MASTER THESIS

Public Health Nutrition

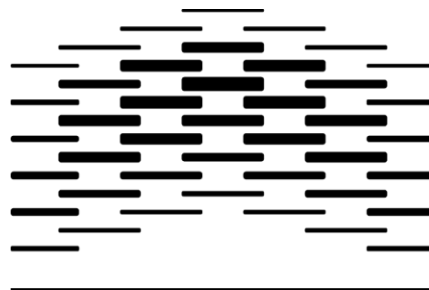2014

The effectiveness of a low-carbohydrate diet in management of type 2 diabetes

A systematic review of the current literature

Henny-Kristine Haugen

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**OSLO AND AKERSHUS
UNIVERSITY COLLEGE
OF APPLIED SCIENCES**

Faculty of Health Sciences

Department of Health, Nutrition and Management

Oslo and Akershus University College of Applied Sciences

In this master thesis a systematic review was conducted to investigate the effectiveness of a low-carbohydrate diet in management of type 2 diabetes. The review was written in conjunction with author guidelines of Diabetologia, where the aim is to get it published.

I developed a personal interest for type 2 diabetes and systematic reviews after having spent one semester at Griffith University, in Australia where I was supervised on how to write a review paper. Systematic reviews are increasingly recognised as the gold standard of evidence to guide health care decisions and this project therefore provide an important opportunity to advance the understanding of the safety and effectiveness of a low-carbohydrate diet in management of type 2 diabetes.

The overall structure of the thesis takes the form of six main headlines, including the review article. The first part deals with the rationale of the thesis, where I elaborate why this issue needs to be investigated. The methods section provides a description of the role of systematic reviews and the conduct of this research project. Thereafter a further presentation of the results from the review and an expanded discussion is presented.

Grateful acknowledgement is given to my supervisors in conduction of the thesis, Dr. Anne-Marie Aas, associate professor at the University of Oslo/clinical dietitian at Oslo University Hospital, and Dr. Kjell Sverre Pettersen, associate professor in Public Health Nutrition at Oslo and Akershus University College of Applied Sciences.

Henny-Kristine Haugen

SAMMENDRAG

Bakgrunn Kosthold har en hovedrolle i behandling av type 2 diabetes (DM2) og bidrar til å bedre sykdomsbildet og forebygge og utsette utviklingen av komplikasjoner. Internasjonale organisasjoner har tradisjonelt anbefalt at diabetespasienter følger et kosthold med redusert inntak av fett, spesielt mettet fett, og et relativt høyt inntak av karbohydrater. Nyere litteratur antyder derimot at et kosthold med redusert karbohydratinnhold kan være like gunstig eller bedre, for å oppnå vektkontroll og bedre metabolske risikofaktorer på kort sikt.

Hensikt Formålet med denne masteroppgaven var å utføre en systematisk litteraturoversikt og meta-analyse, om lav-karbohydratkostholds effekt på vekt, glykemisk kontroll, serumlipider og compliance, hos individer med DM2.

Materiale og metode Et systematisk søk av litteraturen ble gjennomført i følgende databaser: MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source og SweMed+. Randomiserte kontrollerte studier blant pasienter med DM2 der intervensjonen var en lav-karbohydratkost (<40 E%) vurdert mot en kontrollkost med mer en 40 E% fra karbohydrater, ble inkludert.

Resultater Av 1180 studier identifisert via litteratursøk, ble 18 studier med totalt 1832 deltakere, inkludert i litteraturoversikten. Tre studier favoriserte lav-karbohydratkost for vektreduksjon, tre for HbA1c, fire HDL-kolesterol, en LDL-kolesterol, to triacylglycerol, en systolisk blodtrykk og tre diastolisk blodtrykk. Flertallet av disse lav-karbohydratkostene hadde et høyt innhold av fett og ble sammenlignet mot ulike koster som lav-fett, lav-protein, lav-glykemisk indeks, høy-glykemisk indeks, Middelshavskost og standard diabeteskost.

Konklusjon Resultatene fra denne masteroppgaven tyder på at et lav-karbohydratkosthold kan bedre vekt, HbA1c og risikofaktorer for kardiovaskulær sykdom hos individer med DM2, men lav-karbohydratkostholdet ga ikke bedre resultat enn kontrollkoster med et høyere inntak av karbohydrater. Det å følge et kosthold med redusert karbohydratinntak, synes vanskelig på kort og lang sikt. Fremtidig forskning bør derfor fokusere på å kartlegge intervensjoner som kan bedre compliance til et sunt kosthold på lang sikt hos individer med DM2.

ABSTRACT

Background Dietary treatment is a key factor in management of type 2 diabetes (T2D), and facilitation of a healthy diet is essential to achieve treatment goals. Traditionally, a low-fat, high-carbohydrate diet has been recommended in management of T2D, but recent research suggests that a low-carbohydrate diet may be an option in the short term.

Aim/research question The aim of this master thesis was to conduct a systematic literature review and meta-analysis about the effectiveness of low-carbohydrate diets on weight management, metabolic control and compliance in adults with T2D.

Methods/methodology A systematic search of the following databases was conducted: MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source and SweMed+. Randomised controlled trials that investigated the effect of a low-carbohydrate diet (<40 E%) compared to a diet containing >40 E% from carbohydrates, in individuals with T2D, were included in the review

Results Of the 1180 articles identified through the literature search, 29 studies with a total of 1832 participants, were included in the review. Between dietary interventions, three studies favoured the low-carbohydrate diet in weight management, three on HbA1c, four on HDL-cholesterol, one on LDL-cholesterol, two on triacylglycerol, one on systolic blood pressure, and three on diastolic blood pressure. The majority of these low-carbohydrate diets was high in dietary fat, and were compared against low-fat diets, low-protein diets, a low-glycaemic index diet, a high-glycaemic index diet, a Mediterranean diet and standard diabetes care.

Conclusion This master thesis found that low-carbohydrate diets improved weight, HbA1c and cardiovascular risk factors in T2D patients. Still, when compared to control diets with a higher content from carbohydrates, the low-carbohydrate diets were not superior. Compliance to the low-carbohydrate diets appeared to be difficult to achieve and further investigations are needed to identify dietary approaches that can be followed in the long term management of T2D.

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ABBREVATIONS

CVD: Cardiovascular disease

HbA1c: Glycated haemoglobin

HDL-cholesterol: High-density lipoprotein

IGT: Impaired glucose intolerance

LDL-cholesterol: Low-density lipoprotein

OGTT: Oral glucose tolerance test

PROSPERO: International Prospective Register of Systematic Reviews

PICO: Population Intervention Control Outcomes

RCT: Randomised controlled trial

WHO: World Health Organization

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis

BACKGROUND

Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia and disturbance in carbohydrate, fat and protein metabolism (Helsedirektoratet, 2009). In type 1 diabetes, pancreatic insulin production is gradually reduced until depleted and medical supply of insulin to initiate glucose absorption into cells is necessary. In type 2 diabetes, insulin production may be adequate and is often increased, but hyperglycaemia develops due to insulin resistance and relative insulin insufficiency, which ultimately affects the metabolic system (American Diabetes Association, 2012). Late detection of diabetes is frequent however, as the onset of symptoms such as increased thirst, polyuria and reduced general condition often develop over time (Helsedirektoratet, 2009). The conventional criteria used in diagnosis of diabetes includes fasting serum glucose levels >7.0 mmol/l, and venous plasma glucose levels >11.1 mmol/l, 2 hours after a 75-g oral glucose tolerance test (OGTT) (World Health Organization, 2011a). More recently glycated haemoglobin (HbA1c) with a cut-off at 6.5% has been accepted as an equivalent diagnostic tool, and is by some authorities recommended as the primary marker in diagnosis and management of diabetes (Helsedirektoratet, 2012; World Health Organization, 2011c, 2011d).

The prevalence of type 2 diabetes is increasing in every world region and is observed alongside with demographic and social trends, such as population density, urbanisation, development of nations and life expectancy (Wild, Roglic, Green, Sicree, & King, 2004; World Health Organization, 2011b). There is a difference in occurrence between nations and within (Hilary King & Rewers, 1993; Hilary King & Zimmet, 1987; Rewers, LaPorte, King, & Tuomilehto, 1987), and lower socioeconomic status appears to be associated with elevated risk (Helsedirektoratet, 2009; Statistisk sentralbyrå, 2007). Globally, more than 347 million people have diabetes and estimates conclude that the prevalence, independent of lifestyle factors, are likely to reach 366 million by 2030 (Danaei et al., 2011; Wild et al., 2004). Most of this growth is anticipated in the developing part of the world, but increased life expectancy is predicted as the furthermost important factor (Amos, McCarty, & Zimmet, 1997). In Norway similar trends are observed and the most recent publication from 2004, indicated a prevalence of 90 000-120 000 (Stene LC, 2004). These numbers only include the diagnosed cases of diabetes, however just as many people may have undiagnosed diabetes.

The burden of type 2 diabetes and its complications

Type 2 diabetes is predominantly lifestyle related and constitutes 85 to 90% of all diabetes cases (Hu et al., 2001; H. King, Aubert, & Herman, 1998; Steyn et al., 2007). The economic burden of type 2 diabetes and its subsequent complications are increasingly recognised as a serious, worldwide public health concern (Danaei et al., 2011). The annual cost of diabetes care in Norway in 2005 was projected to be €292.5 million (Solli, Jenssen, & Kristiansen, 2010). This included direct costs to hospital care, outpatient care and pharmaceuticals, as well as indirect costs to sickness compensation and permanent disability pension. From the patients point of view, quality of health care and total burden of disease contribute substantially to quality of life (Wändell, 2005). A Nordic review article found that individuals with type 2 diabetes were more likely to experience reduced quality of life, compared to individuals without diabetes or with impaired glucose tolerance (IGT) (Wändell, 2005). This was particularly observed among diabetes patients with present macrovascular disease. Managing complications is thus essential to improve quality of life of patients, as well as to reduce the cost on health care systems (Dall et al., 2009; Koopmanschap, 2002).

Disturbance in micro-and macrovascular circulation is strongly associated with type 2 diabetes (Amos et al., 1997; Litwak et al., 2013) and the World Health Organisation (WHO) recommends that nations implement thorough surveillance of risk factors that may lead to complications (2004). The microvascular diseases retinopathy, nephropathy and neuropathy, are referred to as acute diabetic complications and affect smaller blood vessels in respectively eyes, kidneys and peripheral nerve system (Fowler, 2008). Retinopathy is for instance one of the most common causes of visual disability and blindness (World Health Organization, 2012). Macrovascular diseases affect larger blood vessels and include cardiovascular disease (CVD), peripheral vascular disease and cerebrovascular disease (Fowler, 2008). CVD is the most frequent cause of death among diabetes patients (Morrish, Wang, Stevens, Fuller, & Keen, 2001) and diabetic individuals have 3-5 times higher risk to be affected by CVD than their peers without diabetes (Helsedirektoratet, 2009).

A multifactorial approach is required in diabetes care, as imbalance in metabolic factors such as blood pressure, serum lipids and glycaemia are highly prevalent among the patient group (American Diabetes Association, 2012, 2013). Results from clinical trials demonstrate that thorough metabolic control reduce and delay the incidence of both micro- and macrovascular disease (Adler et al., 2000; Laakso, Lehto, Penttila, & Pyorala, 1993; F. Turnbull et al., 2005; Wu et al., 2014). Blood glucose control has conventionally been the main focus in diabetes care, as hyperglycaemia escalates the process of atherosclerosis and

incidence of microvascular events (UKPDS, 1998). However, the role of hyperglycaemia in macrovascular disease is less clear (Haffner & Cassells, 2003; Libby & Plutzky, 2002). Results from a meta-analysis of four major randomised controlled trials in diabetes (ACCORDE (2008), ADVANCE (2008), UKPDS (1998) and VADT (Duckworth et al., 2009)) indicate that thorough glycaemic control only has a modest effect on outcomes related to macrovascular disease (F. M. Turnbull et al., 2009). Dyslipidaemia and hypertension are thus key factors in the pathology of CVD (American Diabetes Association, 2013) and observational studies show a correlation between LDL-cholesterol, HDL-cholesterol, triacylglycerol, total cholesterol and systolic blood pressure in occurrence of macrovascular complications (Litwak et al., 2013). Therefore, current guidelines recommend that several metabolic risk factors are integral components in the prevention of micro-and macrovascular disease (American Diabetes Association, 2013; Helsedirektoratet, 2009; Members et al., 2013).

