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Trials of Diets for Treatment of Diabetes

- A comparison of diets for treatment of type 2 diabetes, aspects on long and short term effects

Hans Guldbrand

Linköping University
FACULTY OF HEALTH SCIENCES

Division of Community Medicine/General Practice
Department of Medical and Health Sciences
Linköpings universitet, SE-581 83 Linköping, Sweden
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Keywords: dietary intervention, type 2 diabetes, low-carbohydrate diet, blood glucose, blood lipids, insulin, body mass index, quality of life, inflammation, cytokine.

Division of Community Medicine/General Practice
Department of Medical and Health Sciences
Linköpings universitet, SE-581 83 Linköping, Sweden

Tack till min familj:
Min hustru Carin och våra söner Eric och Carl

”Det krävs ett helt nytt sätt att tänka, för att lösa de problem vi skapat med det gamla sättet att tänka.” / Albert Einstein

”Den som inte vågar ta nästa steg, riskerar att bli stående på ett ben resten av livet” / Kinesiskt ordspråk

Contents

ABSTRACT

Background

Type 2 diabetes is a common disease and the prevalence has increased in large parts of the world. In treatment of diabetes the type of diet is of great importance considering metabolic factors such as glucose level and blood lipids. Which diet that is most beneficial to avoid diabetic complications has been heavily debated in recent decades. This thesis is based on two clinical studies designed to compare the effects of different macronutrients.

Methods

A clinical trial was designed to compare a low-carbohydrate diet (LCD) to a low-fat diet (LFD) in treatment of patients with type 2 diabetes. Sixty-one patients at two health care centres were included and randomized to get advice to eat a LCD or a LFD. The LCD had an energy content where 50 energy percent (E%) where from fat, 20 E% from carbohydrates and 30 E% from protein. For the LFD the nutrient composition was similar to what is traditionally recommended for treatment of type 2 diabetes in Sweden. Metabolic factors, anthropometrics and questionnaires were analysed.

To study postprandial effects a trial was designed to compare three different diets. Twenty-one patients with type 2 diabetes were included to in randomized order test the three types of diets on separate test days. On each test day the patients were served breakfast and lunch and blood samples were taken at six times these days. Glucose, lipids and hormones were analysed.

Results

There were equal weight reduction in the two groups in the first trial during the two-year study period. At six month when compliance was good according to diet-records, the glucose-level (HbA1c) was lowered and the HDL-cholesterol was increased in the LCD group. The inflammatory markers IL-6 and IL-1Ra were significantly lower in the LCD group than in the LFD group. At 12 months the physical function, bodily pain and general health scores improved within the LCD group only.

In the second trial the postprandial glucose and insulin levels were lower on the LCD compared to the LFD. However, the LCD resulted in a tendency to higher postprandial triglyceride levels. The Mediterranean type of diet with all energy intake at lunch resulted in a more pronounced insulin response and a glucose level at lunch similar to that of the low-fat diet. The increase-ratio of insulin correlated to the elevation of the incretin glucose-dependent insulinotropic peptide (GIP).

Conclusions

In the two-year study we found benefits for the LCD group regarding glucose control and insulin doses. Furthermore, only the LCD was found to improve the subclinical inflammatory state and there were some aspects of improved well-being in this group. Aiming for 20% of energy intake from carbohydrates is safe with respect to cardiovascular risk factors compared with the traditional LFD and this approach could constitute a treatment alternative.

In the postprandial state, the LCD induced lower insulin and glucose excursions than the LFD but at the same time a tendency of higher triglycerides. The long-term significance needs to be further examined. The accumulation of caloric intake from breakfast to lunch to a single large Mediterranean-style lunch-meal in type 2 diabetes might be advantageous from a metabolic perspective.

LIST OF PAPERS

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals:

I. Guldbrand H, Dizdar B, Bunjaku B, Lindstrom T, Bachrach-Lindstrom M, Fredrikson M, Östgren CJ, Nystrom FH (2012). In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia 55: 2118-2127.

II. Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH (2014). Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med 46: 182-187.

III. Guldbrand H, Lindström T, Dizdar B, Bunjaku B, Östgren CJ, Nystrom FH, Bachrach-Lindström M (2014). Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in type 2 diabetes. Diabetes Res Clin Pract (2014).

IV. Fernemark H, Jaredsson C, Bunjaku B, Rosenqvist U, Nystrom FH, Guldbrand H (2013). A randomized cross-over trial of the postprandial effects of three different diets in patients with type 2 diabetes. PLoS One 8: e79324.

ABBREVIATIONS

AUC	Area under curve
BMI	Body mass index
BP	Bodily pain
CRP	C-reactive protein
E%	Energy percent
GH	General health
GIP	Glucose-dependent insulinotropic peptide
GLP	Glucagon-like peptide
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HDL	High density lipoprotein
HRQoL	Health-related quality of life
IL	Interleukin
kCal	kilocalories
LCD	Low-carbohydrate diet
LDL	Low density lipoprotein
LFD	Low-fat diet
MCS	Mental component score
MH	Mental health
MUFA	Mono-unsaturated fatty acid
PCS	Physical component score
PF	Physical functioning
PUFA	Poly-unsaturated fatty acid
Ra	Receptor antagonist
RE	Role limitations due to emotional problems
RP	Role limitations due to physical problems
SD	Standard deviation
SF	Social function
SF-36	Short Form 36
SFA	Saturated fatty acid
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor antagonist
VAS	Visual analogue scale
VT	Vitality

INTRODUCTION

Diabetes mellitus is a medical condition that is known since ancient times. The word diabetes is Greek (diabainein) which roughly means "something that flows through the body," while the word mellitus comes from Latin and means sweet as honey which was said to be taste of the urine in diabetes. In diabetes, the blood glucose level is increased, which can cause a range of symptoms and complications.

One may classify diabetes mellitus in two main groups, type 1 diabetes and type 2 diabetes. Characteristic of type 1 diabetes is that there is only a little or no production of insulin in the pancreas, as a result of autoimmune reactions. In type 2 diabetes the sensitivity for insulin is reduced. This state is strongly correlated to obesity and reduced physical activity. Another form of diabetes is what is called late onset diabetes in adult (LADA), which is an autoimmune disease similar to type 1 diabetes, but the disease has a later onset with a generally milder course.

Treatment of diabetes has since long time consisted of different diets. Starvation cures, fat regimens and a variety of different diets have been suggested and tested. Before the discovery of the insulin, it was known that a carbohydrate-reduced diet prolonged survival for patients with diabetes. In 1916 the American physician Elliot Joslin described a diet with high fat content as a secure diet in treatment of patients with diabetes[1]. His publication was based on his experiences of treatment of diabetes but he also referred to the good effects of the inuits diet, a diet with a low-carbohydrate content.

In 1921 four Canadian researchers discovered the insulin, the hormone affecting the blood glucose. Two of the researchers, Frederick Banting and James Macleod, were awarded the Nobel Prize in 1923. The discovery of insulin became a breakthrough in the treatment of the diabetic disease.

The Swedish physician Karl Petrén published in 1923 his discoveries in treatment of diabetes[2]. He had demonstrated that a diet with a large content of fat could eliminate ketosis and prolong survival in patients with severe diabetes. In Sweden, this discovery gave rise to the so-called Petrén-diet, a diet with a high fat content by the unlimited intake of pork and butter, some starchy vegetables and a low intake of proteins. This type of diet was used for decades, but was gradually replaced by insulin treatment.

The prevalence of diabetes mellitus is increasing worldwide. In a recent estimation it was found that in 2013 382 million people had diabetes and the number is expected to rise to 592 million in 2035[3]. For all age-groups the prevalence worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030[4]. In Sweden, approximately 4.35% of women and 4.49% of men are diagnosed with diabetes[5].

For thousands of years obesity was rarely seen[6] but in the 20th century, obesity became more common. The World Health Organisation (WHO) has recognized obesity as a global epidemic. An estimation of the number of overweight adults worldwide showed an increased from 857 million people in 1980 to 2.1 billion people in 2013[7]. Since there is a significant association between obesity and type 2 diabetes and also other to cardiovascular risk factors[8], it is of great importance to achieve normal weight for a decreased morbidity. Important factors for a normal weight are lifestyle habits such as physical activity and dietary practices.

