 grams per day in the first phase [1]. The 6 x 6 diet consists of three phases. Phase 1: intensive treatment; phase 2: less intensive, but still less than 50/g per day; phase 3: maintenance through lifestyle. This diet knows no fat or calorie restriction but is based on strong reduction of carbohydrates. A stricter regimen is given to severely insulin resistant patients, e.g. obese patients with T2DM and high doses of insulin of 3 x 6 grams of carbohydrates per day (18 grams) during several months with good results on remission of T2DM [28].

Subject	Quantity
Energy	No energy restriction
Carbohydrates	Phase 1: 36 (6 x 6) g/day (0 - 6 months) Phase 2: 48 - 54 g/day (6 - 12 months). Cooked meal to 12 g carbs/day. Phase 3: Maintenance lifestyle phase: 80 - 100 g/day Very severe IR: 3 x 6 g/day Sweeteners: polyols calculated as carbohydrates [45]
Protein	Phase 1 and 2: 1 g/kg present weight. Phase 3: 1 g/kg present weight
Fat	Phase 1 and 2: no restriction Liquid fats for frying, cooking Phase 3: 40-50 energy%, divided as: 10% PUFA; 20% MUFA; 10-20% SFA. Lean meat; whole fat dairy
Omega 6-3 ratio	< 4:1; suppletion omega-3 (200 mg/day)
Fiber	25 g/day (women), 30g (men), spread over 6 meals
Liquids	2 liter/day
Micronutrients	All patients: Daily intake of 800 IU vitamin D 3 Phase 1 and 2: 1 multivitamin per day containing iodine
Sleep	> 7 hours per night or more; and sleep hygienic measures (e.g. screen time)
Exercise	Building up to 60 minutes every day; spread over two time frames; or 150 min intensive per week
Stress and emotional health (anxiety, depression, trauma)	Taking away the causes of stress; counseling, e.g. CBT, ACT and mindfulness

Table 1: *Outline of low carb high protein diet e.g. 6x6diet® for treatment of IR*.*
**: This table reflects the outlines of the 6x6diet® [1] plus latest insights about management of IR and obesity, which demand a multifactorial approach, including sleep, physical exercise and emotional wellbeing, which are monitored by registered dietitians.*

Carbohydrates

Carbohydrate intake must be decreased significantly to reverse IR [16]. Rule of thumb is: the more severe IR or its comorbidities, the stronger the positive effects from rigorous carbohydrate restriction. The strongest effects have been reported on daily intake of < 50g carbohydrates in the first intensive phase of a dietary regime [29,30]. These diets are referred to as ketogenic or very low carbohydrate diets and have been administered from the year 1797 onwards [31,32]. Low carbohydrate diets can be as low as 20 g/day [33]. By eating 6 g of carbohydrates per meal the pancreas is not further stimulated to produce insulin, thus reducing IR [1]. Spread over three meals and three

snacks this leads to a total intake of 36 grams of carbohydrates. A carbohydrate intake lower than 50 g/day during a long period, leads to decreased insulin levels [34]. Moreover, even the normalization of the insulin production has been reported [35]. On the other hand, on a population level overall carbohydrate intake have risen over the years, and sometimes, patients' daily intakes of 80 energy percent of carbohydrates are registered, with the consequence of a protein intake below recommended quantities. NHANES published increased carbohydrate intakes in the US population between 1974 and 2000 in men from 42 to 49 and in women from 45 to 52 energy% [36].

Outcomes of a vigorous carbohydrate reduction should be a 5 - 15% body weight reduction; a reduction or remission of comorbidities; and a reduction or cessation of medication to control MetS. In the maintenance phase, carbohydrate intake needs individual adaptation carefully monitored by the dietitian. In contrast to general dietary guidelines patients with treated IR always need to eat reduced amounts of carbohydrates, e.g. 80g per day. Only if weight is stable, the intake of carbohydrates can be increased up to 100 grams per day, which means in practice the use of modest meal size portions with restricted quantities of carbohydrates. In table 2 food recommendations for the very low-carb/high-protein diet as MNT are shown discerning its intensive and maintenance phase.