Lifestyle factors in management of diabetes

It is well established that diet and physical activity are key factors in the prevention and management of type 2 diabetes (Hu et al., 2001; Steyn et al., 2007; World Health Organization, 2004). In fact, nearly two thirds of all risk factors for type 2 diabetes are related to diet (World Health Organization, 2003). An unhealthy diet refers to a low intake of fruit and vegetables, high intake of saturated fat, sugar and alcohol, as well as a diet containing energy dense foods and poor macronutrient composition (World Health Organization, 2003, 2004). The pathology of diabetes is strongly connected with weight (World Health Organization, 2003), and the majority of all type 2 diabetes patients are overweight or obese (Colosia, Palencia, & Khan, 2013; Daousi et al., 2006). Increased adiposity initiates insulin resistance, which may lead to elevated serum glucose, when beta-cell dysfunction is present at the same time. A healthy diet is accordingly central to achieve weight control, and to improve overall health (World Health Organization, 2003).

Lifestyle interventions that incorporate dietary modifications have observed beneficial effects on disease progression independent of weight loss (Pan et al., 1997; Ramachandran et al., 2006) and pharmacological supplements (Knowler et al., 2002). Furthermore, short term dietary interventions have demonstrated long-term carryover effect on risk profile and health outcomes (Eriksson & Lindgarde, 1998; Li et al., 2008). These findings indicate that a healthy diet, even when improved for a limited period, may result in long term health advantages. However, compliance to lifestyle interventions is generally poor among individuals with

chronic diseases (Desroches et al., 2013). Compliance to a healthy diet is ultimately essential to improve weight and metabolic factors (Dansinger, Gleason, Griffith, Selker, & Schaefer, 2005), and public health strategies that enable individuals with type 2 diabetes to improve dietary habits in the long term, are required (Desroches et al., 2013).

Dietary management of type 2 diabetes

Current guidelines in diabetes management recommend that dietary advice is patient-centred to support quality of life (Evert et al., 2014). Patient-centred care is a process where the care provided by health professionals is adjusted after patients' needs (Committee on Quality of Health Care in America: Institute of Medicine, 2001). The aim is to enable individuals to take an active part in the disease management, and to gain empowerment over own health. In order to achieve this, factors such as food and taste preference, culture and metabolic goals should be considered when providing dietary advice (Evert et al., 2014).

Traditionally a low-fat, high-carbohydrate diet has been recommended in management of type 2 diabetes, with a subsequent energy restriction for overweight and obese individuals (American Diabetes Association, 2002; Canadian Diabetes Association, 1999; Helsedirektoratet, 2009; Mann et al., 2004; Nutrition Committee of the British Diabetic Association's Professional Advisory Committee, 1992). In recent years, results from clinical trials have suggested that several dietary approaches and macronutrient compositions may be effective in weight management, as well as in improving risk factors for micro-and macrovascular disease (Bonnie J. Brehm et al., 2009; Estruch et al., 2013; Fabricatore et al., 2011). A newly published systematic review by Ajala, English and Pinkney (2013) found that low-carbohydrate diets as well as high protein diets, Mediterranean diets and low-glycaemic index diets (Low-GI), induced favourable effects on metabolic factors in type 2 diabetes patients. Especially the low-carbohydrate diet and Mediterranean diet resulted in greater improvements in weight, compared to the comparator diets. Furthermore, a review by Wheeler and associates (2012) investigated the impact of macronutrient compositions, dietary trends and food groups in management of diabetes. The review supported previous literature indicating that several dietary patterns, including traditional low-fat diets, low-carbohydrate diets and Mediterranean diets, induce favourable effects on health outcomes in diabetes. For instance, it was found that the low-carbohydrate diet resulted in significant improvements in serum lipids, glycaemic control and insulin sensitivity.

Dietary carbohydrates

Modifications in the quantity and quality of dietary carbohydrates are central in diabetes care (Evert et al., 2014). Carbohydrate containing foods are important in glucose metabolism, and contribute with vitamins and minerals, antioxidants and dietary fibre. Dietary intake should thus come from healthy sources that are low in fat and added sugar, such as fruit and vegetables, whole grains, whole meal products, and legumes (Evert et al., 2014). Reducing the carbohydrate amount in one or more meals is often necessary to achieve glycaemic control, and a low-carbohydrate diet is considered an option in the short term treatment for weight loss in diabetes. There is however no universal agreement of what amount of carbohydrates that defines a low-carbohydrate diet (Accurso et al., 2008). Throughout this thesis <40% of the total daily energy intake of carbohydrates, is regarded as a low-carbohydrate diet.

The role of different macronutrient compositions in treatment of overweight and obesity, and chronic diseases, such as type 2 diabetes, are a central focus of research (B. J. Brehm & D'Alessio, 2008). A low-carbohydrate diet may especially be of advantage to individuals with type 2 diabetes, as it reduces the glycaemic load and improves insulin sensitivity (Manninen, 2004). When carbohydrates are significantly restricted, a subsequent increase in fat oxidation occurs, and utilisation of ketones becomes the main source of energy for the body (Adam-Perrot, Clifton, & Brouns, 2006). When the glycogen storages in the liver and muscle tissues are depleted, increased fat oxidation in combination with a reduced energy intake, enables weight loss, which furthermore may improve metabolic factors (Manninen, 2004). For instance, a review of randomised controlled trials found that low-carbohydrate diets resulted in improvements in glycaemic control and risk markers for CVD in the short term, just as well as, or better than traditional low-fat diets (Hite, Berkowitz, & Berkowitz, 2011). The energy intake on a low-carbohydrate diet is often reduced, which may be due to the satiating role of elevated protein-intake and/or limited diversity of types of foods (B. J. Brehm & D'Alessio, 2008). It is however unclear whether the health benefits observed on a low-carbohydrate diet is a result of reduced energy intake, or alterations in dietary carbohydrate amount, or a combination of both.

The safety and efficacy of low-carbohydrate diets have been debated in the academic community (B. J. Brehm & D'Alessio, 2008). Some of the concern revolves around the potential adverse effects of increasing the fat and protein content of the diet (Hite et al., 2011). High intake of saturated fat is associated with dyslipidaemia and increased risk of CVD, as well as overweight and obesity (FAO/WHO, 2009). Furthermore, elevations in dietary protein may trigger renal dysfunction and enhance calcium loss (Breslau, Brinkley, Hill, & Pak, 1988;

Wylie-Rosett, 1988). Nevertheless, clinical trials investigating the effect of a low-carbohydrate diet have failed to produce sufficient data to support these concerns.

Previous systematic reviews and meta-analysis

Several attempts have been made to investigate the effect of a carbohydrate restricted diet in diabetes care. Nevertheless, reviews of the literature have yielded inconsistent results. A systematic review by Castañeda-González, Bacardí Gascón and Jiménez Cruz (2011) found that low-carbohydrate diets induced favourable effects on weight and HbA1c in randomised controlled trials (RCTs) lasting 12 weeks and longer. However, the effect was not superior compared to the control diets, and the authors concluded that the overall findings were inconsistent. Even though the review intended to investigate the long term effect of carbohydrate restricted diets, only two of the included studies lasted longer than 12 months. Kodama et al. (2009) found that low-carbohydrate diets improved HbA1c, fasting serum glucose, LDL-cholesterol and total cholesterol equally well as low-fat, high-carbohydrate diets. However, the comparator diets initiated significant adverse effects on fasting insulin, triacylglycerol and HDL-cholesterol, when compared to the low-carbohydrate diets. In this meta-analysis, studies of short duration (12 weeks and less) and with carbohydrate content from 50 E% and less in the low-carbohydrate group, were included. These study characteristics may explain the discrepancies with findings from other meta-analysis.

Kirk et al. (2008) observed significant improvements in HbA1c, fasting serum glucose and triacylglycerol in favour of the low-carbohydrate diet, in the short- and long term management of diabetes. Furthermore, the authors presented results suggesting that triacylglycerol levels would decrease by 23%, when reducing dietary carbohydrates from 65 to 35 % of the total energy intake. Despite this, the results from the review ought to be interpreted with caution, as it included non-randomised trials, was limited to studies conducted in North-America and only incorporated two studies lasting longer than six months. Dyson (2008) published a systematic review of the effect of very-low carbohydrate diets (<50 g) in management of diabetes. The review observed improvements in weight, HbA1c and triacylglycerol, with little or no effect on other serum lipids. The authors concluded that carbohydrate restricted diets could be safe in the short term management. Still, they warned readers to interpret the results with caution, as the review incorporated non-randomised, one arm trials with short intervention time. According to a meta-analysis of Garg (1998), a low-carbohydrate intervention lasting six weeks and less, may induce greater improvements on glycaemia and lipid-profile (including triacylglycerol, total cholesterol and

HDL-cholesterol) in diabetes patients, compared to higher carbohydrate diets. The review is one of few that have assessed the effect of a low-carbohydrate diet on blood pressure in diabetes patients, but the results were stated as inconclusive.

The focus of the master thesis

In summary, previous literature on low-carbohydrate diets have in general included studies with short duration (Garg, 1998; Kodama et al., 2009), non-randomised study design (Dyson, 2008; Kirk et al., 2008), trial participants without type 2 diabetes (Gougeon, Carrington, & Field, 2006), and incorporated diets with a moderate and high carbohydrate content (>40 E%) (Garg, 1998; Kirk et al., 2008; Kodama et al., 2009). The current literature base does suggest that reducing the carbohydrate content of the diet may have favourable effects on weight and risk profile in diabetes. Still, the physiological safety and effectiveness of a low-carbohydrate diet in the long term management of type 2 diabetes has not been established. The majority of research has focused on the short term effect, and has failed to consider compliance to a carbohydrate restricted diet over time. Apart from the review of Garg et al. (Garg, 1998), there is also a lack of research investigating the effect of a carbohydrate reduced diet on blood pressure in type 2 diabetes patients. A number of researchers have reported the need for rigours conduct of systematic reviews to investigate the effect of a low-carbohydrate diet (Castañeda-González et al., 2011; Wheeler et al., 2012). The question that emerges from the current literature base, is thus whether reducing the dietary carbohydrate amount has advantages on the long term management of type 2 diabetes, and if the diet is feasible and safe to adhere to in the long term.

AIMS AND OBJECTIVES

The aim of this master thesis was to conduct a systematic literature review and meta-analysis about the effectiveness of a low-carbohydrate diet on weight management, metabolic control and compliance in adults with type 2 diabetes. The following outcomes were assessed:

- Weight management
- Glycated haemoglobin (HbA1c)
- Serum cholesterol (LDL-cholesterol, HDL-cholesterol and total cholesterol), and serum triacylglycerol
- Blood pressure
- Compliance to dietary intervention

In line with current recommendations HbA1c was used as a marker on glycaemic control in the review. HbA1c represents the percentage of glucose attached to haemoglobin over time, and is considered a more stable measurement of glycaemic control than fasting serum glucose and OGTT (World Health Organization, 2011d). In order to assess compliance to the low-carbohydrate diet, data were extracted on attrition rates, and the actual dietary intake of carbohydrates, compared to the recommended intake.

METHODS AND RESEARCH DESIGN

Systematic reviews and meta-analysis in health care

A systematic review of the literature was performed to assess and evaluate the effect of a low-carbohydrate diet in management of type 2 diabetes. A systematic literature review, also known as evidence summary, uses pre-established criteria to answer a specified research question relevant to health care (Higgins, Green, Wiley, & Cochrane, 2008; Stevens, 2001). What makes a review systematic is the use of explicit eligibility criteria, thorough documentation of search strategy, and critical appraisal of the studies included in the review (Higgins et al., 2008). The aim of systematic reviews is thus to facilitate health care decisions by providing evidence based knowledge for health care practitioners, researchers and consumers, as well as to form the base of clinical recommendations.

Systematic reviews and meta-analysis of randomised controlled trials are considered the gold standard of evidence (Chalmers I, 2002). What underpins their methodology is that synthesis of results from several trials obtains more power than results from a single trial (Higgins et al., 2008). A meta-analysis is accordingly a systematic review that applies statistical methods to analyse and sum up the effect estimates of interventions across trials. Conduction of meta-analysis depends on the type of data material retrieved, the heterogeneity across studies and factors related to the internal validity of studies. A meta-analysis may for instance show deceptive results if the validity of studies are low (Higgins et al., 2008). In many reviews a narrative approach to sum up the effect of interventions are therefore more feasible, as not all types of data material can be nor should be, summarised by statistical methods.