The diet for treatment of diabetes has for a long time been considered to be important. However, there are different views on what is the most appropriate diet composition. In the late 1900s the Seven Countries study[9] was of great importance for the treatment of diabetes and for cardiovascular risk factors. The risk with intake of fat was emphasized, which led to recommendations to substitute fats for carbohydrates in many western countries. These recommendations have been subjected to strong criticism and a lively debate about the appropriate composition of the diet. Especially the significance of fat intake has been discussed.

The theory of evolution and the human development with adaptation to different conditions, has been used to understand the significance of eating habits. The diet and the evolution of the earliest human ancestors have been described based on knowledge in particular from the appearance of skulls and teeth[10]. From studies of a people with eating habits similar to eating habits from a previous time period, the Paleolithic era, the effects of such a diet have been described by Staffan Lindeberg[11-16]. He described that the Paleolithic diet contained mainly products such as meat, fish, vegetables, fruits and nuts and he found that this diet, without content of cereals and dairy products, had beneficial effects on metabolic factors and satiety.

Public health authorities have for many years recommended a reduction of the intake of fat. In particular, it has been recommended a reduced intake of saturated fats. In Sweden, the National Food Administration (Livsmedelsverket) until recently, had a recommendation for fat intake of 30 energy percent (E%), for carbohydrates 55-60 E% and for proteins 10-15 E%[17]. Recommendations have also been and still are, to replace saturated fats to poly-unsaturated fats. This has resulted in a shift to dairy products with a low content of fat and a reduced use of regular milk, cream and butter.

In 2009 experts appointed by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) reviewed the state of knowledge regarding fats and fatty acids. Metabolic effects, effects of fats on coronary heart disease and inflammation and other aspects on the effects of fats were reviewed[18-24]. Regarding dietary fat and coronary heart disease were summarised that intake of total fat was not significantly associated with CHD mortality and that intake of total fat was unrelated to CHD events. It was also stated that dietary fat intake has no clear effect on blood pressure, inflammation, fibrinolysis or insulin sensitivity, whereas these risk factors are strongly influenced by obesity. Observational evidence is convincing that trans fatty acids (TFA) are associated with increased risk of CHD events, but for n-3 long chain poly-unsaturated fats (LCPUFA) or fish intake there is an inverse association. Need for further studies was expressed, especially studies of postprandial effects after intake of fat.

Swedish Council on Health Technology Assessment (SBU) published in 2010 a report reviewing knowledge about food and diabetes[25]. It was stated that in type 2 diabetes a low-fat diet (LFD) and a moderate low-carbohydrate diet (LCD) have similar beneficial effects on glucose control and body weight. Also was stated that there were no studies of sufficient quality to determine appropriate nutrient intake distribution during the day or determine the importance of diet on quality of life.

In another report Swedish Council on Health Technology Assessment has reviewed the current knowledge about food in obesity[26]. In conclusion, it was stated that in the short term (six months) advice on strict or moderate carbohydrate diets are more effective for weight loss than low-fat diets advice. In the long term, there is no difference in the effect on weight loss between strict and moderate carbohydrate diets, low-fat diet, high-protein diets, Mediterranean diets, diets focuses on low glycaemic load or diets with a high proportion of mono-unsaturated fats.

In recent years a number of studies have been presented where LCD have been compared to LFD in treatment of diabetes mellitus or obesity[27-51]. Several of these studies have indicated beneficial effects of a high-fat, low-carbohydrate diet in treatment of diabetes[34-36,39-42,45,47,50,51].

There is also a number of expert briefings and meta-analyses conducted in recent years, which has identified the importance of the diet in the treatment of diabetes and for metabolic factors associated with different risk factors[52-54].

The Nordic Nutrition Recommendations (NNR)[55] were revised in 2012. This was a work of more than one hundred selected experts led by a working group under the Nordic Council of Ministers. The report summarizes effects of various nutrients on cardiovascular risk factors and it refers to a large number of studies, including meta-analyses and reviews[19,56-59] dealing with fatty acids. A large randomized clinical trial referred to was the Women´s Health Initiative[37], which concluded that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of coronary heart disease or stroke in postmenopausal women. The summarized conclusions in NNR 2012 has a stronger focus than previously on the whole diet and emphasize the quality of the food and the specific sources for the nutrients, not just the quantities of for example fat and carbohydrates. Population range for total fat intake has been adjusted to 25-40 E%, compared to 25-35 E% in NNR 2004. For total carbohydrates the population range has been changed to 45-60 E% compared to 50-60 E% in NNR 2004, as a consequence of the ranges for other macronutrients and also in line with studies on dietary patterns and health outcomes.

This thesis was initiated by the discussions during the early 2000s, about appropriate diet for patients with diabetes. There was already strong arguments for that a low-carbohydrate diet could provide better blood glucose control in patients with diabetes. In Sweden, low-carbohydrate diets had become popular for weight loss and for those with diabetes. Critics and National Food Administration warned however for low-carbohydrate diets because of the risks of the high fat content. Since no studies on low-carbohydrate diet compared with low-fat diet were carried out in primary healthcare in Sweden, we decided to perform a pilot-study to compare the effects of these types of diets. In 2007, 28 patients with type 2 diabetes were recruited at the health care centre of Lyckorna, Motala, Sweden. The patients were randomized to get advice to eat a low-carbohydrate diet or a low-fat diet during six months. The results indicated a better reduction of weight in the low-carbohydrate group and also for this group a tendency to better blood-glucose control without any adverse effects on blood lipids.

We found the results from this pilot study interesting and were encouraged to larger studies. To compare the long term effects of a low-carbohydrate diet with a low-fat diet in treatment of type 2 diabetes, we designed a two-year randomized clinical trial where the effects on metabolic factors, well-being and inflammation were studied.

We also were interested in the postprandial effects of these diets, which is why we designed a clinical trial comparing the levels of blood-glucose, blood-lipids and different hormones after breakfast and lunch with different compositions. Besides a low-carbohydrate diet and low-fat diet, we also studied a type of Mediterranean diet in this clinical trial.

AIMS OF THE STUDY

General aim

- To compare the effects of different diets in treatment of type 2 diabetes.

Specific aims

- To study the long term effects of low-carbohydrate diet and low-fat diet in treatment of type 2 diabetes.
- To study the effects of low-carbohydrate diet and low-fat diet on inflammatory markers in patients with type 2 diabetes.
- To study the effects of low-carbohydrate diet and low-fat diet on well-being in patients with type 2 diabetes.
- To study the postprandial effects of a low-carbohydrate diet, a low-fat diet and a type of Mediterranean diet in treatment of type 2 diabetes.

STUDY POPULATIONS

Paper I, II, III

In paper I, II and III data were analysed from a clinical trial started in March 2009 and completed in March 2011. Patients with type 2 diabetes in two health care centres, Vårdcentralen Borensberg and Vårdcentralen Marieberg, in the area of Motala, Sweden, were engaged. A total of 72 patients were asked by their diabetes nurse to participate. Of these, 61 patients agreed to participate and were also suitable according to the inclusion criteria. The inclusion criteria were a diagnosis of type 2 diabetes treated with diet with or without additional oral glucose-lowering medication, incretin-based therapy or insulin. There were no weight or age exclusion criteria, but patients who had difficulties in understanding the Swedish language, were suffering from severe mental disease or malignant disease, or who were abusing drugs could not participate in the study. The patients were randomized by drawing ballots to get advice to eat low-carbohydrate diet (LCD) or low-fat diet (LFD). At one of the health care centres 16 patients were randomly assigned to LFD and 15 patients to LCD, whereas at the other health care centre 15 patients were assigned to LFD and 15 patients to LCD.

In the LFD group, the mean age was 62.7 years, there were 13 men and 18 women and the mean duration of known type 2 diabetes was 8.8 years. Corresponding figures for the LCD group were 61.2 years, 14 men and 16 women and a duration of known type 2 diabetes of 9.8 years.