Product	Quantity, servings
Dairy	**Phases 1 and 2:** 2 x 150 ml/day full fat yoghurt or cottage cheese **Phase 3:** up to 450 ml/day: 2-3 servings
Vegetables Pulses	**Phase 1:** 150-200 g/day in the cooked meal (low carb vegetables with 0-1g carb/100 g). Lunch: salad of low carb vegetables with low carb bread; or vegetables 6g/100 g without bread. **Phase 2:** 250 g vegetables (up to 6 g/meal) **Phase 3:** > 250 g vegetables/day **Phase 2 and 3:** 50 grams pulses 2 times per week
Eggs	**Phase 1 and 2:** 1 per day or 2 every other day **Phase 3:** 4 per week
Meat, poultry, game	**Phase 1 and 2:** 150 g/day in the cooked meal (200 g for BMI > 40 kg/m^2). **Phase 3:** 100-125 g/day. Products for sandwiches and snacks are additional and not quantified (dependent on weight loss progress)
Cheese	**Phase 1 and 2:** 80-120 g/day. **Phase 3:** 80-100 g/day
Fats, oils[a]	**Phase 1, 2 and 3:** 2 spoons olive oil (traditional or virgin *) +1-2 tablespoons real butter or margarine for use on crackers or bread; No coconut oil or palm oil in all phases

Omega-3	**Phase 1,2 and 3:** 1-2 x fatty fish per week **Fish oil:** If no fish is consumed: suppletion 200 mg/day; Flax seed as addition also for extra fiber
Fruit	**Phase 1:** x 60 g/day combined with protein **Phase 2:** 1 x 100 g/day combined with protein **Phase 3:** 1 - 2 x 100 g/day combined with protein (12 grams carbohydrates)
Nuts, seeds, pits	**Phase 1 and 2:** 50 g/day (as snack) or in meals or with dairy. **Phase 3:** 25 g/day or 50 g every other day
Bread	**Phase1:** 2-3 low carb bread or low carb crackers (<6 g/serving); **Phase 2:** 4 low carb bread or crackers. **Phase 3:** Low carb bread or crackers dependent on satiation. Normal bread as exception when it fits the carbohydrate content of the diet.
Pasta, rice, bulgur, taco, noodles,	**Phase 1 and 2:** Low carb versions 2 spoons. Maximum 2 x per week. Preferably 2 vegetables and meat/fish/poultry instead of pasta. Pasta based on vegetables: if carbohydrate content fits the diet. **Phase 3:** Low carb versions or 2 spoons normal versions 1 or 2 x per week, fitting the carbohydrate content of the diet
Potatoes	**Phase 1 and 2:** Replace by vegetables with less carb content. **Phase 3:** 100 g/day 2 times per week
Drinks	Water, coffee (with cream), tea, light soft drinks and light syrups 2 liters/day
Alcohol	**Phase 1 and 2:** None **Phase 3:** Only: maximum 1 serving/day (wine)

Table 2: *Food based guideline for MNT as low carb high protein e.g. 6 x 6 diet®*.*
*[a]Virgin olive oil is for uncooked foods/salads only. *This table reflects the outlines of the 6 x 6 diet® plus latest insights about management of IR and obesity as described in this article on: choice and quantity of fats, omega6/3 ratio, fish oil suppletion, micronutrients.*

Proteins

General guidelines on dietary management for healthy populations recommend 0.8 g protein per kilo ideal weight to be sufficient and in agreement with weight maintenance and a healthy lifestyle. This recommendation is often confused with MNT aiming to suppress IR. However, in patients with overweight/obesity and IR addition of more proteins in a diet (1.0g protein per kilo present weight) is more effective in terms of weight loss, and Free Fat Mass (FFM) and Basal Metabolism (BM) preservation [36,37]. Both, the DIOGENES and DIRECT studies adapted this vision through administration of high protein meal replacements in the first 12 weeks, the induction phase