In recent years, granting agencies often require results from systematic reviews to support new research, as well as international organisations and health authorities implement reviews prior to publication of recommendations. For example, the approval of HbA1c as a marker in diagnosis of diabetes (World Health Organization, 2011d) was based on findings from a systematic literature review sponsored by the WHO (World Health Organization,

2011c). Furthermore, the elaboration of the Nordic Nutrition Recommendations (NNR 5) included conduct of systematic reviews on iodine intake in human nutrition, as well as on dietary composition and weight management (Fogelholm, Anderssen, Gunnarsdottir, & Lahti-Koski, 2012; Gunnarsdottir & Dahl, 2012). However, as with any research, the quality of systematic reviews varies. All from the applicability and relevance of the research question till the methods used in synthesising data may introduce bias in the research process. Cochrane Collaboration with others, strongly recommend that review authors work from a registered protocol to reduce the chance of publication bias (D. Moher, Liberati, Tetzlaff, & Altman, 2009). However, with the exception of Cochrane reviews, only 10% of systematic reviews appear to have a protocol (David Moher, Tetzlaff, Tricco, Sampson, & Altman, 2007). This makes assessment of the planned conduct of a review, compared to the actual conduct, difficult and underpins the importance of registering reviews.

Methodological tools

With the increasing popularity and acknowledgement of systematic reviews, several methodological tools have been developed to assist researchers in its conduct (American Dietetic Association, 2008; Glasziou, 2001; Higgins et al., 2008; D. Moher et al., 2009). The Cochrane Collaboration is thus considered to be the leading organization within the field. They work prospectively to improve the evidence base for health care decisions, as well as elaborating methods used in systematic reviews (David Moher et al., 2007). The organisation consists of more than 15.000 contributors, allocated in over 100 countries and the underpinning of their work is to synthesis up-to date evidence of interventions to enable prevention and management of relevant health problems. Evidence based practise and evidence based nutrition should thus stem from and incorporate empirical evidence from systematic reviews.

In line with this, the literature review in this master thesis was written in conjunction with Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (Higgins et al., 2008) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis: The PRISMA Statement (D. Moher et al., 2009). Additionally, the review was written in conjunction with author guidelines for Diabetologia, where the aim is to get it published.

Following is a description of the Cochrane Handbook and the PRISMA Statement and an elaboration of each step in the research process.

Cochrane Handbook for Systematic Reviews of Interventions

Cochrane handbook is a methodological tool developed by the Cochrane Collaboration to assist review authors maintain, update and prepare Cochrane reviews of intervention studies. The Cochrane Collaboration aim to facilitate a rigorous evidence base for health care decisions and their concept is widely adopted in the international scientific society (Higgins et al., 2008; David Moher et al., 2007).

The handbook is also applicable in conduction of reviews that are not aimed at being published in the Cochrane library, and for reviews of observation and diagnostic studies.

The Cochrane Handbook provides up-to-date evidence supported guidance, on how to conduct systematic-reviews and meta-analysis in health care. Their methods are considered the gold standard in evidence summary, and were for that reason chosen as a tool in the conduct of the systematic review in this master thesis.

The handbook is made of three parts, each with several chapters. Part 1 elaborates the methodology and overall features of Cochrane reviews. Part 2 describes the methods applied in Cochrane reviews and meta-analyses, which includes everything from how to develop a research question by using the PICO-format, to how to sum up the results and write the final conclusion. Part three of the handbook is devoted to special topics, such as how to conduct a review on data material from non-randomised controlled trials.

The Cochrane handbook was utilised throughout the research process of this master thesis, and was referred to when facing methodological challenges in regard to the conduct and reporting of the review.

The PRISMA Statement

The Preferred Reporting Items for Systematic reviews and Meta-Analysis: The PRISMA Statement (D. Moher et al., 2009) is a tool developed to assists review authors in improving the reporting of systematic reviews and meta-analysis. The PRISMA Statement is an update of the Quality Of Reporting Of Meta-analyses (QUOROM Statement (David Moher et al., 1999)) and was elaborated by an international group of clinicians, systematic review authors, methodologists and a consumer in 2005 (D. Moher et al., 2009). The statement consists of a 27-item checklist and study eligibility flow diagram for review authors to take into consideration when conducting systematic reviews and meta-analysis. It may also be utilised as a critical appraisal tool for readers of systematic reviews.

The PRISMA statement is endorsed by the Cochrane Collaboration and inclusion of the flow-diagram and consultancy of the 27 item checklist is a prerequisite for Cochrane

reviews (Higgins et al., 2008). The Explanation and Elaboration paper of the PRISMA guidelines, which provides an extensive explanation of the evidence base for each checklist item, was also utilised to help assist the conduct of the systematic review in this master thesis (Liberati et al., 2009). As required by the Journal of the European Association of the Study of Diabetes (EASD), Diabetologia, this review has acknowledged the 27-item checklist and incorporated a flow-diagram of the study eligibility process as indicated in the PRISMA-Statement (D. Moher et al., 2009).

The "review cycle"

The main steps of the systematic literature review are captured in figure 1. Following is a description of the conduct of the review with an emphasis on the PICO-format, PROSPERO-registration, search strategy and assessment of risk of bias.
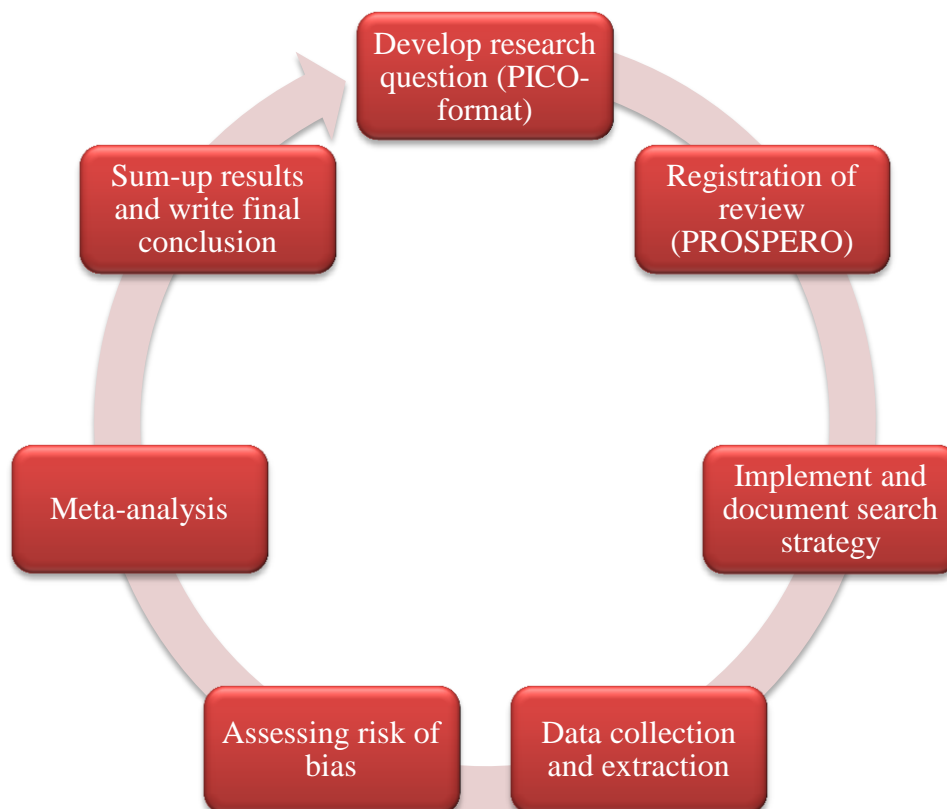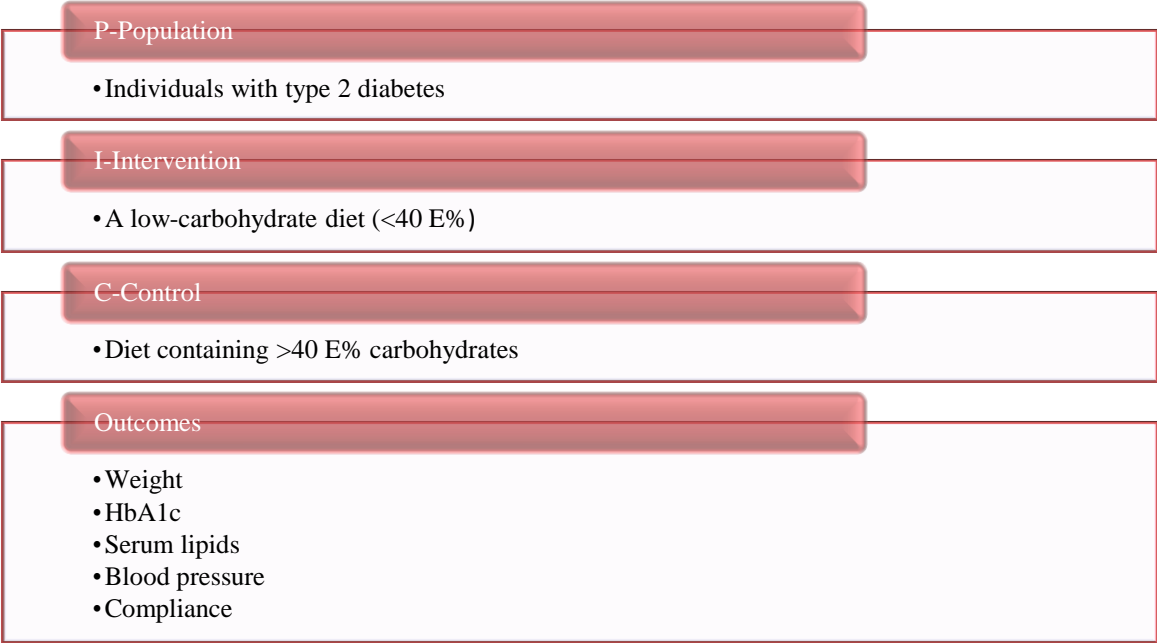

Figure 1 The main steps of the review process

PICO-Format and eligibility criteria

The first step in the research process was to develop a specified research question in a defined area relevant for clinical practise. The rationale for investigating dietary intervention in type 2

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diabetes has already been elaborated in the background of this master thesis. The research question was thus developed using the PICO-format, which is captured in figure 2.

P-Population
• Individuals with type 2 diabetes

I-Intervention
• A low-carbohydrate diet (<40 E%)

C-Control
• Diet containing >40 E% carbohydrates

Outcomes
• Weight
• HbA1c
• Serum lipids
• Blood pressure
• Compliance

Figure 2 Research question developed using the Pico-format

Each letter in the PICO-format considers the population of interest (P), definition of the intervention and control (I-C), and the outcomes that are to be assessed (O). In the following review the population of interest were adult individuals 18 years of age or older, with established type 2 diabetes; intervention was a low-carbohydrate diet (<40 E% of carbohydrates); control was a diet containing >40 E% carbohydrate and outcomes were weight management, glycaemic control, serum lipids, blood pressure and compliance.

Figure 3 shows the specific eligibility criteria that were set in regard to features related to study design, duration of interventions, language and year of publication. For example, HbA1c was used as an outcome measure on glycaemic control in the review. Therefore, a minimum of three months study duration was put as inclusion criteria. Furthermore, only randomised controlled trials were included, as this study design provides the strongest evidence for health care interventions (Kunz, Vist, & Oxman, 2007). In order to assess the effect of a low-carbohydrate diet as a single factor in management of type 2 diabetes, studies that implemented parallel interventions, such as proactive physical activity advice and use of pharmacological substances, were excluded.

Inclusion criteria

- Randomised controlled trials
- Duration >3 months
- Adult study population, 18 years and older
- Inpatient/outpatient with established type 2 diabetes
- Published: January 1983 – September 2013
- Language: English, Danish, Norwegian, Swedish

Exclusion criteria

- Non-randomised study design
- Systematic reviews/meta-analysis
- Duration <3 months
- Study population <18 years of age
- Published prior to January 1983
- Language other than English, Danish, Norwegian, Swedish
- Dietary intervention with meal replacements/enteral feeding etc.
- Implementation of other interventions in addition to dietary intervention that may infer with observed effect

Figure 3 Eligibility criteria for the inclusion and exclusion of studies

PROSPERO

The review was registered at PROSPERO prior to the literature search (registration number: CRD42013005825). PROSPERO is an international database of prospectively registered systematic reviews in health and social care, provided by the department Centre for Reviews and Dissemination (CRD) at University of York. The aim of registering a systematic review at PROSPERO is thus to avoid duplicates of systematic reviews and meta-analysis, and to reduce publication bias by working prospectively from a registration form.