At start of the trial the mean body weight was 91.4 kg for the LCD group and 98.8 kg for the LFD group. The glucose level measured by HbA1c was 58.5 mmol/mol for the LCD group and 55.6 mmol/mol for the LFD group. There were no significant differences between the groups concerning weight, body mass index (BMI), HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides nor the doses of metformin, statins and insulin. At baseline, two patients in the LFD group and two in the LCD group were treated with diet only, 13 in the LFD group and 15 in the LCD group were using oral glucose-lowering medication only, and 11 in the LFD group and 10 in the LCD group were treated with a combination of insulin and oral medication. No patients were lost to follow up at 24 months and data on HbA1C were complete. Data for weight were lacking for one patient at 24 months.

For the analysis of inflammatory markers there were missing data for two of the 61 patients. At the start of the trial the SF-36 questionnaires were completed by 30 patients in the LFD group and by 30 patients in the LCD group. The questionnaire was answered by 22 patients at 6 months, 28 patients at 12 months and 29 patients at 24 months in the LFD group while the corresponding figures for the LCD group were 23, 27 and 25 respectively.

Paper IV

In paper IV the data are analysed from a clinical trial performed during the first months of 2012. In this trial, 21 patients with type 2 diabetes from the area of Motala, Sweden, were engaged in testing three different menus with breakfast and lunch during three days of testing. Because of technical difficulties in blood-sampling two of the patients were excluded. The inclusion criteria was type 2 diabetes, with or without medical treatment, however patients with insulin or sulfonylureas could not participate because of the risk of hypoglycaemia. The patients were recruited by nurses and physicians at the diabetes unit at Motala Hospital and at two adjacent primary care health centres, Vårdcentralen Lyckorna and Vårdcentralen Marieberg.

In the study group, consisted of 19 patients, the mean age was 63 years, there were ten men and nine women and the mean duration of known diabetes was seven years. The mean body weight was 84.4 kg and the mean body mass index (BMI) 29.8. Metformin was used by eight patients and lipid lowering agents by nine patients. Three patients had no medical treatment.

METHODS

Paper I, II, III

A prospective, randomised, non-blinded, parallel clinical trial was conducted. The 61 patients, suitable according to the inclusion criteria, were contacted individually by one of three study nurses, who also had been responsible for the care of these patients ahead of the study start. The patients were randomized to either a low-carbohydrate diet or a traditional low-fat diet, both with an energy content of 1,600 kcal/day for women or 1,800 kcal/day for men. Randomization was not stratified and was based on drawing blinded ballots.

The low-carbohydrate diet had an energy content where 50 energy per cent (E%) was from fat, 20 E% was from carbohydrate and 30 E% was from protein. The low-fat diet had a nutrient composition that was similar to that traditionally recommended for the treatment of type 2 diabetes in Sweden, with 30 E% from fat (less than 10 E% from saturated fat), 55–60 E% from carbohydrate and 10–15 E% from protein.

Group information was used to inform the randomized patients about which food items to choose from. This information was given at baseline and at 2, 6 and 12 months, by two different physicians. One dedicated dietician provided the participants from both groups with suitable recipes at each group meeting and was also available during the trial for questions from the participants. All information was given at the group information meetings and no individual meetings with the dietician were scheduled. Menus for one week were provided to the participants as meal suggestions by the dietician. Each patient had the same dedicated nurse during the whole study period and the nurses could also provide information about food to the patients during regular consultations. The patients were recommended to check plasma glucose levels before and after meals after initiation of the study to allow for proper adjustment of medication to avoid hypoglycaemia. No information was given to increase the level of physical activity to the study groups. The physician responsible for each patient at the primary healthcare centre was allowed to individually adjust lipid lowering and antihypertensive medications consecutively during the trial if necessary.

Investigations of anthropometrics and laboratory tests were performed at baseline and at 6, 12 and 24 months. For future analysis needs and for analysis of inflammatory markers, additional blood samples were frozen at baseline and at 6 months. Diet records were performed at the four mentioned time-points, with one additional recording at 3 months. The diet records were conducted during 3 consecutive days, of which one day was a Saturday or a Sunday. The participants were provided with dedicated scales and notebooks from the organisers with which to weigh and record all food items that were consumed during these periods (food frequency questionnaires were not used). Sagittal abdominal diameter was measured with a sliding beam set square as the highest abdominal level above the upper surface of the corresponding bed.

The laboratory tests were analysed at the Department of Clinical Chemistry at the University Hospital of Linköping as part of clinical routine analyses, and fasting LDL-cholesterol was thus calculated using the Friedewald formula.

At baseline, 6, 12 and 24 months the participants were asked to fill out questionnaires of wellbeing. The generic Short Form-36 (SF-36) questionnaire designed to measure individual health-related quality of life (HRQoL) in clinical practice research and other population surveys was used. The 36 item questionnaire comprises eight health domains: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role limitations due to emotional problems (RE), and mental health (MH) and one single item rating health status over one year. From these domains the combined Physical component score (PCS) and Mental component score (MCS) were calculated. At 12 months the participators were interviewed regarding aspects on following the low-fat or low-carbohydrate diet, also VAS-scales about appetite and satiety were answered at this time point. The study activities are summarized in table 1.

Table 1

Scientific activities during the clinical trial.

	Start	**2 months**	**3 months**	**6 months**	**12 months**	**24 months**
Randomization	X					
Recording of food	X		X	X	X	X
Blood sampling	X			X	X	X
Measuring	X			X	X	X
Group information	X	X		X	X	
Questionnaire	X			X	X	X

Paper IV

A randomised, cross-over, clinical trial was performed. Twenty-one patients were engaged according to the inclusion criteria. They were asked not to change their regular diets or exercise habits during the complete time-period of the study. Each patient were exposed to all the three different diets in a randomized order. Randomisation to determine the sequence of the diets was performed at one single time by drawing ballots for all patients. The maximally allowed time-span between each diet test was 3 weeks and there had to be at least one day of wash-out between experimental days to avoid any carry-over effect. The patients were fasting from 22.00 pm the previous day, when arriving for assessment of each diet. Anthropometric data were collected in the morning and a venous cannula was inserted on the forearm of the patients from which blood was drawn at 07.30 am (fasting), 09.15 am (corresponding to after breakfast or coffee), 11.00 am (before lunch), 12.45 pm (after lunch), 14.30 pm (late after lunch) and the last sample was taken at 16.15 pm. All study meals were consumed under supervision by the study organisers at the Diabetes ward of Motala Hospital.

The total caloric intake each of each period of the experimental days at the hospital (not including food eaten at home later during the day) was 1025–1080 kcal in men and 905–984 kcal for the women. During the intervention day the participants were served breakfast, or only black coffee for the day with the Mediterranean food, at 8.00 am and lunch was served at 11.30 am. Food and macronutrient compositions of the three different diets are shown in table 2. The patients remained in the dining room area during the days of the experiments when they also were asked to abstain from exercise or walking. Dinner or evening meals after 16.15 pm during the trial days were eaten according to their individual preferences at home.

Table 2

Compositions of breakfast and lunch. Women received the low-energy meals (LE) and men received the high-energy (HE) meals. Energy % (E%) was calculated based on protein, fat and carbohydrate content.