[36]. In general, sufficient protein intake is critical in weight loss management [37]. Whey protein, which originates from liquid dairy, preserves muscle mass optimally, especially in combination with physical activity [38], and plays a role in satiation and satiety [37]. Amirani concluded in a meta-analysis of 22 studies that whey consumption led to significant reductions of insulin, HOMA-IR, TG, HbA1c, total C, LDL and HDL/C ratio [38]. One of the hazards of weight loss in the middle aged and elderly is the loss of FFM including hard and soft tissues, ultimately leading to sarcopenia [39,40]. Sarcopenic obesity in BMI > 30 kg/m^2 is characterized by elevated cytokine levels (IL-6; CRP; IL-1 and IL-6 receptors ($P < 0.05$)); gain of visceral fat (VF); and increase of chronic inflammation, leading to a vicious circle of even more sarcopenia [40]. Intake of protein that is spread over 3 to 6 eating moments enhances satiety and satiation effects and is important to maintain FFM. Any protein boost suppresses ad libitum food intake in contrast to high resorbable sugar-containing snacks through biological effects, for example through the increase of GLP-1 concentrations [37].

Fat

Saturated fats, trans fats and hydrogenated fats

A low carb high protein contains usually average 35 - 40 energy per cent fat. In patients with untreated IR triglycerides (TG) and LDL cholesterol are often increased and HDL is below normal values [41,42]. However, during the weight loss process, VF and LDL and TG levels decrease, while HDL tends to increase [27]. Furthermore, postprandial LDL oxidation diminishes as glucose metabolism restores [43,44]. Volek compared a low-fat diet to a low-carbohydrate/high-protein diet and found that despite a 3-fold higher fat intake, Saturated Fatty Acids (SFAs) in TG and cholesterol, as well as palmitoleic acid (16:1-7) decrease, and insulin sensitivity improves. A low-carbohydrate/high-protein diet induced 10% weight loss with a favorable LDL fat particle distribution [27]. Similar findings have been confirmed in other studies [45]. The PURE study showed that high intake of dairy (> 2 servings) compared to no intake, regardless of fat content, was associated with a lower risk of cardiovascular events, total mortality, and cardiovascular mortality [43,44]. Distribution of LDL particles can help to predict cardiovascular disease: small LDL particles predict more CVD risk than large ones. In untreated IR, LDL particles are small but become bigger after weight loss through a low-carbohydrate/high-protein diet. Any low carbohydrate containing menu will induce larger particles, thus reducing the risk of CVD regardless of LDL level [27]. A lower consumption of snacks, take away meals, chocolate, sweets, ice-cream and pastries, reduces the intake of SFAs as well with possible beneficial effects on cholesterol values. Consumption of palmitoleic fatty acid, a SFA present in all processed foods and a marker of lipogenesis, becomes reduced. Within the low carb/high protein diet we present, the butter and consumption of animal fats does not exceed SFAs intake, therefore staying within the normal range of healthy nutrition. Coconut oil is a different story: it is regarded by part of the general public as a healthy alternative for PUFAs. In the tropics, coconut oil that contains almost 50% lauric acid, is known for its antiseptive qualities, and improvement of the cholesterol/HDL ratio [46]. However, the coconut oil used in India and Pakistan is of a very different composition than the solid hydrogenated coconut oil sold in the Western world, which could be harmful to patients with IR [47]. By hydrogenation soluble fats, derived from seeds or nuts change during a factory procedure from liquid to solid. Through this process PUFAs are changed into SFAs. This could be harmful in the long run, because SFAs derived from solid hydrogenated fats have a worse impact on development of CVD than dairy fats, or oils rich in PUFAs. Trans fats (TFAs) are produced as by-effects of hydrogenation. Control on TFA presence in cooking fats is strict; but they also originate in frying processes in snacks - with very little control on their levels [47].

MUFAs

Mono unsaturated fatty acids, MUFAs, also classified as omega-9 fatty acids are known to reduce IR and CVD risk factors [48]. The best example of MUFA is olive oil, also the basis of the Mediterranean Diet [49]. Olive oil is high in antioxidants (polyphenols) and has anti-inflammatory benefits because of its high content of oleic acid (72%). Extra virgin olive oil has been proven to reduce CVD risk [49]. Olive oil is therefore a preferable fat for cooking up to 200^0C.