The systematic literature review in this master thesis was accepted and registered at PROSPERO the 14. October, 2013. The registration contained detailed information about the planned conduct of the review. Several criteria had to be accounted for, including a complete description of the review authors; full name and title, affiliations, web-sites and funding; databases to be searched, rationale of the review and so forth. The elaboration of the registration at PROSPERO was an in-depth and systematic process that required pre-research.

For example, which approach to use in data synthesis had to be accounted for (quantitative or narrative (descriptive)). If a quantitative approach was planned, elaboration of the analytical methods was desired.

PROSPERO accepts retrospective changes to a review, and request updates on the procedures of the research process. However, explanatory justifications must be provided. Changes to the original protocol of the conduct of the systematic review in this master thesis were registered and accepted by PROSPERO, and updated at the CRD-website throughout the research process:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005825

Search strategy

The purpose of providing a detailed description of the search strategy used in a systematic review is to ensure reproducibility, and to enable readers to assess the validity of the search (Liberati et al., 2009). Therefore, a thorough documentation of the search process used in the systematic review in this master thesis was implemented. Prospectively, this included information about the search strategy; which databases to use in the literature search, the planned Medical Subject Headings (MeSH) and search terms, and eligibility criteria restrictions, such as language and year of publication. Additionally, retrospective information was provided about other sources of literature retrieval, date of the literature searches, total number of studies found, retrieved, excluded, included with reasons why, and number of studies read by title and abstract or full-text. A meeting was arranged with a librarian at Oslo and Akershus University College of Applied Sciences to help assist with MeSH and search terms, as well as training in database searching. The databases utilised in the literature search were:

- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL
- Food Science Source
- SweMed+

A combination of MeSH and search terms were used in the literature search:

- For diet intervention: Diet, carbohydrate-restricted (MeSH) OR Low carbohydrate diet OR Dietary carbohydrates OR Ketogenic diet (MeSH) OR Atkins diet OR Diabetic diet (MeSH)

- For Type 2 diabetes: Diabetes mellitus, type 2 (MeSH) OR Type 2 diabetes OR Diabetes OR Non-insulin dependent diabetes mellitus

The literature search was conducted between September and November, 2013. The total number of studies identified through database searching and cross-reference list citation search was 1180. Eighteen of the studies met inclusion criteria and were included in the review. Explanatory reasons for exclusion are provided in the review article.

The Cochrane Collaboration and The PRISMA Statement advice that authors of systematic reviews provide a detailed description of at least one complete database search (Higgins et al., 2008; Liberati et al., 2009). Figure 4 shows the search strategy used to retrieve literature from the database EMBASE the 9th of October 2013. A combination of MeSH and key words were used. Of the literature screened, one article from this search was included in the systematic review (Goldstein et al., 2011).

Search strategy: EMBASE 9.10.2013

1 [Diabetes Mellitus, Type 2/dh, pc, th [Diet Therapy, Prevention & Control, Therapy]] (0)

2 Diet, Carbohydrate-Restricted/ (1395)

3 low carbohydrate diet.mp. (1943)

4 2 or 3 (1943)

5 1 and 4 (0)

6 Diabetes Mellitus, Type 2/ (133311)

7 4 and 6 (277)

8 limit 7 to randomized controlled trial (33)

9 limit 7 to systematic reviews [Limit not valid in Embase; records were retained] (277)

10 from 8 keep 4-6,8-10,12,14-15,17-23 (16)

11 10 not 8 (0)

12 8 or 10 (33)

13 non insulin dependent diabetes mellitus/ (133311)

14 4 and 13 (277)

15 limit 14 to randomized controlled trial (33)

Figure 4 The full search strategy utilised in the database EMBASE

Assessing risk of bias

The studies included in the review were assessed for bias using the Cochrane Handbook chapter 8 (assessing risk of bias in included studies) (Higgins et al., 2008), and a computer software by the Cochrane Collaboration: Review Manager (RevMan) version 5.2. (Review Manager (RevMan), 2012).

When assessing risk of bias in randomised controlled trials, a thorough evaluation of the internal validity of studies is performed, to consider the chance of underestimation or overestimation of intervention effects (Higgins et al., 2008). This is not an evaluation of the methodological quality of studies (whether they are of the best possible standard), but rather a critical appraisal of their appropriateness and implementation. Hence, is the observed effect estimates due to the interventions, or is it due to study bias (systematic error), and if so; how far do the results deviate from the truth. When considering bias one also assesses the homogeneity/heterogeneity of the results of studies included in the review (Higgins et al., 2008). Heterogeneous results may be present despite studies having high validity. However, if much variation across studies is present and the assessment of risk of bias suggests that difference in internal validity may be the reason behind the observed effect, then the conclusion of the systematic review is not as strong.

To assess risk of bias in randomised controlled trials, Cochrane collaboration suggests that the following six domains are considered (Higgins et al., 2008):

- Sequence generation
- Allocation concealment
- Blinding of participants, personnel, and outcome assessors
- Incomplete outcome data
- Selective outcome reporting
- Other potential threats to validity

Each of the domains in the assessment tool consists of several question criteria to assist researchers in judging risk of bias (Higgins et al., 2008). The questions may be answered with yes (low-risk), no (high-risk), or unclear (insufficient information provided). An explanatory description by the researchers is thus necessary for each domain to clarify sufficiently the reason or reasons behind the judgement. For example, the study of Facchini and Saylor (2003) was thoroughly assessed to answer each of the domains, and overall rated to have low/unclear-risk. For instance, the study was assessed to have "unclear risk" in

regards to selection bias, due to lack of information about the proceedings used when allocating study participants to intervention or comparator group. Furthermore, the study authors provided insufficient information about whether study personnel and/or participants were blinded of the outcome assessment after randomisation. Blinding of participants in randomised controlled trials incorporating dietary interventions are difficult and sometimes impossible to achieve (Higgins et al., 2008). Therefore, it was decided in consensus that lack of blinding of participants per se, would not be likely to affect the outcome measures (low-risk). However, in the study of Facchini and Saylor (2003), no information was provided about blinding of study personnel and the study was therefor considered to have "unclear risk".

In RevMan, a graph and summary figure were created after having assessed the risk of bias in the studies included in the review. The risk of bias graph, which was incorporated in the systematic review, shows the overall risk of bias in the studies included in the review. The risk of bias summary as shown in figure 5 shows the risk of bias in each single study included in the review.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brinkworth 2004	+	?	?	?	+	+	–
Daly 2006	+	?	–	?	?	–	–
Davis 2009	+	?	?	?	+	+	?
Elhayany 2010	?	?	?	?	+	–	+
Facchini 2003	?	+	?	?	+	+	?
Garg 1994	+	?	?	?	?	–	–
Goldstein 2011	?	?	+	?	+	?	+
Guldbrand 2012	+	?	?	?	+	+	?
Jönsson 2009	–	–	–	–	+	+	–
Krebs 2012	+	?	+	+	–	+	?
Larsen 2011	+	?	?	+	+	+	–
McLaughlin 2007	?	?	?	?	+	+	?
Samaha 2003	+	?	–	–	+	+	–
Shai 2008	+	?	+	+	+	–	–
Walker 1995	?	?	?	?	?	+	?
Walker 1999	?	?	?	?	–	–	?
Westman 2008	+	?	–	–	?	+	?
Wolever 2008	+	+	?	?	+	+	–

Figure 5 Risk of bias summary of the studies included in the review. Studies were rated as low risk of bias (green), uncertain risk of bias (yellow) or high risk of bias (red)

DISCUSSION

Further discussion of results

The aim of this master thesis was to conduct a systematic literature review and meta-analysis about the effectiveness of a low-carbohydrate diet on weight management, metabolic control and compliance in adults with type 2 diabetes. The results from the review indicate that a low-carbohydrate diet may improve weight, Hba1c and certain cardiovascular risk factors, in the short and long term management of type 2 diabetes. However, when compared to a higher-carbohydrate diet, the low-carbohydrate diet did not appear to be superior.

Significant improvements in weight, HbA1c, HDL-cholesterol and triacylglycerol were frequently observed on the low-carbohydrate diet. When compared to the control diets however, only three studies favored the low-carbohydrate diet on weight (Daly et al., 2006; Jönsson et al., 2009; Westman, Yancy, Mavropoulos, Marquart, & McDuffie, 2008), three on HbA1c (Elhayany, Lustman, Abel, Attal-Singer, & Vinker, 2010; Jönsson et al., 2009; Westman et al., 2008), four on HDL-cholesterol (Davis et al., 2009; Elhayany et al., 2010; Jönsson et al., 2009; Westman et al., 2008) and two on triacylglycerol (Elhayany et al., 2010; Jönsson et al., 2009). As mentioned in the discussion of the literature review, the short term improvements in weight in favor of the low-carbohydrate diets, and the significant improvements in HDL-cholesterol and triacylglycerol within the low-carbohydrate diets, are consistent with previous literature in diabetes patients (Castañeda-González et al., 2011; Dyson, 2008; Wheeler et al., 2012). This indicates that even though a low-carbohydrate diet may not be superior to a higher carbohydrate diet, it may be equally good to improve weight and metabolic risk factors in the management of type 2 diabetes.

As with LDL-cholesterol and total cholesterol, the low-carbohydrate diet initiated few significant findings on blood pressure within and between groups. These results support those of Garg (1998) who in a systematic review found inconsistent results on blood pressure, with high-monounsaturated, low-carbohydrate diets. However, a newly published meta-analysis of high-protein diets (some of which were low in carbohydrates) experienced significant reductions in systolic- and diastolic blood pressure in type 2 diabetes patients (Dong, Zhang, Wang, & Qin, 2013). However, the pooled-analysis in the latter review incorporated trials with short duration and low study quality, whereof only two trials contained <40 E% from carbohydrates. Our extensive literature search did not identify more RCTs investigating the effect of a low-carbohydrate diet on blood pressure in type 2 diabetes patients, which suggests an abundant room in the literature for further progress on this topic.

The quantity and quality of dietary macronutrients in the studies included in the review varied substantially. Of the studies that found significant improvements in outcomes in favour of the low-carbohydrate intervention, carbohydrate intake ranged from 13-43 E%, fat intake from 28-59 E% and protein intake from 19-28 E% (Brinkworth, Noakes, Parker, Foster, & Clifton, 2004; Daly et al., 2006; Elhayany et al., 2010; Jönsson et al., 2009; Westman et al., 2008; Wolever et al., 2008). These interventions were compared to low-fat diets (Daly et al., 2006; Davis et al., 2009), low-GI diets (Westman et al., 2008; Wolever et al., 2008), a low-protein diet (Brinkworth et al., 2004), a high-glycaemic index diet (high-GI) (Wolever et al., 2008), a Mediterranean diet (Elhayany et al., 2010) and standard diabetes care (Elhayany et al., 2010; Jönsson et al., 2009). It is interesting to note that in five out of seven of these low-carbohydrate interventions, dietary intake of fat was high (39-59 E%) (Daly et al., 2006; Davis et al., 2009; Jönsson et al., 2009; Westman et al., 2008; Wolever et al., 2008). Hence, the majority of studies with significant improvements in outcomes in favour of the low-carbohydrate diet, were low in carbohydrates and high in fat. In contrast, the quality of fat consumed in these trials differed substantially, as saturated fat intake ranged from 8-28 E%, mono-unsaturated from 12-40 E% and poly-unsaturated from 5-17 E%. As mentioned in the background if this thesis, one of the concerns of a low-carbohydrate diet is the possible effect of a high fat intake on especially LDL-cholesterol. However, none of the studies included in the systematic review reported significant adverse effects on LDL-cholesterol with low-carbohydrate, high-fat diets. A possible explanation of this may be because the relative increase in fat intake in these studies appeared to be attributed by monounsaturated fat, and not saturated fat.