	Low-fat diet		**Low-carbohydrate diet**		**Mediterranean diet**	
Breakfast (HE/LE)	Wholegrain bread		Bacon (40g/30g)		Black coffee (200ml)	
	(60g/60g)		2 Eggs			
	Black coffee (200 ml)		Swedish ryebread (24 g)			
	Cucumber		Pepper			
	Pepper		Butter (10g)			
			Black coffee (200 ml)			
	High-energy	**Low-energy**	**High-energy**	**Low-energy**	**High-energy**	**Low-energy**
Energy (kJ)	1281	1239	1834	1834	17	17
Protein (E%)	18	19	25	25	20	20
Protein (g)	13.6	13.8	26.9	26.9	0.2	0.2

Carbohydrate (E%)	45	48	16	16	80	80
Carbohydrate (g)	33.7	35.3	17.3	17.3	0.8	0.8
Fat (E%)	37	33	59	59	0	0
Fat (g)	12.9	11.0	29.2	29.2	0.0	0.0
MUFA (E%)	12	10	24	24	0	0
MUFA (g)	4.2	3.5	11.8	11.8	0.0	0.0
PUFA (E%)	5	4	7	7	0	0
PUFA (g)	1.8	1.5	3.4	3.4	0.0	0.0
SFA (E%)	17	15	22	22	0	0
SFA (g)	5.9	5.1	11.0	11.0	0.0	0.0
Lunch (HE/LE)	Ricenoodles (100g/80g)		Mixed vegetables (150g/100g)		Tomato (70g/70g)	
	Sweet chili sauce (9g/9g)		Cheese 28% (10g)		Cucumber (40g/40g)	
	Japanese soy (18g)		Swedish ryebread (12g)		Rucola (50g/60g)	
	Chicken (100g/80g)		Cottage cheese (40g/30g)		Olives (38g/38g)	
	Liquid margarine (20g/20)		2 Eggs		White bread (150g/160g)	
	Sugar snap peas (50g/40g)		Butter (15g/10g)		1 piece of garlic (3g/3g)	
	Pepper (60g/30g)		Pear (100/50g)		Salmon (100g/80g)	
	Broccoli (70g/50g)				Red pepper (50g/30g)	
	Red onion (30g)				Cashew nuts (7g/5g)	
	Cashew nuts (10g/5g)					
	1 piece of garlic (3g/3g)				Red wine JP Chenet Cabernet-Syrah 14% alc. (200ml/150ml)	
	High-energy	**Low-energy**	**High-energy**	**Low-energy**	**High-energy**	**Low-energy**

Energy (kJ)	3136	2558	2458	1955	4505	4103
Protein (E%)	17	17	28	28	15	14
Protein (g)	31.7	25.0	40.3	32.1	38.8	33.6
Carbohydrate (E%)	56	55	24	21	32	35
Carbohydrate (g)	103.9	82.6	34.3	24.2	85.6	84.1
Fat (E%)	26	29	48	51	40	41
Fat (g)	22.4	19.7	32.1	26.9	49.0	45.1
MUFA (E%)	16	17	16	17	24	25
MUFA (g)	13.2	11.8	10.2	9.0	29.1	27.4
PUFA (E%)	5	6	4	4	7	7
PUFA (g)	4.5	4.0	2.6	2.3	8.3	7.3
SFA (E%)	4	4	23	23	7	7
SFA (g)	3.4	2.8	15.5	12.3	8.1	7.3

Abbreviations: alc, alcohol; E%, energy percent; MUFA, mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; SFA, saturated fatty acid.

Statistical methods

Paper I

Statistical calculations were made using PASW 18.0 software (SPSS, Chicago, IL, USA). Linear correlations were calculated as stated in the text. Comparisons within and between groups were made with Student’s paired and unpaired two-tailed t tests or as stated in the results section.

The mean (standard deviation) is given unless otherwise stated. Statistical significance was considered to be present at the 5% level ($p \leq 0.05$). ANOVA with repeated measures was used for calculations of the changes during the total duration of the study.

The sample size of the study was based on an earlier six month pilot study of 28 participants with type 2 diabetes who were randomized to the same diets as in the study presented in this paper. Twenty individuals completed the pilot study and both diet groups achieved similar weight reductions, while HbA1c levels tended to be lowered in the low-carbohydrate group only, without taking change in medication into account. Based on these results, the study sample size was increased to at least 30 individuals in each group in the present study. None of the participants in the pilot study participated in the trial presented in this paper.

Paper II

IBM SPSS Statistics 19 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Differences within and between groups were analysed with Student´s paired and unpaired two-tailed t test except for inflammatory markers that were not normally distributed. For CRP, IL-6, TNFR1, TNFR2 and IL-1Ra, Mann-Whitney U test was used for between-group comparisons differences and Wilcoxon signed ranks test for within-group comparisons. For correlation analyses Spearman´s rank correlation was used. A linear multiple regression analysis was performed to assess the independent contribution of different factors to changes in cytokine levels. Values are presented as mean (SD) or median (inter-quartile range).

Paper III

Statistical calculations were done with PASW 20.0 software (SPSS Inc. Chicago, IL, USA). Linear correlations were calculated, as stated in the text. Comparisons within and between groups were done with Student's paired and unpaired 2-tailed t-test or in the case of questionnaires by Wilcoxon and Mann-Whitney tests. Mean (standard deviation) is given unless otherwise stated. Statistical significance was considered to be present at the 5% level ($p \leq 0.05$). ANOVA with repeated measures was used for calculations of the changes during the total study duration.

Paper IV

Statistical calculations were done with PASW 18.0 software (SPSS Inc. Chicago, IL, USA). Comparisons between groups were done with pairwise comparisons using Wilcoxon's signed rank paired test with the low-fat diet serving as control in the analyses. The pairwise comparisons of different time points during the test days were only analysed if there were differences in the area under curve (AUC) as compared with the low-fat diet, except for the glucose-dependent insulinotropic peptide (GIP), that is a hormone specifically affected acutely by the meals and which thus was expected to be low before the meals. Spearman's rank was used for calculation of correlations. Mean (standard deviation) is given unless otherwise stated. Statistical significance for paired comparisons was considered to be present as $p<0.0063$ after Bonferroni correction, i.e. $p = 1-(1-\alpha)^{1/k}$ where α is the traditional p-value of 0.05 and $k = 8$ (i.e. the number of variables tested). In correlation analyses statistical significance was set as $p<0.05$. The AUC were calculated based on the trapezoidal rule.

The sample size was determined based on the experiences of our earlier long-term study of a low-carbohydrate compared with a low-fat diet in which we found substantial differences between these two groups in a total of 32 subjects that reported reasonable compliance with the diets at two years[60]. In that study we clinically observed larger difference in postprandial glucose levels than in fasting levels of glucose and that it was possible to substantially reduce insulin doses in those compliant with the diets, thus indirectly demonstrating lower insulin requirement by the different diets. Since all participants in the present study should eat the meals of the diets in company with the study organizers in the trial reported here, compliance was assumed to be excellent and hence to give high statistical power, but due to risk of attrition, we planned to include about 20 subjects. We also chose a cross-over design to increase statistical power. As stated in the introduction, we found no published earlier studies in patients with type 2 diabetes of postprandial effects of different diets on which to base a more exact power calculation.

Ethics

Paper I, II, III

The study was approved by the Regional Ethics Committee of Linköping (Dnr M216-08) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects. The study was registered with trial number NCT01005498 at ClinicalTrials.gov

Paper IV

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Regional Ethics Committee of Linköping, Sweden (Dnr 2011/418-31). All participants gave written informed consent to participate. The study was registered with trial number NCT01522157 at ClinicalTrials.gov.

RESULTS AND DISCUSSION

Paper I

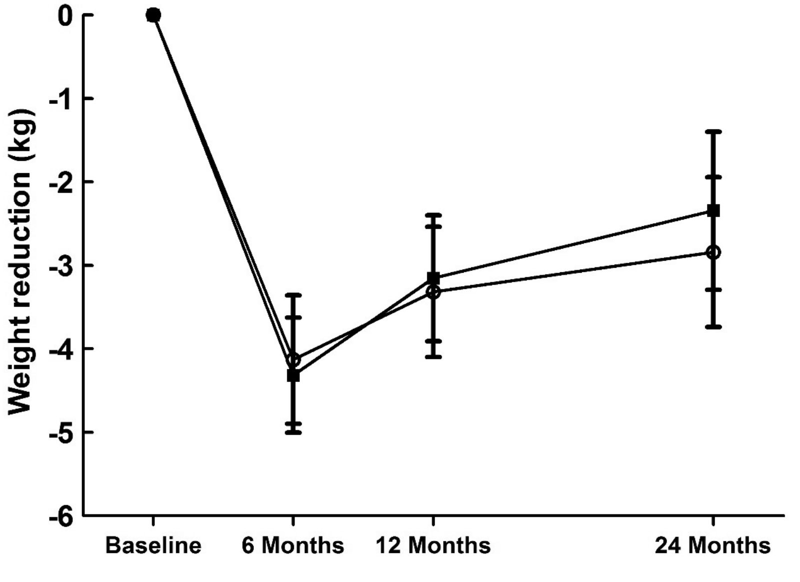
In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss.