Omega 3, and 6

The intake of omega 3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) is a critical point. It has been suggested that mankind in its evolution used a diet with an approximate omega 6 to 3 ratio of 1/1. In Western diets this ratio has risen to 15/1 [50]. A high omega 6-omega 3 ratio promotes the pathogenesis of cardiovascular disease, cancer, and inflammatory and autoimmune diseases, like rheumatoid arthritis, whereas a ratio of 4/1 or 2.5/1 improves outcomes in colorectal and breast cancer, rheumatoid arthritis and asthma, although outcomes also depend on genetic predisposition [51]. The omega-3 PUFA, EPA and DHA, from fish oil are more biologically potent than plant-based alpha-linolenic acid (ALA) [51]. Omega-3 fatty acids suppress interleukin 1beta (IL-1beta); tumor necrosis factor-alpha (TNF-alpha); and interleukin-6 (IL-6), thus reducing IR symptoms. Arachidonic acid (AA) and linoleic acid (LA) increased the risk for CVD in patients with genetic variation of the 5-lipoxygenase (5-LO) by 80%, contrary to EPA and DHA that reduced this risk [81]. AA promotes release of prostaglandins and leukotrienes that are mediators of inflammation, whereas consumption of fish oil replaces AA by EPA in inflammatory cell membranes, suppressing low grade inflammation. EPA also suppresses the production of pro-inflammatory cytokines [52].

Whereas EPA and DHA are present in fatty fish (mackerel, herring, sardines, salmon and trout), in white fish (traces) and shellfish, who metabolize it from algae in the sea, and in plant based margarines as supplement, it is particularly ALA that is present in many basic food products like: olive oil, flax oil, rapeseed oil, walnut (oil), avocado, green leafy vegetables (small quantities). Table 3 gives the omega fatty acids, their sources and quantities.

Fatty acid	Products	Quantities needed
EPA/DHA (animal omega-3)	Oily fish such as salmon, herring, mackerel, and sardines; fish oil; eggs	1 - 2 x per week fatty fish 1% of daily calories (e.g. 250 mg - 2 g/2000 kcal.)
Omega-6	Safflower oil, sunflower oil, corn oil, soybean oil, sunflower seeds; pumpkin seeds	5 - 10% of daily calories (e.g. 10 - 20 g/2000kcal.); liquid baking oils (No coconut oil)
ALA (plant based omega-3)	**Oils:** Olive oil, flax oil, rapeseed oil, walnut (oil). **Vegetables:**, avocado; broccoli; cauliflower; green cabbage; kale; Brussel sprouts; spinach; tofu. **Seeds and nuts:** almonds; chia seeds, fax seeds; hazelnuts; pecan nuts, peanuts, walnuts,	1 - 3g per day NB. Vegetables, nuts, seeds and tofu contain 0.4 g/100g. With the exception of walnuts: 9 g/100g.

Table 3: *Omega fatty acid sources and advised quantities per day.*

Omega-6 fatty acids can also be derived from non-hydrogenated plant-based oils [53-56]. A review showed the effects of omega-6 fatty acids in lowering blood pressure and LDL, while increasing HDL cholesterol, insulin sensitivity and glucose metabolism [56]. Furthermore, a meta-analysis of 6 RCTs demonstrated replacing saturated fats by omega-6 fats reduced the risk of CVD by 24% [54]. Another review showed similar results replacing monounsaturated fats or carbohydrates into omega-6 and omega-3 fats [55].

Fiber

Sufficient fiber as part of the diet is essential for gut health and is protective against colorectal cancer [57], T2DM [57] and obesity [58]. Dietary fiber content, whether soluble or non-soluble, showed to be inversely correlated to CRP levels in healthy, obese, and diabetic

adults, in hypertension and other metabolic disorders [59,60]. Therefore, in the 6x6 diet, low carb crackers and bread, rich in fiber, as well as nuts, seeds and vegetables are an essential part of the diet. Additionally, pulses are advised from phase 2 and sufficient liquid intake is monitored.

Balance of microbiota

The importance of a balanced distribution of gut microbiota has become clear in human studies regarding IR (1). The food composition keeps the intestines healthy through the influence of the gut microbiome. Negative factors are animal proteins and artificial sweeteners apart from Stevia. Paoli., *et al*. examined the consequences for the maintenance and improvement of intestinal health in the case of a low-carbohydrate diet, expressed in table 4 [61].