Unfortunately, the systematic review in this master thesis has been unable to demonstrate if compliance to a low-carbohydrate diet is achievable in the long term. Overall, the results indicate that compliance to a very low-carbohydrate diet is difficult to achieve in the short and long term. To exemplify this, eight out of ten trials that experienced non-compliance to the interventions (defined by a deviation of >5 E% in carbohydrate intake from that prescribed) were very low-carbohydrate diets, with an intervention aiming for 5 to 22 E% from carbohydrates (Daly et al., 2006; Davis et al., 2009; Goldstein et al., 2011; Guldbrand et al., 2012; Iqbal et al., 2010; Samaha et al., 2003; Shai et al., 2008; Westman et al., 2008). The six interventions that found compliance to dietary intake, were prescribed a higher amount of carbohydrates that ranged from 32-40 E% (Brinkworth et al., 2004; Jönsson et al., 2009; Larsen, Mann, Maclean, & Shaw, 2011; McLaughlin et al., 2007; Walker, O'Dea, & Nicholson, 1999; Walker, O'Dea, Nicholson, & Muir, 1995). However, the actual intake of

carbohydrates among the majority of the compliers were still over 40 E%, which is not regarded as low-carbohydrate in the definition applied in this master thesis. Overall, this indicates that compliance to a low-carbohydrate diet, and especially a very-low carbohydrate diet, is difficult to achieve. Nevertheless, the results from the review are inconclusive, and as compliance to dietary advice is crucial to achieve treatment goals, further research should investigate strategies that can enable individuals with type 2 diabetes to improve their diet in the long term.

Methodological considerations

There are several limitations to this master thesis. It is for instance important to note that a meta-analysis was planned, but not conducted, due to heterogeneity in the studies included in the review. A narrative description of the data material was therefore carried out, as a meta-analysis would have increased the risk of overestimation or underestimation of study effects (Higgins et al., 2008). The heterogeneity across studies emerged from discrepancy in the reporting of results, and from low validity within studies. Both of which made it difficult to synthesise and assess the data. For instance, the majority of trials omitted to report confidence intervals, standard deviations and standard errors, which ultimately are necessary measurements to include in the conduct of a meta-analysis. Additionally, the study level quality assessment indicated high risk of bias in the included trials, which have implications for the generalizability of the findings. A notable example is that one trial excluded participants that not adhered to the dietary intervention (Walker et al., 1999). Thus, only participants that were able to follow the dietary regime were included in the final analysis. At review level, no criteria were set in regards to fat and protein content in the intervention and control diets. As mentioned earlier, both the quantity and quality of fat and protein differed between studies. It is therefore important to acknowledge the potential of confounding in study effects, as a result of variability in macronutrient content.

A major strength of this master thesis is that a standardised and systematic method was applied to answer the research question. Systematic reviews and meta-analysis of randomised controlled trials are considered the gold standard of evidence to form the base of clinical recommendations and health care decisions (Higgins et al., 2008). In accordance with the methodology of systematic reviews, and with the aim of providing rigorous knowledge for evidence based health care, a series of steps were implemented to ensure transparency and reproducibility of the research process. For instance, a registration of the review with explicit eligibility criteria was registered at PROSPERO prior to conducting an extensive literature

search. Though the majority of research was performed independently by the student of this master thesis, certain aspects of the review were implemented in unity and consensus with the main supervisor to concur with guidelines as recommended by Cochrane Handbook (Higgins et al., 2008). The quality of studies, data assessment and data extraction, was therefore conducted independently by the student and the main supervisor. This was done in order to minimize researcher bias, and to provide reliable and accurate evidence of the intervention effects. Finally, to investigate the effect of a low-carbohydrate diet as a single factor on type 2 diabetes management, trials with simultaneous lifestyle interventions, such as physical activity, were not considered for inclusion in the review.

The evaluation of dietary therapy by systematic reviews and meta-analyses

Even though systematic reviews and meta-analysis are the gold standard for evaluating medical treatments, it may be questioned if this is the ultimate method to evaluate dietary interventions. Firstly, as demonstrated in this review dietary treatment is difficult to standardise, especially in the long term (>6 months). Controlled feeding trials where all foods are provided and quantified are almost impossible to conduct for more than a week or two, and even if the dietary intake is standardised, it is difficult to separate one dietary intervention from another. For instance, if you change the carbohydrate content of the diet, you will automatically also change the energy content or the macronutrient balance, or both. Thus, it is difficult to identify what part of dietary interventions that cause the effects observed.

Secondly, in contrast to drug therapy, dietary interventions are to a greater extent dependent on compliance to the "prescribed" diet. To exemplify this, feeding trials and short-term proof-of-concept studies can demonstrate impressive effects. However, this evidence may not be applicable for individuals with chronic diseases such as type 2 diabetes, if the diet is impossible to follow over time. The role of compliance is essential in dietary treatment of type 2 diabetes, and that is why we incorporated and emphasized compliance to the low-carbohydrate diet as an outcome in this review.

Thirdly, although rigours conduct of RCTs is implemented there are some obvious features inherent in dietary interventions that make the evidence base for dietary treatments weak:

1) It is impossible to blind patients to the dietary intervention, which may bias the results.
2) It is notoriously difficult to measure what people eat and drink, thus it is difficult to control for possible confounders.

3) Whenever there is a change in body weight, the effect of the weight change will always confound the results of the change in dietary composition

In dietary recommendations for patient groups, as well as for the general population, there is a trend towards focusing on dietary patterns and different food groups, rather than the macronutrient composition of the diet. This has emerged from the recognition of that the effect of macronutrients can vary immensely. It depends on the subclass the macronutrient belongs to, in which foods they are eaten and in which context (meal, preparation) it is eaten; i.e. the glycaemic effect of 50 g of carbohydrates obtained from a sugar-sweetened drink would differ enormously from the same amount of carbohydrates eaten as raw carrots. Hence, the physiological effect of a low-carbohydrate diet is dependent on the carbohydrate sources that remain in the diet, and which foods the carbohydrate-rich foods are substituted with. The same aspects apply to the comparator diets, and this may explain the heterogeneity observed in the different outcomes investigated in this systematic review.

Despite the mentioned limitations accompanying systematic reviews and meta-analysis of dietary interventions, it is important to utilise this methodology as it provides the best evidence for elaboration of dietary recommendations. Rigorous conduct of systematic reviews may also identify knowledge gaps that can guide future research in the field. It is however important to note that dietary recommendations are not exclusively based on scientific evidence, but also on patients' and health professional's experiences, values and thoughts. Hence, a patient-centred approach to dietary treatment, which incorporates evidence from systematic reviews, as well as consensus statements from health care professionals, may form the ultimate base for dietary recommendations.

CONCLUSION AND FUTURE PERSPECTIVES

The findings from this master thesis support previous literature showing that low-carbohydrate diets may improve weight, HbA1c, and cardiovascular risk factors in the short and long term management of type 2 diabetes. Still, when compared to control diets with a higher content of carbohydrates, the low-carbohydrate diet was not superior. The review contributes additional evidence on the implications of following a low-carbohydrate diet over time, as the majority of studies found poor compliance to the interventions, especially with the very low-carbohydrate diets. However, the generalizability of these results is subject to certain limitations, as the quality of studies included in the review was unsatisfactory, and because the intervention and control diets differed vastly in macronutrient content and quality. As demonstrated in this thesis, a reduction in carbohydrate intake increases the dietary content

of protein and/or fats. Further research needs to be done to establish the long term effect of a low-carbohydrate diet with different quantity and quality of protein and fat. Although this review set out to investigate the effect of a low-carbohydrate diet on blood pressure, the findings were inconclusive and conduct of large randomised controlled trials could provide more definitive evidence on this matter. Finally, it is important to acknowledge the importance of a patient-centred approach in dietary treatment of type 2 diabetes. A key public health priority should therefore be to investigate dietary approaches and macronutrient compositions that are 1) palatable, satiating and nutrient dense 2) that facilitates long term compliance, so that prevention and control of complications are enabled in the long term treatment of type 2 diabetes.

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ARTICLE

A low-carbohydrate diet for management of type 2 diabetes – a systematic review and meta-analysis

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Authors: Henny-Kristine Haugen

Henny-Kristine Haugen **(corresponding author)**

Student, Master of Public Health Nutrition

Faculty of Health Sciences

Department of Health, Nutrition and Management

Oslo and Akershus University college of Applied Sciences

Norway

Ph +47 41455996

E-mail: s185370@stud.hioa.no

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ABSTRACT

Aims/hypothesis Recently it has been acknowledged that a range of dietary compositions, including low carbohydrate diets (LCD), may be effective in the short term management of type 2 diabetes. The following review aims to investigate the effectiveness of a LCD on weight management, metabolic control and compliance in adults with type 2 diabetes.

Methods A systematic search of the literature was conducted to identify randomised control trials investigating the effect of a LCD (40% and less of energy from carbohydrates) compared to a higher carbohydrate diet (>40% of energy from carbohydrates), in management of type 2 diabetes. The databases searched were MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source and SweMed+.

Results Eighteen studies, totalling 1832 participants were included in the review. Improvements in weight, HbA1c, HDL-cholesterol and triacylglycerol were frequently observed on the LCD, but only three studies found greater effect on weight and HbA1c, two on LDL-cholesterol and triacylglycerol, four on HDL-cholesterol, and one on blood pressure with the LCD. Attrition was considerably higher on the LCD, and compliance to the very low-carbohydrate diet (VLCD) was overall poor.

Conclusions/interpretations The results from this review indicate that a LCD may be an option in the short and long term management of type 2 diabetes, but that it is not superior to a higher carbohydrate diet. Compliance to a LCD and VLCD may be difficult to achieve over time, and a patient centred approach, where dietary advice is adjusted to individual preferences and metabolic needs, are necessary in dietary treatment of type 2 diabetes.

Keywords Blood Pressure; Cholesterol, HDL; Cholesterol, LDL; Compliance; Diabetes Mellitus, Type 2; Diet, low carbohydrate; Hemoglobin A, Glycosylated; Review; Triglycerides; Weight

Abbreviations CVD, cardiovascular disease; DBP, diastolic blood pressure; LCD, low-carbohydrate diet; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerol; VLCD, very low-carbohydrate diet

A low-carbohydrate diet for management of type 2 diabetes – a systematic review and meta-analysis

INTRODUCTION

Lifestyle approaches, such as diet and physical activity, are cornerstones in the prevention and management of type 2 diabetes [1]. More than 80% of all patients with type 2 diabetes are overweight or obese [2, 3], and weight control supported by a healthy diet and physical activity are essential components in diabetes care [4]. Increased adiposity affects the metabolic system as it induces insulin resistance, resulting in elevated serum glucose [5]. Over time, hyperglycaemia is a risk factor for complications occurring in blood vessels and nerves [6]. Therefore, current lifestyle interventions and public health initiatives are attempting to control hyperglycaemia through weight control and promotion of healthy lifestyle behaviours [7].

Cardiovascular disease (CVD) is the leading cause of death among patients with diabetes [8]. The prevalence of risk factors for CVD, such as dyslipidaemia and hypertension are high among the patient group, and may also contribute to microvascular diseases such as retinopathy, nephropathy and neuropathy [9, 10]. As established in the United Kingdom Prospective Diabetes study (UKPDS), glycaemic control reduces the risk of microvascular complications [6]. As a result, this has been the key focus of diabetes care. However, serum lipids and BP may be of greater importance in CVD-risk reduction, and it is recommended that these metabolic factors are integral components in diabetes care [11, 12].

Intensive lifestyle interventions that incorporate dietary advice can improve glycaemia, BP and lipid profile in individuals with type 2 diabetes [13]. Furthermore, dietary interventions may be equally, or more effective than medical treatment in achieving metabolic control [14]. Facilitating individuals to improve dietary habits is nevertheless a public health challenge [15]. Despite populations generally displaying a positive attitude towards the advantages of

healthy eating, actually improving dietary behaviour still remains a challenge [15]. Among individuals with lifestyle related chronic diseases, such as type 2 diabetes, compliance to lifestyle changes are generally poor [16]. Low compliance to dietary advice makes it more difficult to achieve treatment goals and prevent acute and long-term complications. Thus, effective dietary interventions that can help individuals with diabetes to improve dietary habits are needed.

Dietary guidance is a standard component in the management of type 2 diabetes [17]. Up-to-date evidence-based recommendations suggest that nutritional care should be patient-centred in order to facilitate a healthy diet and maximise quality of life [17-19]. Traditionally, international organizations have recommended a low-fat calorie restricted diet with a carbohydrate content ranging from 45 to 60% of the total energy intake [20-23]. However, recently it has been acknowledged that a range of dietary compositions, including low carbohydrate diets (LCD), may be effective in the short term management of type 2 diabetes [19, 24, 25]. Especially has a LCD been observed as a beneficial approach to achieve weight loss in the short term.