Results (I)

The mean BMI of the patients in the LFD group at baseline was 33.8±5.7 and in the LCD group 31.6±5.0. Weight loss did not differ between the groups during the two-year study. Weight loss (figure 1a) was maximal at 6 months: LFD -3.99±4.1 kg, LCD -4.31±3.6 kg. At 24 months, patients at LFD had lost −2.97±4.9 kg and those on LCD −2.34±5.1 kg compared with baseline.

Figure 1a

Weight reduction
The weight reduction did not differ between the groups (p=0.33 for all time points).
LCD: squares; LFD: circles.

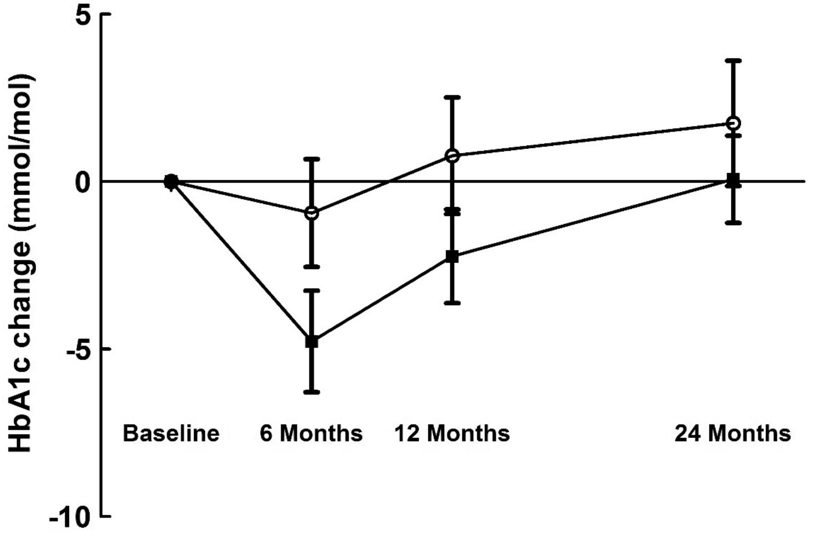


At baseline the mean HbA1c in the LFD group was 55.6±8.0 mmol/mol and in the LCD group 58.5±10.2 mmol/mol. HbA1c fell in the LCD group only: LCD at 6 months −4.8±8.3

mmol/mol, at 12 months −2.2±7.7 mmol/mol, LFD at 6 months −0.9±8.8 mmol/mol (figure 1b).

Figure 1b

HbA1c change.
The reduction in HbA1c level was statistically significant within the LCD group (p=0.005 for all time points) but did not differ between the groups when compared at all time points (p=0.76). LCD: squares; LFD: circles.



HDL-cholesterol had increased at 6 months with the LCD from 1.13±0.33 mmol/l to 1.25±0.47 mmol/l while LDL-cholesterol did not differ between groups. Insulin doses were reduced in the LCD group: 0 months, LCD 42±65 E, LFD 39±51 E; 6 months, LCD 30±47 E, LFD 38±48 E.

Discussion (I)

We found that weight loss was equal in both groups. This is in contrast to other studies which have found LCD more efficient in weight reduction[28,30,35,41,42,61]. However, in our study, the study design suggested an equal energy intake in both groups. We had also few resources to achieve compliance. The resources were the standard primary care with only four extra group meetings during the first year of the study. As in many other studies, compliance with the LCD was reduced after six months according to the increase in weight and to the food records.

Our findings support the use of an LCD with 20 E% from carbohydrates as an alternative to traditional LFD to improve glycaemic control. In both groups there were no significant changes in blood-lipids except for the HDL-cholesterol, which was increased in the LCD group at six months. The use of statins and some changes in the statin doses made these findings inconclusive regarding the dependence of the diet. However, the effects on HbA1c and HDL-cholesterol of the LCD was in line with the LCD effect in other studies[41,44,47].

Paper II

Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet.

Results (II)

The levels of IL-1β and TNF were below the limits of detection in all participants. The levels of CRP, IL-1Ra, IL-6, TNFR1 and TNFR at baseline and after 6 months are presented in table 3. At baseline, no differences were seen between the two groups. After 6 months, CRP levels did not show any significant changes within the groups. IL-1Ra levels, on the other hand, decreased significantly in the LCD group while no change was seen in the LFD group. The levels of IL-6 increased in the LFD group only. After 6 months, both IL-1Ra and IL-6 levels were significantly lower in the LCD group than in the LFD group. TNFR1 levels did not change in any of the groups while TNFR2 tended to increase in LFD patients ($p = 0.064$). During the study period, statin therapy was initiated in two LCD patients and hence, 24 patients in each group were treated with statin at 6 months. At baseline, the levels of CRP, IL-1Ra, IL-6, TNFR1 and TNFR2 did not differ significantly between statin users ($n = 46$) and non-statin users ($n = 15$), neither did changes in inflammatory markers differ between statin and non-statin users after 6 months. If the two LCD patients receiving statin during the study period were excluded from the analysis, the reduction of IL-1Ra remained significant in the LCD group ($p = 0.002$).

Table 3

Levels of inflammatory markers at baseline and 6 months in the two intervention groups. Data are given as median (interquartile range). *P* values ≥ 0.10 are listed as non-significant (NS). LFD: low-fat diet; LCD: low-carbohydrate diet.

	LFD n=30	**LCD** n=29	p between groups
CRP, mg/L			
Baseline	1.41 (0.45– 4.01)	1.12 (0.37– 3.32)	NS
6 months	1.67 (0.80– 3.24)	0.87 (0.29– 2.74)	NS
p within group	NS	NS	
IL-1Ra, pg/mL			
Baseline	1333 (784– 2153)	1298 (818– 1873)	NS
6 months	1216 (974– 1822)	978 (664– 1385)	<0.05
p within group	NS	<0.01	
IL-6, pg/mL			

Baseline	2.16 (1.77– 3.59)	2.45 (1.39– 4.10)	NS
6 months	3.39 (2.25– 4.79)	2.15 (1.65– 4.270)	<0.05
p within group	<0.05	NS	
TNFR1, ng/mL			
Baseline	1371 (1227– 1760)	1340 (1149– 1637)	NS
6 months	1423 (1200– 1687)	1320 (1145– 1610)	NS
p within group	NS	NS	
TNFR2, ng/mL			
Baseline	2627 (2162– 3150)	2530 (2094– 2973)	NS
6 months	2680 (2322– 2968)	2480 (2266– 2927)	NS
p within group	0.064	NS	

Discussion (II)

We found that advice to follow a low-carbohydrate diet reduces the subclinical pro-inflammatory state in type 2 diabetes. Despite similar total energy intake and similar weight loss in the LFD and in the LCD group, cytokines levels were affected differently. After six months when compliance to the diets was good due to food records, IL-1Ra showed a significant decrease in patients who were randomized to follow LCD, while IL-6 increased in those who followed LFD. Results that are in line with our findings have been reported[62] but also a study where IL-6 differences not were found comparing LFD and LCD[63].

Paper III

Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in type 2 diabetes.

Results (III)

There was no difference in baseline values in any of the domains between the low-fat and low-carbohydrate groups. The low-carbohydrate showed improvements in the Physical function, Bodily Pain, General Health and Vitality domains of the SF-36 at 12 months compared to baseline (p values 0.042-0.009). In contrast to this no change was observed in the low-fat group at any time during the study. The change from baseline to 12 months showed improvements in Bodily Pain and General Health in the LCD group in comparison with the LFD group (p=0.017 and 0.022 respectively). At 12 months there was also an improvement in the combined Physical Component Score (PCS) in the LCD group compared to baseline (p=0.009) and also compared to the LFD group (p=0.028).