Nutrient	Products
Whey	Liquid dairy, preferably as yoghurt, buttermilk or cottage cheese
Plant proteins	Peas, pulses, soy and nuts
Fermented foods and drinks	Yoghurt; kefir; kimchi; fermented vegetables
Omega 6-3	Improve ratio to 4:1 (see table 3)
MUFAs and PUFAs	Avoid hydrogenated fats (idem)
Artificial sweeteners	Avoid, with exception of Stevia
Prebiotics and probiotics	Use, in case of problems

Table 4: *Measures to improve gut microbiome.*

Hydration

Sufficient intake of liquids is crucial for health in general, but also for weight loss [62]. A total of two liters per day is enough. Increased water intake is associated with loss of body weight via lowering of caloric intake and increased lipolysis [62]. Insufficient hydration is correlated to increased body weight, hypertension and the risk for hyperglycemia [63]. Increased hydration leads to an increase in cell volume, consequently, to increased insulin sensitivity [64].

Glycaemic index, glycaemic load and inflammation

The evidence on GI and glycaemic load on inflammation is conflicting. Observational studies showed a relation between high GI diets on CRP and/or adiponectin in patients with and without T2DM [65] but intervention studies in normal weight or healthy obese did not confirm this [66]. GI and GL are no specific objective in low carb/high protein diets, as these are low GI by nature.

Discussion

Very low-carb/high-protein diets are the tool to reduce IR and restore health. They have been accepted for treatment of T2DM [30,36] and CVD [26,29,67], but are often seen in the field of health care as a short-term approach to weight loss. In this review we have presented a diet that is very low-carb/high-protein that can be administered long term to restore health, because it alters to the phase the patient finds himself in. The diet is part of a lifestyle. Patients are monitored for several years. The results, presented in our initial study on the effects showed that patients were very satisfied with the guidance by their dietitians and liked to come to the visits, to discuss their health outcomes and receive further counseling and practical advice [1]. Registered dietitians are equipped to administer this diet as MNT, as they must be tailored to each patient to achieve the intended goals. In this review, we tried to emphasize that a very low-carb/high-protein

diet is beneficial for significant weight loss, reduction of inflammatory markers and IR, restoration of insulin sensitivity, and overall health. The modern low-carbohydrate diet includes foods that are considered healthy in all respects. In that sense, it is quite similar to Mediterranean Diet (MeDi). The difference lies in two elements. First, the MeDi has a higher energy percentage of carbohydrates, although rich in fiber. This can prevent significant weight loss, especially in people who are severely insulin resistant, due to the mechanism that carbohydrate intake promotes insulin release and consequently fat storage. In addition, the composition of the MeDi is not well defined and can differ per region. The second element is protein intake, which is higher in the very low-carbohydrate/high protein diet. Obese patients require a high protein intake to restore health and FFM. Similarities are the emphasis on intake of sufficient plant-based foods and healthy fats (MUFA, PUFA and omega-3 fatty acids).

One of the aspects preventing the paradigm shift needed to improve treatment and outcomes in patients with IR is that administering the diet and counseling patients requires well-trained and skilled health professionals, dietitians. Due to the large number of patients, there is a tendency to refer to less skilled professionals to treat patients. Medical Nutritional Therapy in patients with severe IR and demonstrable comorbidities, however, needs expertise and experience that can only be provided by registered dietitians. The benefits outweigh the costs because the treatment can take place in the primary health care setting, in community settings, rather than in hospitals.

Conclusion

Very low-carbohydrate/high-protein diets are effective for weight loss, to restore insulin sensitivity and reduce inflammation in patients with severe IR and comorbidities. Because of their complexity they should be administered by registered dietitians as part of Medical Nutrition Therapy.

Conflict of Interest

The authors declare they have not been funded or sponsored to write the article.

Author Contributions

EG did the first selection on the literature and wrote the draft. DHS designed the article. WB and AL added specific information concerning the 6 x 6 diet and corrected the manuscript. HV and BJ corrected the manuscript with special attention to technical details.

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