The ADA recommends that dietary carbohydrate intake is not limited below 130 grams per day, as carbohydrate rich foods are an important source of energy for the brain and central nervous system [18]. Additionally, carbohydrate rich foods are an important source of water-soluble vitamins, minerals, as well as to dietary fibre. However, studies conducted in both diabetic and non-diabetic subjects suggest that a diet containing less than 40% of the total energy from carbohydrates, may be superior compared to a high carbohydrate diet in short and long term weight management [26, 27], as well as in long term improvements in HDL-cholesterol, triacylglycerol (TG) and diastolic blood pressure (DBP) [27].

When dietary carbohydrates are significantly restricted, the body largely relies on fatty acids for its energy consumption [28]. As the glycogen-depot in the liver and muscle tissues are depleted, fat oxidation accelerates and ketone bodies become an important source of energy for the body [29]. Oxidation of ketones is thus an energy consuming process that requires more energy, than metabolism of carbohydrates do. Ectopic fat deposited in liver and muscle, induces insulin resistance, and depletion of these energy storages on energy-reduced diets, may increase insulin sensitivity. Furthermore, reduced dietary glycaemic load from LCD, will initiate favourable effects on glycaemic control, insulin demand as well as HDL-cholesterol and TG [29]. With the simultaneous mobilisation of fatty acids, loss of adipose tissue with subsequent weight reduction may occur [25].

On a LCD the selection of food choices are often limited [30], as energy dense foods that may be high in both carbohydrates and fat, such as bread, pasta, rice, cakes, biscuits, crisps and sweets are avoided . Furthermore, the intake of dietary proteins may be elevated, and a high protein intake is recognised to increase satiety [31, 32]. Reducing the intake of energy dense foods [10] and increasing the intake of dietary proteins, are both factors known to facilitate weight reduction [33]. However, whether the favourable effects observed on LCD are due to limited energy consumption per se, or the restricted carbohydrate content, or both, is unknown.

Controversy still remains about the safety and efficacy of a LCD as an independent factor in diabetes management [24]. The main concerns are that a potential increase in saturated fat and protein consumption may result in negative health outcomes in the long term [33]. Saturated fat is associated with increased risk of CVD, overweight and obesity [34], and an increase in protein consumption may initiate renal dysfunction [35]. However, results from clinical trials have been inconclusive [36], and the long-term effect of a LCD diet in type 2 diabetes, is still unclear [24].

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Many individuals with diabetes experience reduced quality of life due to acute and long term complications [37]. It is therefore important that further investigations look to identify a diet that is palatable and facilitates healthy dietary behaviour in the long term management of type 2 diabetes. Previous reviews and meta-analyses investigating the effect of LCD in type 2 diabetes management, have generally included studies with heterogeneous design [38, 39], short duration [40, 41], moderate to high carbohydrate intakes [38, 40, 42], non-diabetic study samples [42], and been limited to studies completed in North-America [38]. Therefore, the following review aims to investigate the effectiveness of a LCD on weight management, metabolic control and compliance in adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The following review was conducted in conjunction with Cochrane Handbook for Systematic Reviews of Interventions [43] and the Preferred Reporting Items for Systematic reviews and Meta-Analysis: The PRISMA Statement [44]. A full record of the conduct of the systematic review was registered at PROSPERO prior to the literature search, and is available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005825

Search strategy for identification of studies

A variety of definitions of a LCD persists [24, 45, 46]. In this paper it was defined as a diet containing 40 energy per cent (E%) and less, from carbohydrates. A search strategy was developed to identify studies investigating the effect of a LCD in management of type 2 diabetes. The literature search was conducted between September and November 2013. The databases searched were MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Food Science Source and SweMed+. The following Medical Subject Headings (MeSH) and search terms were used:

- For diet intervention: Diet, carbohydrate-restricted (MeSH) OR Low carbohydrate diet OR Dietary carbohydrates OR Ketogenic diet (MeSH) OR Atkins diet OR Diabetic diet (MeSH)

- For Type 2 diabetes: Diabetes mellitus, type 2 (MeSH) OR Type 2 diabetes OR Diabetes OR Non-insulin dependent diabetes mellitus

All randomised controlled trials published between 1983 and November 2013 in English, Danish, Norwegian or Swedish, with at least one search term from each category were considered for inclusion in the review. Cross-matching reference lists were conducted to identify additional studies.

Study selection

The study selection process is captured in figure 1. Studies that addressed one or more of the study factors, lasting three months or longer, were included in the review. Inclusion criteria included adult subjects above 18 years of age, with diagnosed type 2 diabetes. Intervention diets were to contain maximum 40% of the energy intake from carbohydrates, and the comparator diet more than 40%. The majority of studies reported recommended macronutrient intake using E%. In order to ensure consistency, studies providing carbohydrate amount in grams (g) were calculated into E%. Co-morbidities such as nephropathy, CVD and depression were accepted. Studies that included individuals with impaired glucose tolerance and/or type 1 diabetes were not considered for inclusion, unless sub-group analyses of type 2 diabetes patients were provided.

Data extraction

Articles considered for inclusion were assessed independently by two researchers. Disagreements and inconsistencies were discussed and resolved by consensus. For each study features concerning the participants, study design and the intervention and comparator diets,

were extracted. In order to assess the impact of a LCD on weight management, metabolic control and compliance, the following outcomes were considered:

- Weight management

- HbA1c

- Serum cholesterol (LDL-cholesterol, HDL-cholesterol and total cholesterol), and serum triacylglycerol

- Blood pressure

- Compliance to dietary intervention

In order to assess compliance, data were extracted on food records and attrition rates. A dispersion in carbohydrate intake of 5% from that prescribed, was set as a limit to determine compliance to the LCD. Data on outcomes were extracted at the end of study, and at three, six and 12 months, when the information was available.

Assessment of risk of bias

The validity of studies included in the review was assessed using specific criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [43]. The results obtained from the assessment are captured in figure 2. In each study, seven domains were evaluated and rated as low risk, unclear risk or high risk of bias. The computer software Review Manager (RevMan) version 5.2. [47], was utilised to create a risk of bias graph. The study level assessment was completed independently by two researchers, and disagreements were discussed prior to reaching consensus.

RESULTS

Search results and characteristics of the included studies

Out of 1180 studies identified through database searches and cross reference list matching, 18 studies were included in the review [48-65]. Articles were immediately rejected if the

reviewer could detect from the title or abstract that the review question was not addressed. Of the 168 records screened by full text, 150 were excluded as inclusion criteria were not met. Reasons for exclusion were such as diet intervention not being low-carbohydrate, and study sample consisting of non-type 2 diabetes individuals. For example, one randomised controlled trial was rejected, as none of the three intervention diets were low-carbohydrate [66].

The total participant number in the 18 articles included in this review was 1832. More specifically, there were 897 participants in the low-carbohydrate group and 1034 participants in the control group. Two studies included participants with and without type 2 diabetes [52, 56]. In these studies, only data on the type 2 diabetes participants were extracted. The follow up time ranged from three months [49, 50, 54, 55, 60] to 3 ± 1.8 years [51]. Studies were published between 1994 [48] and 2012 [64, 65], six were conducted in the USA [48, 51, 52, 55, 57, 59], three in Europe [54, 60, 64], four in Australia [49, 50, 53, 63], three in Israel [56, 61, 62], one in Canada [58] and one in New Zealand [65]. Randomised crossover design was used in four studies [48-50, 60], and parallel randomised control trials with one or two control groups were implemented in 14 studies [51-59, 61-65].

A summary of findings from the included studies are presented in table 1. Of the outcomes relevant to the review, 15 studies investigated the effect of a LCD in weight management [49-51, 53-55, 57-65], 16 studies on HbA1c [49-54, 56-65], 16 studies on serum lipids [48-51, 53-55, 57-65] and 12 studies on BP [49, 53-55, 57-60, 62-65]. Compliance was measured by food records [49, 50, 53-57, 59, 60, 62-65], 24-hour dietary recall [52, 59, 61] and attrition [48, 51-58, 61-65]. Eleven studies included individuals who were either overweight or obese [52-57, 59, 61-63, 65]. Physical activity was not specifically addressed in any of the studies, but several trials promoted general recommendations for physical activity.

The LCD was compared to either low-fat diets [52, 54-56, 59, 64], standard diabetes care [60-62], high carbohydrate diets [48, 50, 63], low-protein diets [51, 53], Mediterranean diets [56, 61], high carbohydrate, low-fat diets [49, 65], low-glycaemic index diets [57, 58] or a high-glycaemic index diet [58]. The dietary amount of carbohydrates in the low-carbohydrate interventions ranged from 5 [57] to 40% [48-50, 53, 55, 63, 65] of the total energy intake. In fourteen out of 14 studies carbohydrate intake was statistically significant between the LCD and the comparator [49, 50, 52, 54-56, 58-65]. In four of the low-carbohydrate interventions [49, 50, 55, 61], and seven of the comparator diets [49, 50, 55-57, 61, 62] participants consumed energy restricted diets that ranged from 1200 [62] to 1800 [56] kcal per day. Conversely, several trials permitted study participants in the intervention to eat ad libitum while limiting carbohydrate intake.

Duration of diabetes among the participants varied from one to ten years and frequently used medications included insulin therapy [51-53, 56, 57, 59, 63-65], anti-hypertensive drugs [50, 51, 53, 55, 58, 60, 65] lipid lowering medications [50, 51, 53, 55, 58-60, 64, 65] and oral hypoglycaemic agents, such as metformin [51, 52, 57, 59, 60, 64], sulfonylurea [48, 51, 52, 59, 60, 64] and thiazolidinedione [60]. Dietary advice was provided by health professionals, such as dietitians and diet counsellors [50, 52, 53, 55-59, 61-65], physicians [64] and nurses [64] and incorporated both individual meetings and group sessions.

Risk of bias in included studies

Three studies provided sufficient information about the proceedings of allocation concealment. Two of them were rated as low risk [51, 58], and one study as high risk of bias [60]. As expected, few studies reported blinding of study participants and personnel to dietary interventions (with the exception of three studies [56, 62, 65]). Only three studies reported blinding of study personnel to the study outcomes assessed [52, 57, 60]. Furthermore, two

studies [50, 65] were rated as high risk due to incomplete reporting of outcome date, as only compliers were incorporated in analysis and non-adhering participants were excluded.

Weight management

The effect of a LCD on weight was measured in weight lost in kilos (kg) and difference in BMI. Twelve out of 13 studies found significant improvements in weight within the low-carbohydrate group. This was observed at three months [49, 50, 55, 60], six months [57], 12 months [58, 61-63], 16 months [53] and 24 months [64, 65]. Seven of these studies included participants that were either overweight or obese. Total weight lost ranged from 0.4 [58] to 11.1 kg [57], compared to 0.1 to 7.7 kg in the control groups [58, 61]. Between diets, three out of 15 interventions favoured the LCD over the comparators, low-fat diet, low-glycaemic index diet and standard diabetes care [54, 57, 60]. None of the trials found that weight lost was significantly greater in the comparator diet. A study by Westman and colleagues [57] found that obese patients with type 2 diabetes experienced the greatest weight loss of 11.1 kg after six months on a low-carbohydrate ketogenic diet, compared to 6.9 kg in the low-glycaemic index diet control group. However, studies with duration more than six months, found no significant difference in weight lost in favour of the LCD.

Glycaemic control

Six out of 11 trials found that HbA1c was significantly reduced with a LCD, both in the short term [60] and long term management [56, 57, 61-63]. Furthermore, three out of 16 studies observed significant difference in improvements in HbA1c between groups, in favour of the low-carbohydrate intervention. Difference in reduction in these trials ranged from of 0.4 to 2.0% [57, 60, 61]. The interventions lasted from three to twelve months, contained 5 to 35% of the total energy from carbohydrates, and were compared to a low-glycaemic index diet [57] and standard diabetes care [60, 61]. One trial by Wolever et al. [58] found that a moderate

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LCD had adverse effects on HbA1c after 12 months. However, the elevation of HbA1c, from 6.1 to 6.3%, was similar in all three dietary arms in the study.