Discussion (III)

In obesity, with or without coexisting type 2 diabetes, intentional reduction of body weight is considered to improve health-related quality of life (HRQoL)[64]. After 12 months, improvements of HRQoL were found only in the LCD group. The improvements related to physical function and to vitality and general health while the domains relating to mental health showed no change. In the SF-36 a difference of five points in an individual domain or 2-3 points in PCS or MCS are considered clinically significant[65,66]. The changes that were found in our study are thus considered to be clinically significant. There are different possible mechanisms for the improvements of these results during the study including reduction of body weight in the patients, who had a mean BMI of 32 when entering the study, improvement of glycaemic control but also the change of macronutrients per se. Our finding that there was no change in SF-36 after 6 months when reduction of body weight was maximal in both groups argues against this being only an effect of weight reduction. A limitation of our study is that not all patients filled out the questionnaire at this time, while the answering frequency was good at 12 months. This makes the 6 months results more uncertain. Furthermore the magnitude of weight reduction was similar in both groups but the improvement in HRQoL occurred only in the LCD group. In the LFD group associations were found between changes of PCS and both changes of BMI and HbA1c while no such associations were found in the LCD group which might suggest that other factors, possibly the diet per se, might have been of importance for the improvements found in PCS in the LCD group. In this study no scale specifically addressing anxiety and depression was used but we could not find support for that the LCD caused deterioration of the mental scores of SF-36. These results might seem contradictory to the results from a study of Brinkworth et al[67] but there are major differences between this study and ours. A major difference was that a very low-carbohydrate diet aiming at only 4 % of the energy intake consisting of carbohydrates was used while we prescribed a more moderate carbohydrate restriction to 20 E%.

In conclusion, weight-changes did not differ between the diet groups while improvements in HRQoL only occurred after one year during treatment with LCD. No changes of HRQoL occurred in the LFD group in spite of a similar reduction in body weight.

Paper IV

A Randomized Cross-Over Trial of the Postprandial Effects of Three Different Diets in Patients with Type 2 Diabetes.

Results (IV)

The low-carbohydrate diet induced lower insulin and glucose excursions compared with the low-fat diet, but the low-carbohydrate diet with a higher contents of fat showed a tendency to slightly higher triglyceride levels. For the Mediterranean-style lunch-meal there was a pronounced insulin-response and the postprandial glucose-level was similar to the glucose level after the low-fat lunch-meal with less energy intake. The increase-ratio of insulin for the Mediterranean-style lunch-meal correlated with the elevation of the incretin glucose-dependent insulinotropic peptide (GIP). The effects of the three different diets on glucose, insulin, triglycerides and GIP are shown in figure 2a-d.

Figure 2

Effects of three different diets on glucose, insulin, triglycerides and glucose-dependent insulinotropic peptide (GIP). Effects of a low-fat diet (open circles, regular lines), low-carbohydrate diet (open squares, dashed lines) and a Mediterranean-type diet (open triangles, dotted lines) with similar total energy intake as the low-fat and low-carbohydrate diets contained for both breakfast and lunch combined but eaten only at lunch paired with a glass of red wine.

Figure 2a
Effects on glucose.

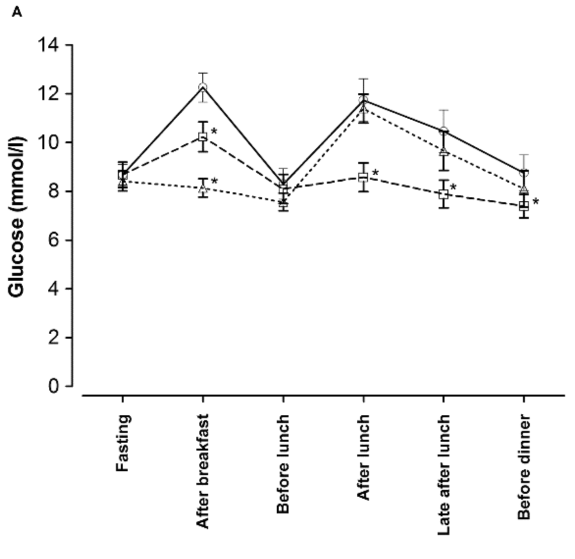


Figure 2b
Effects on insulin.

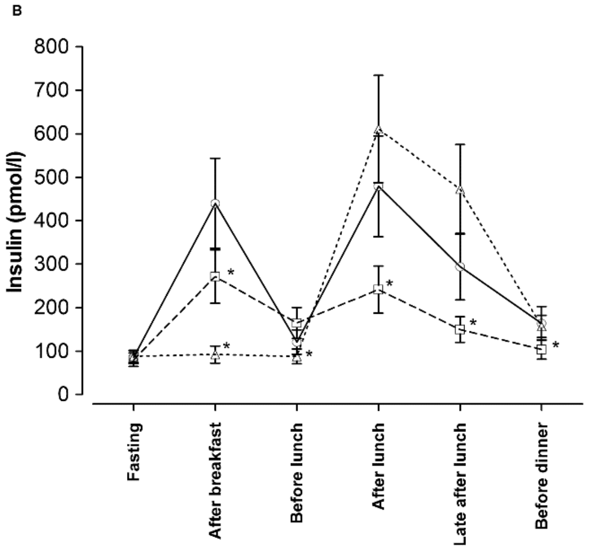


Figure 2c
Effects on serum triglyceride levels.

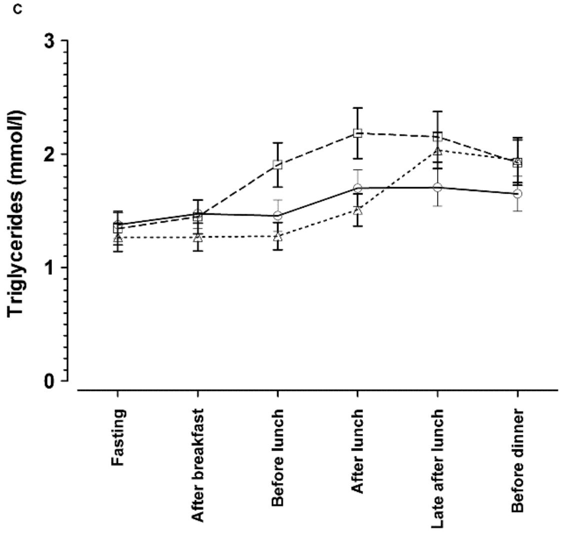
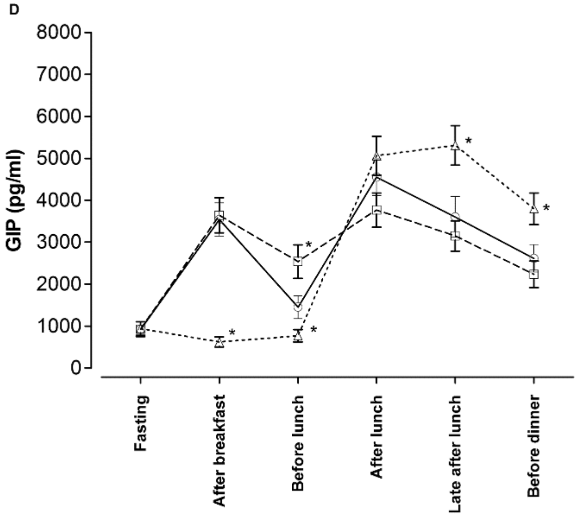


Figure 2d
Effects on the incretin hormone GIP.



Discussion (IV)

We found that a low-fat diet induced higher levels of both insulin and glucose compared with a low-carbohydrate diet, measured as area under curve (AUC), after test meals with breakfast and lunch with similar energy intake. This is in line with our earlier study of long term effects[60]. The tendency to higher triglyceride levels after the low-carbohydrate meals could provide a risk for cardiovascular disease. However, in studies where fasting triglycerides have been measured, the triglyceride-levels have decreased or remained unchanged by LCD[35,40-42,60,68].