Serum lipids and blood pressure

The results for changes on serum lipids were inconsistent throughout studies. Three out of 11 trials found that the LCD reduced LDL-cholesterol [58, 61, 64], seven out of 13 found an effect on HDL-cholesterol [51, 53, 57, 59, 61, 63, 64], six out of 11 found an effect on TG [48, 55, 57, 60, 61, 63], and one out of 11 found an effect on total cholesterol (TC) [61]. Improvements in serum lipids were observed at three months [55, 60] until three years, and after [51]. However, significant differences in improvements between dietary groups were less frequent. Four studies observed that the LCD induced greater improvements in HDL-cholesterol [57, 59-61], one on LDL-cholesterol [61], and two on TG [60, 61]. A 12 month, three arm randomised trial by Elhayany et al. [61] found that participants on a low-carbohydrate, Mediterranean diet had a significant decrease in LDL-cholesterol compared to the ADA diet. Additionally, the LCD resulted in greater improvements in HDL-cholesterol and TG, compared to both the ADA and traditional Mediterranean diet. Thirteen studies investigated the effect of a LCD on TC [48, 49, 51, 53, 55, 57, 58, 60-65]. Nevertheless, none of the studies found that the intervention diet resulted in significantly greater improvements. Adverse findings on LDL-cholesterol [49, 57], HDL-cholesterol [65], TG [58] and TC [48, 51] were observed with the low-carbohydrate interventions, but none of them reached statistical significance.

Of the eight trials that examined the effect of a LCD on BP, three found significant improvements on systolic blood pressure (SBP) [57, 60, 64] and four on DBP [53, 57, 58, 64]. Between dietary groups, only one study observed greater improvements in SBP [53], and three observed greater improvements in DBP [53, 58, 60], with LCD. Time by diet ranged from three months to 64 weeks. Westman et al. [57] reported the greatest reduction in SBP

and DBP (16.6 and 8.1 mmHg, respectively) with a very low-carbohydrate, ketogenic diet. These findings were however not significantly different from that of the comparator, a low-glycaemic diet.

Compliance

By using 24-hour recalls and food records, six out of 15 studies found that dietary intake of carbohydrates in the LCD were 5 E% within of what was recommended. The interventions lasted three months [49, 50, 53, 55, 60], and 12 months [63], and contained 32 to 40 E% of carbohydrates. In seven out of nine trials that observed low compliance, participants commenced very low-carbohydrate diets (VLCD) with 5 to 22 E% from carbohydrates [52, 54, 56, 57, 59, 62, 64]. Four of these studies were based on an Atkins diet [56, 57, 59, 62]. Of the 14 studies reporting attrition rates, six found that attrition was higher among the low-carbohydrate group [53, 56, 57, 62, 63, 65], three studies reported no loss to follow-up in either group [48, 55, 64], and five found that attrition was higher among the comparator. However, few studies reported if the difference in attrition was statistically significant between dietary groups.

DISCUSSION

This systematic literature review shows that LCD may induce favourable effects on weight, HbA1c, HDL-cholesterol and TG in the short and long term management of type 2 diabetes. However, the LCD was not as effective when compared to control diets with a higher content of carbohydrates. No consistent effects were observed on LDL-cholesterol, TC and BP with the LCD. Compliance to the moderate LCD was found, however the ability to follow a diet with very low-carbohydrate content in the short and long term was generally poor.

Weight and HbA1c were frequently improved within the low-carbohydrate group. Still, only three studies found that improvements on weight [54, 57, 60] and HbA1c [57, 60, 61] were

significantly greater than on the control diets. In regards to weight loss, all of these trials lasted six months or less. This short term effect on weight is consistent with previous findings [26, 39, 67], and suggests that there are initial advantages of a LCD in weight management. However this is not consistent over time, when compared to other diets. The long term improvements in HbA1c that were found in favour of the LCD in this review, are in accordance with those of Ajala et al. [25] and Castañeda-González et al. [67]. Both authors found improvements in HbA1c in favour of the LCD in the long term (24 and 48 months). In contrast, a review of VLCD in type 2 diabetes patients [39] observed no significant benefit on HbA1c in the long term. However, this review included non-randomised controlled trials, with small study samples, which may account for the discrepancy in the results.

Significant improvements in serum lipids and BP were observed both in the short [48, 55, 60] and long term [51, 53, 57-59, 61, 63, 64], but few studies actually found greater improvements with the LCD. The interventions appeared to have less effect on LDL-cholesterol and TC, than on the other serum lipids. The findings of beneficial effects of LCD on HDL-cholesterol and TG are consistent with previous literature, which incorporated both individuals with [24] and without [26] type 2 diabetes. For instance, a review by Wheeler et al. [24] observed more notable changes on HDL-cholesterol and TG than on other serum lipids, with LCD and VLCD. Altogether, these results suggest that a LCD may have beneficial effects on HDL-cholesterol and TG in type 2 diabetes, and furthermore, have an impact on preventing micro- and macrovascular complications. However, one of the concerns regarding a LCD is the possible negative effect it may have on serum LDL-cholesterol, as this is a key risk factor in CVD. Even though some of the studies in this review did experience an increase in LDL-cholesterol, these adverse effects did not reach significance [49, 57].

In regards to compliance, it was found that attrition was slightly higher on the LCD than for the comparator diets. However, many studies failed to report whether this difference was

statistically significant. Nevertheless, this review supports the notion that compliance to a VLCD is difficult to achieve over time, as non-compliance were greater among participants on the VLCD, compared to those on moderate LCD. However, carbohydrate intake in the majority of these studies was still less than 40 E%, indicating that a moderate LCD is achievable over time. It is important to bear in mind the different study populations included in the review, as some populations display more positive attitudes towards reducing carbohydrate intake, and do it with more ease, than others. For example, attrition and non-compliance was high among the Israeli study population on the LCD in the trial of Goldstein et al. [62]. The authors questioned therefore the feasibility of a LCD in the Mediterranean area, where access and consumption of carbohydrate rich foods, such as bread, pasta, milk products, fruit and vegetables, are high. This highlights the importance of taking cultural and personal preferences into consideration when providing dietary advice.

The majority of studies that experienced improvements on glycaemic control, serum lipids and blood pressure, were the same studies that experienced significant improvements in weight. Weight reduction on its own may enable improvements in metabolic factors [68], and the findings from this review seem to corroborate with this notion. More specifically, six out of seven studies that found significant improvements in HbA1c [57, 58, 60-63], and six out of eight that found significant improvements in HDL-cholesterol on a LCD [53, 57, 60, 61, 63, 64], also experienced significant reductions in weight. These findings question the applicability of a LCD in the phase of weight stabilisation, as it is unclear whether the effects observed are due to alterations in carbohydrate intake, or a result of weight loss from energy restriction. However, significant improvements in outcomes were also observed on the LCD without significant changes in weight [51, 59]. Research in this area is required in order to fully understand the effect of LCD as a single factor on metabolic markers.

This systematic review has several limitations. Firstly, it is important to bear in mind the possible risk of bias in the included studies, which ultimately affects the generalizability of the findings. In general, the trials provided insufficient information about their proceedings of conduct, making it difficult to establish the degree of bias in the results. For instance, though the majority of studies reported sufficient information on random sequence generation, few trials actually stated whether participants and study personnel were blinded to dietary interventions and study assessments. Blinding of participants to dietary interventions are difficult to achieve, and the influence of non-blinding in this review, is unclear. However, blinding of study personnel is completely attainable in dietary interventions, and is ultimately a great threat to validity when not implemented [43]. Secondly, a meta-analysis was not able to be conducted as the quality and systematic differences in results reported would have further increased the risk of misleading results [43]. Thirdly, no restrictions were put on the macronutrient content of fat and protein in the intervention and control diets. The LCD and control diets differed in regards to the quantity and quality of protein and fat, and quality of carbohydrates and fibre content, and this may have interfered with the results. For instance, the majority of interventions that found significant improvements in outcomes in favour of the LCD in this review, contained a high amount of fat (39-59 E%), but differed in regards to the quality of fat [54, 57-60]. Hence, future reviews and meta-analysis should address the role of clearly defined quantity and quality of fat and protein content in LCD.

There are also several strengths to this review. For instance, a registration of the planed conduct of the review was implemented prior the literature search, and two researches independently extracted and assessed the data material. Furthermore, only randomised controlled trials were incorporated in the review, as this study design is subject to less biases then observational studies, and is the gold standard of evidence to base clinical recommendations on [43]. Furthermore, compliance to the LCD was included as an outcome

measure in this review, and this factor has not been sufficiently investigated in the scientific literature so far. Compliance, or lack of it, is an important implication in management of type 2 diabetes, and is ultimately a key factor to reach treatment goals [16]. Further attention on dietary approaches that are palatable and achievable in the long term management of type 2 diabetes should therefore be the focus of future research.

We have shown that LCD may have favourable effects on weight, HbA1c and some cardiovascular risk factors in the short and long term management of type 2 diabetes. However, when compared to a higher carbohydrate diet, the LCD did not appear to be superior. Compliance to a LCD and VLCD may be difficult to achieve over time, therefore a patient centred approach, where dietary advice is adjusted after individual preferences and metabolic needs, is critical in dietary treatment of type 2 diabetes.
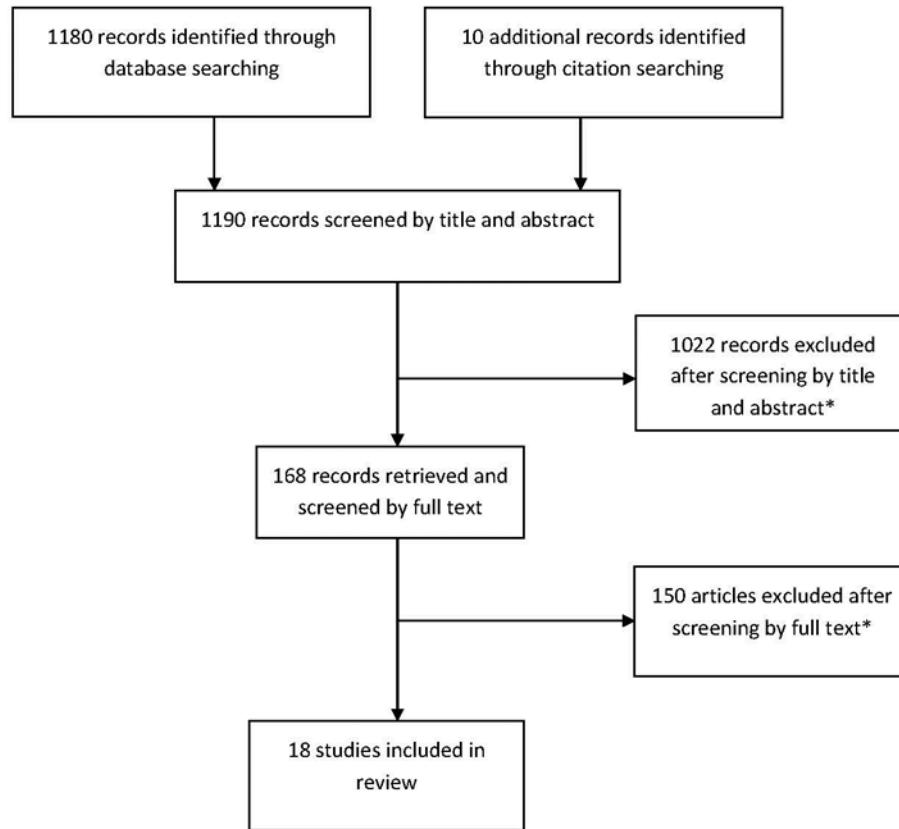
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│  1180 records identified    │     │  10 additional records      │
│  through database searching │     │  identified through citation│
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               │ 1190 records screened by title    │
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               │ 168 records retrieved and         │
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                              ├─────────────▶│ 150 articles excluded     │
                              │              │ after screening by full   │
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               │ 18 studies included in            │
               │ review                            │
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* **Exclusion criteria**