The Mediterranean-style diet with all the energy contents at lunch showed a glucose-level similar to the low-fat diet at lunch despite the large difference in energy contents. A possible explanation is found in the increase in GIP, an incretin stimulating the release of insulin. The ingestion of few large meals rather than several smaller meals to achieve a more efficient GIP-release has earlier been advocated by other authors[69].

GENERAL DISCUSSION

The main finding in this thesis is that our clinical trials where we have compared diets in treatment of diabetes, have indicated advantages for LCD in comparison with LFD regarding glycaemic control in a short and a long perspective, and also regarding wellbeing. Despite a high content of total fat and also an increased proportion of saturated fat in the LCD, we did not find any negative effects on blood-lipids in a two-year perspective. However, we found a tendency of higher postprandial triglycerides with LCD. If this fact could be a cardiovascular risk factor in the long term is unclear. We also found positive effects of the LCD on markers of inflammation, IL-6 and IL1-Ra, in contrast to the LFD.

An interesting result was seen in the trial of postprandial effects where a Mediterranean-style lunch was tested. Despite a higher energy content than a compared LFD lunch, we found similar glucose levels after lunch. An explanation of this result could be a higher insulin secretion triggered by a substantial increase in the incretin glucose-dependent insulinotropic peptide (GIP).

In paper I we found when comparing LCD and LFD during two years, an equal weight loss in both groups, maximal at 6 months, when the compliance to the diets regarding food diaries was good. At the same time point the LCD group had lowered HbA1c and mean insulin use. The improved glucose control of the LCD is in accordance with other clinical studies[34,41,42,47]. At six months, HDL-cholesterol had increased with the LCD while LDL-cholesterol did not differ between groups. In the LFD group no improvements were seen in blood-lipids, despite a substantial weight reduction. Similar effects on blood lipids are reported in other studies[42,47]. There were no significant changes in triglycerides during the two years and no significant differences between the groups.
In a completers analysis based on compliance with fat intake at 24 months, a reduced sagittal abdominal diameter was recognised in the LCD group. This result indicates that a high carbohydrate intake is correlated to abdominal obesity.

Interestingly, in a meta-analysis of studies comparing low-carbohydrate and low-fat diets[54] were found that persons on low-carbohydrate diets experienced a slightly but statistically significantly lower reduction in total cholesterol and LDL-cholesterol, but a greater increase in HDL-cholesterol and a greater decrease in triglycerides.

In another meta-analysis[70] the decrease in total cholesterol was significantly more pronounced following low-fat diets, whereas rise in HDL-cholesterol and reduction in triglyceride levels were more distinct in the high-fat diet groups. Including only hypocaloric diets, the effects of low-fat vs high-fat diets on total cholesterol and LDL-cholesterol levels were abolished. Meta-regression revealed that lower total cholesterol level was associated with lower intakes of saturated fat and higher intakes of poly-unsaturated fat, and increases in HDL-cholesterol levels were related to higher amounts of total fat largely derived from mono-unsaturated fat in high-fat diets whereas increases in triglyceride levels were associated with higher intakes of carbohydrates. In addition, lower LDL-cholesterol level was marginally associated with lower saturated fat intake. The results of this meta-analysis do not allow the authors for an unequivocal recommendation of either low-fat or high-fat diets in the primary prevention of cardiovascular disease.

In paper II we report an advantage for the LCD group compared with the LFD group regarding markers of inflammation. Despite similar weight loss, IL-1Ra and IL-6 levels were significantly lower in the LCD group than in the LFD group after 6 months, when the compliance to the given advice was good. We have found two other studies in this area with somewhat contrasting results[62,63] but in another study a carbohydrate-rich diet itself has been associated with pro-inflammatory effects[71]. In a substudy of the PREDIMED study[72] data are supporting that advice to reduce fat intake, and thereby increased carbohydrate intake, is associated with pro-inflammatory effects. Several mechanistic studies have reported that exposure to carbohydrates induces a pro-inflammatory response[73-75]. The type of carbohydrate may have a major influence on inflammation[76,77]. Also the nature of dietary fats can modulate inflammation. Several studies have reported that a meal enriched in saturated fatty acids is followed by a pro-inflammatory response but the results are inconsistent[78,79]. On the other hand, diets high in unsaturated or poly-unsaturated fatty acids have been associated with anti-inflammatory effects[72,78,80,81].

In the clinical trial described in paper I-III we found an equal weight reduction in the two groups. A number of studies comparing weight reduction of LCD and LFD have found a larger weight reduction for the LCD[28,30,35,41,42,61,82,83]. In a report from Swedish Council on Health Technology Assessment[26] was stated that in the short term (six months) is advice on strict or moderate carbohydrate diets more effective for weight loss than low-fat diets advice, in the long term, there is no difference in the effect on weight loss. A recent published meta-analyse[84] comparing the two types of diets conclude that significant weight loss was observed with any low-carbohydrate or low-fat diet and weight loss differences between individual named diets were small. These results have been questioned because of the study sample in which the levels of carbohydrate and fat are different in the studies. Reasons for the results in different studies are dispersing, could be the follow-up time, the selection of participators, the study design and resources invested. In our study described in paper I-III we compared a moderate LCD with a traditional LFD and the study design was adapted to the usual clinical resources with only four extra group-meetings during the first year. A considerable strength of our study is that we had no loss of patients, everyone could be followed up by diabetes nurses.

The result in paper IV where the LCD had a more advantageous postprandial glucose level compared with a LFD is in line with other studies, both postprandial and in a longer perspective[34,39,41,42,47,51]. The tendency of a higher triglyceride level postprandial after the LCD with a relatively high content of fat is a result of uptake by the small intestine of fat and the transport of triglycerides of chylomicrons in the blood stream. Prolonged postprandial hypertriglyceridemia is a potential risk factor for cardiovascular disease but the type of fat could be important[85]. However, the importance of postprandial hypertriglyceridemia for the LCD in long term is uncertain in the view of studies that demonstrated lower fasting triglycerides after LCD[30,41,42,86].

Poly-unsaturated fats which are largely represented in Mediterranean diet have been found to have beneficial effects[51]. It has also been demonstrated that replacement of saturated fats to poly-unsaturated fats has cardio-metabolic benefits[78]. Whether the replacement of saturated fats to poly-unsaturated fats would be beneficial from a clinical perspective, however, is uncertain since it has also been demonstrated that an increased intake of saturated fats has no negative effect on cardiovascular morbidity[38].

The glucose level after a high energy Mediterranean-type of lunch presented in paper IV is interesting. The results demonstrate a correlation between the insulin-secretion and the incretin GIP. The substantial increase of GIP and the resulting insulin secretion explain the effect on the glucose level. If the macronutrients, the wine or the large meal size per se explains the result is unclear. However, the results indicate that that a large meal of Mediterranean diet type may be more beneficial than several LFD meals. In a recent published study[87] two larger meals a day have been compared with six smaller meals a day regarding effects on body weight, hepatic fat content, insulin resistance and beta cell function. The results suggest that for type 2 diabetic patients on a hypoenergetic diet, eating larger breakfasts and lunches may be more beneficial than six smaller meals during the day. These results together with the results we found for the Mediterranean diet is a cause for further discussion and research regarding appropriate meal order.

The Mediterranean diet has also been studied in several other clinical trials. In the PREDIMED study[51] a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. A recent update on research[88] where a number of medical conditions were considered, have found evidence supporting the concept that the Mediterranean diet is one of the healthiest diets.

An important contribution in the research on long-term effects of lifestyle intervention was the LOOK AHEAD trial, published in 2013[89]. In this trial 5145 patients were included with a median follow-up time of 9.6 years. Despite an intensive lifestyle intervention focusing on weight loss, no reduction in the rate of cardiovascular events in overweight or obese adults with type 2 diabetes was found. The intervention group in this study were recommended physical activities and a low-fat diet with reduced caloric intake (1200-1800 kcal/day and < 30 E% from fat). The results from this study give reason to question the dietary guidelines where low-fat intake and high intake of carbohydrates has been recommended.