- Did not address the main objective of the study (n=1034)
- Diet intervention not low-carbohydrate (n=42)
- Non-randomised controlled trials (n=41)
- Duration of intervention less than 3 months (n=25)
- Multiple interventions implemented (n=17)
- Study population without type 2 diabetes (n=11)
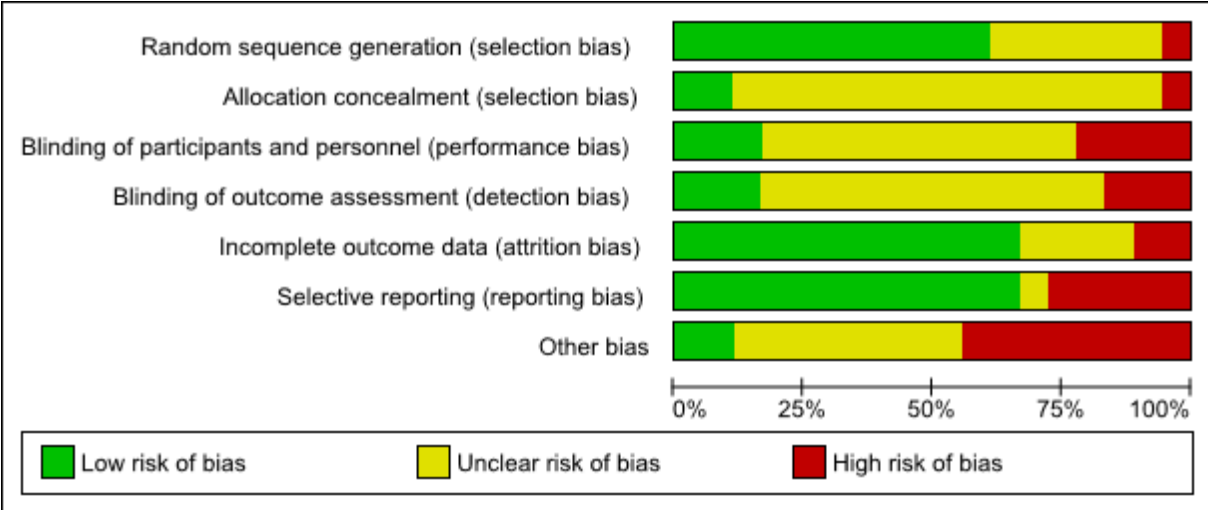- Published prior to 1983 (n=2)

Figure 1

Figure 2

Table 1

Study details	Study design	Sample	LCD	Comparator	Outcome	Duration	Weight/BMI	HbA1c	Serum lipids	Blood pressure	Compliance to LCD – Presented as mean±SD
Garg et al., [48] USA (1994)	Randomised crossover trial	21 type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	55 E% CH 30 E% fat 15 E% protein	LDL, HDL Total cholesterol Triacylglycerol	14 weeks	NA	NA	TG reduced (p=0.03). No significant difference between groups	NA	NA
Walker et al., [49] Australia (1995)	Randomised crossover trial	24 type 2 diabetes patients	40 E% CH 40 E% fat	59 E% CH 21 E% fat	Weight BMI HbA1c LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance	3 months	Weight and BMI reduced (p<0.005). No significant difference between groups	NS	NS	NS	40±0.7 E% CH 36±0.9 E% fat 22±0.6 E% protein
Walker et al., [50] Australia (1999)	Randomised crossover trial	34 post-menopausal women with type 2 diabetes	40 E% CH 40 E% fat	60 E% CH 20 E% fat	Weight HbA1c HDL Triacylglycerol Compliance	3 months	Weight reduced (p<0.01). No significant difference between groups	NS[a]	NS[a]	NA	43.4±4.9 E% CH 32.6±4.7 E% fat 21.4±1.6 E% protein
Facchini et al., [51] USA (2003)	Randomised control trial	191 type 2 diabetes patients	35 E% CH 30 E% fat 25-30 E% protein	65 E% CH 25 E% fat 10 E% protein	Weight HbA1c LDL, HDL Total cholesterol	Mean follow-up 3.0±1.8 years	NS	NS	Significant increase in HDL[a] No significant difference between groups	NA	NA
Samaha et al., [52] USA (2003)	Randomised controlled trial	52 obese type 2 diabetes patients	8 E% CH	51 E% CH[b] 30 E% fat 16 E% protein[b]	HbA1c Compliance[c]	6 months	NA	NS[a]	NA	NA	37±18 E% CH 41±16 E% fat 22±9 E% protein
Brinkworth et al., [53] Australia (2004)	Randomised controlled trial	66 obese type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance[d]	16 months	Weight reduced (p<0.01). No significant difference between groups	NS	HDL increased (p<0.001). No significant difference between groups	DBP reduced (p<0.05). Significant difference in SBP and DBP reduction between groups (p=0.04 and <0.008)[e]	42.6±0.4 E% CH 27.6±0.3 E% fat 27.7±0.3 E% protein
Daly et al., [54] UK (2006)	Randomised controlled trial	102 obese type 2 diabetes patients	22 E% CH	45 E% CH[b] 33 E% fat[b] 30 E% protein[b]	Weight HbA1c Triacylglycerol Systolic blood pressure Compliance	3 months	Significant difference in weight lost between groups (p=0.001)[a]	NS[a]	NS[a]	NS[a]	33.5 E% CH 40.1 E% fat 26.4 E% protein
McLaughlin et al., [55] USA (2007)	Randomised controlled trial	29 overweight and obese type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	60 E% CH 25 E% fat 15 E% protein	Weight BMI LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance	3 months	Weight and BMI reduced (p<0.001). No significant difference between groups	NA	TG reduced (p=0.007). No significant difference between groups	NS	43 E% CH 38 E% fat 19 E% protein

Study	Study type	Participants	Intervention	Comparison	Outcomes	Duration	Weight/BMI	HbA1c	Lipids	Blood pressure	Diet composition achieved
Shai et al., [56] Israel (2008)	Randomised controlled trial	46 moderately obese type 2 diabetes patients	6 E% CH for two months, then max 34 E%	51 E% CH[b] / 30 E% fat / 19 E% protein[b] / 50 E% CH[b] / 35 E% fat / 19 E% protein[b]	HbA1c / Compliance[c]	24 moths	NA	Hba1c reduced (p<0.05). No significant difference between groups	NA	NA	40.4±7.1 E% CH / 39.1±.5 E% fat / 21.8±3.9 E% protein
Westman et al., [57] USA (2008)	Randomised controlled trial	84 obese type 2 diabetes patients	5 E% CH	55 E% CH[b] / 36 E% fat / 20 E% protein[b]	Weight / BMI / HbA1c / LDL, HDL / Triacylglycerol / Total cholesterol / Blood pressure / Compliance	6 months	Significant difference in weight lost and BMI reduction within (p<0.05) and between groups (p=0.008 and 0.05)	Significant difference in HbA1c reduction within (p=0.009) and between groups (p=0.03)	HDL and TG improved (p<0.05). Significant difference in improved HDL between groups (p<0.001)	SBP and DBP reduced (p<0.05). No significant difference between groups	13 E% CH / 59 E% fat / 28 E% protein / Kcal/day: 1550±440
Wolever et al., [58] Canada (2008)	Randomised controlled trial	162 type 2 diabetes patients	39 E% CH / 40 E% fat / 19 E% protein	47 E% CH / 31 E% fat / 20 E% protein / 52 E% CH / 27 E% fat / 21 E% protein	Weight / HbA1c / LDL, HDL / Triacylglycerol / Total cholesterol / Blood pressure / Compliance	12 months	Weight reduced (p=0.003). No significant difference between groups	Significant increase in HbA1c (p<0.0001). No significant difference between groups	LDL reduced (p=0.0079). No significant difference between groups	Significant difference in DBP reduction within (p=0.0080) and between groups (p=0.020)	
Davis et al., [59] USA (2009)	Randomised controlled trial	105 overweight type 2 diabetes patients	5-6 E% CH with 5 g increase each week	50 E% CH[b] / 25 E% fat / 19 E% protein[b]	Weight / HbA1c1 / LDL, HDL / Triacylglycerol / Blood pressure / Compliance	12 months	NS[a]	NS[a]	Significant increase in HDL within and between groups (p=0.002). No significant findings in other serum lipids[a]	NS[a]	33.4±13.2 E% CH / 43.9±10.8 E% fat / 22.7± 6.7 E% protein
Jönsson et al., [60] Sweden (2009)	Randomised crossover trial	13 type 2 diabetes patients	32 E% CH / 39 E% fat / 24 E% protein	42 E% CH / 34 E% fat / 20 E% protein	Weight / BMI / HbA1c / LDL, HDL / Triacylglycerol / Total cholesterol / Blood pressure / Compliance	3 months	Significant difference in weight lost and BMI reduction within (p=0.005 and 0.01) and between groups (p=0.01 and 0.04)	Significant difference in HbA1c reduction within (p=0.0001) and between groups (p=0.02)	TG reduced (p=0.003). Significant difference in improved HDL and TG between groups (p=0.03 and 0.003)	SBP reduced (p=0.048). Significant difference in DBP reduction between groups (p=0.03)	32±7 E% CH / 39±5 E% fat / 24±3 E% protein
Elhayany et al., [61] Israel (2010)[f]	Randomised controlled trial	259 overweight type 2 diabetes patients	35 E% CH / 45 E% fat / 15-20 E% protein	50-55 E% CH / 30 E% fat / 20 E% protein	Weight / BMI / HbA1c / LDL, HDL / Triacylglycerol / Total cholesterol / Compliance	12 months	Weight and BMI reduced (p<0.001). No significant difference between groups	Significant difference in HbA1c reduction within (p<0.001) and between groups (p=0.021) [g, h]	LDL, HDL, TG and TC improved (p<0.001). Significant improvements in LDL[g], HDL[g, h] and TG[g] between groups (p=0.036, <0.001 and <0.001)	NA	41.9 E% CH
Goldstein et al., [62] Israel (2011)	Randomised controlled trial	56 obese type 2 diabetes patients	6 E% CH for 6 weeks, then 10 E% CH	80 E% divided between CH and fats	Weight / HbA1c / HDL	12 months	Weight reduced (p<0.001). No significant	Significant reduction in HbA1c.	NS	NS	20 E% CH

Study	Type	Population	LCD macronutrients	Control macronutrients	Outcomes measured	Duration	Weight	HbA1c	Lipids	Blood pressure	Actual intake
				10-20 E% protein	Triacylglycerol Total cholesterol Blood pressure Compliance		difference between groups	No significant difference between groups			
Larsen et al., [63] Australia (2011)	Randomised controlled trial	108 overweight and obese type 2 diabetes patients	40 E% CH 30 E% Fat 30 E% Protein	55 E% CH 30 E% Fat 15 E% Protein	Weight HbA1c LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance	12 months	Weight reduced (p<0.001). No significant difference between groups	HbA1c reduced (p<0.001). No significant difference between groups	Significant improvements in HDL and TG[a] No significant difference between groups	NS[a]	41.8 E% CH 30.7 E% fat 26.5 E% protein
Guldbrand et al., [64] Sweden (2012)	Randomised controlled trial	61 type 2 diabetes patients	20 E% CH 50 E% fat 30 E% protein	55-60 E% CH 30 E% fat 10-15 E% protein	Weight BMI HbA1c LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance	24 months	Weight and BMI reduced (p=0.020 and 0.011). No significant difference between groups	NS	LDL and HDL improved (p=0.020 and <0.001). No significant difference between groups	SBP and DBP reduced (p=0.012 and 0.004). No significant difference between groups	31±6 E% CH 44±5 E% fat 24±4 E% protein
Krebs et al., [65] New Zealand (2012)	Randomised controlled trial	419 overweight and obese type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL Triacylglycerol Total cholesterol Blood pressure Compliance	24 months	Weight reduced (p<0.001). No significant difference between groups	NS[a]	NS[a]	NS	45.5±6.9 E% CH 32.8±6.3 E% fat 20.6±3.9 E% protein

LCD, low-carbohydrate diet; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triacylglycerol; TC, total cholesterol; E%, percent of energy from macronutrient; CH, carbohydrate; NS, not significant; N/A, not assessed. [a] P value on effect within diet group not provided. [b] Macronutrient value shows the actual intake during study/end of study. [c] Data on macronutrient intake during study was extracted from the whole study population. [d] Compliance measured at three months. [e] P value represent between groups change from week 12 to 64. [f] Two control groups with the same macronutrient composition (American Diabetic Association (ADA) vs. Traditional Mediterranean Diet (TMD). [g] LCD significantly improved compared to ADA. [h] LCD significantly improved compared to TM

Figure 1 Study eligibility flow chart

Figure 2 Risk of bias graph. Summary of the internal validity of the included studies

Table 1 Characteristics and summary of findings of studies selected for inclusion in the review. Outcomes show significant findings within the low-carbohydrate group, and between dietary groups favouring the low-carbohydrate diet