In recent years several review articles on low-carbohydrate diets in various respects has been published[90-93]. There are different conclusions in these articles about the advantages and disadvantages of low-carbohydrate diets, which may seem somewhat contradictory but it is essential to note that various types of low-carbohydrate diets with different macronutrient content are included in the analysis.

A systematic review and meta-analysis was published in 2014 comparing long term effects of high-fat diets and low-fat diets on cardio-metabolic risk factors in subjects with abnormal glucose metabolism[94]. The conclusion was that high-fat diet (low-carbohydrate diet) compared with low-fat diet exert beneficial effects on triglyceride levels, HDL-cholesterol, blood-pressure and fasting glucose levels in pre-diabetic patients or in manifested type 2 diabetes. It is emphasized that this should lead to a recommendation of high-fat diet (low-carbohydrate diet). However, it is expressed that the composition of fat, i.e. higher amounts of mono-unsaturated fatty acids (MUFA) and poly-unsaturated fatty acids (PUFA) and lower amounts of saturated fatty acids (SFA), is still an issue.

Another systematic review was published in 2014[95]. Dietary, circulating and supplement fatty acids and the risk of coronary disease were analysed. Both observational studies and randomized, controlled trials were included. The conclusion was that current evidence does not clearly support cardiovascular guidelines that encourage high consumption of poly-unsaturated fatty acids and low consumption of total saturated fats.

In a publication in Diabetes Care[96] regarding treatment of diabetes, the position of the American Diabetes Association (ADA) is described. In this position statement it is emphasized the importance of an individualized eating plan, energy balance and that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people with diabetes and therefore macronutrient distribution should be based on individualized preferences and metabolic goals. Similar positions are expressed in the Nordic Nutrition Recommendations (NNR)[55]. However, criticism has been directed against these recommendations, since the conclusions largely are based on associations and observational studies, not on randomized clinical trials with hard endpoints.

Comparing a LCD with a LFD we have in two clinical trials found advantages for a LCD regarding blood-glucose control, inflammation and wellbeing. Postprandial we found a tendency of higher triglycerides with a LCD with a high fat content but in longer perspective we found no negative effects on blood-lipids. Whether fats have adverse effects in a short and a long perspective have been controversial and is still under debate. The publications referred to in the introduction section demonstrates the complexity of fat metabolism and the difficulties in determining appropriate fat intake.

Limitations of the research

Paper I, II, III

Generalizability of the results must be questioned because of a relatively small sample size, which may not be representative for all the patients with type 2 diabetes. Also the method used for the selection of patients could affect the generalizability. The patients were asked by the study nurses to participate in the trial. The study nurses were also the patients´ diabetic nurse who had taken care of the same patients before the study start. When identifying potential participants according to inclusion and exclusion criteria it cannot be excluded that the study nurses might have selected suitable participants for various reasons. The selection method and the fact that the study nurses also were the patients´ diabetic nurses may limit the generalizability. However, the high participation rate that was achieved is an advantage in terms of adherence to dietary advice, which may affect the generalizability in a positive way.

In dietary studies, it is generally difficult to find out what participants eat in order to evaluate the efficacy of a particular diet. To obtain an estimate of food intake, we have in the two-year study used food diaries that participants filled in for three consecutive days on five occasions during the study period. It will be an uncertainty in the food diaries, because of individual differences and accuracy in reporting in these diaries. Also, it is not excluded that the reporting in food diaries per se influenced what patients ate and that eating habits during other time was different from what was reported.
The included patients were all followed up during the study time. However, some data were missing. It was mainly the food diaries and the relatively extensive questionnaires that some participants did not provide. This may have affected the possibilities to show differences between variables, in particular in the analysis of the questionnaires.

Paper IV

The recruitment of patients was performed within a limited selection of patients and was not randomized and there is uncertainty about how well the sample may represent patients with type 2 diabetes. Since the differences between the diets are studied for each patient, the representativeness may be less important but generalizability may still be affected.
The compliance to the tested meals under supervision at the diabetes ward was excellent. However, it reduces the generalizability of the tested meals if these were instead to be used as diet suggestions in the clinic.

Another limitation in this study was that we had no control on dietary intake the days before and between the trial days. However, to reduce the effect of this dietary intake, a crossover design was used and the patients were asked to fasten the night before trial days and also return to their regular eating habits between these days. A minimum of 44 hours were set between trial days to reduce the carry-over effects.

Clinical implications

A moderate low-carbohydrate diet with 50 E% fat, 20 E% carbohydrates and 30 E% protein improved glycaemic control, both in a short and in a long perspective, without any adverse effects on wellbeing. At least the long-term effects on blood lipids appear to be favourable of such a diet. A reduction of the blood glucose-lowering medications such as insulin was achieved and since insulin in a high degree contributes to the cost of diabetes treatment, adherence to a low-carbohydrate diet may have great economic benefits for the individual as well as for society.

In addition to these positive blood glucose-lowering effects and economic impact, positive effects from a low-carbohydrate diet has also been observed on inflammatory markers. The effect on inflammation is important in the process of atherosclerosis affecting the cardiovascular morbidity.

In the clinical trial described in paper I-III a method was used which was adapted to primary health care with extra resources just in form of four group meetings. This demonstrate a realistic method which could be used in clinical practise to obtain advantages for patients with type 2 diabetes and also to provide cost benefits.

Future research

After the two clinical studies described in this thesis had been completed, a number of studies have been submitted in the same area of knowledge. There are also a several publications previously referred to, where the benefits of a low-carbohydrate diet in treatment of diabetes have been demonstrated. A considerable uncertainty still remains with regard to the really long-term effects of such a diet, especially regarding the significance of the quantity and type of fat. Benefits of poly-unsaturated fats in comparison with saturated fats have in some studies been found but there is still uncertainty about the appropriate distribution of fat intake. To gain additional knowledge is needed long-term, randomized clinical trials with hard endpoints, in which the distribution of various nutrients can be tested. Further studies of the significance of the meal size and the number of meals a day appears also to be of great importance, especially in light of the study on postprandial effects presented here.

CONCLUSIONS

In the two-year study we compared a low-fat diet and a low-carbohydrate diet in patients with type 2 diabetes. We found benefits for the low-carbohydrate diet group regarding glucose control where we saw a larger reduction of HbA1c. No adverse effects on blood lipids were seen in the low-carbohydrate diet group despite the high intake of fat in this group. In the low-fat diet group no improvements of blood lipids were seen despite a substantial weight loss at six months. Weight changes did not differ between the diet groups but insulin doses were reduced significantly more with the low-carbohydrate diet at six months when compliance was good. Furthermore, only the LCD was found to improve the subclinical inflammatory state. Some aspects of well-being improved in the low-carbohydrate diet group only.

Comparing postprandial effects of a low-carbohydrate diet and a low-fat diet we found that the low-carbohydrate diet induced lower insulin and lower glucose excursions than a low-fat diet but a tendency of higher levels of triglycerides. We also found that the accumulation of caloric intake from breakfast to lunch to a single large Mediterranean-style lunch-meal might be advantageous from a metabolic perspective in treatment of type 2 diabetes. Benefits of a Mediterranean diet from cardiovascular risk point has been demonstrated in a number of studies. Our study gives rise to need for further research on the nutritional contents of this type of diet but also the questioning of the current advice on portion size and meal order.

We conclude that a low-carbohydrate diet aiming at an intake of 20 E% from carbohydrates has advantages in comparison with a low-fat diet and without any apparent adverse effects on cardiovascular risk factors over a two-year period, in treatment of type 2 diabetes. The low-carbohydrate approach could constitute a treatment alternative and it could provide cost benefits. A Mediterranean style diet might be beneficial due to metabolic reasons, in the treatment of type 2 diabetes.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Typ 2-diabetes är en sjukdom som i stora delar av världen blivit allt vanligare på senare år. Levnadsvanor har stor betydelse för sjukdomens utveckling. Det är känt att övervikt och fetma är starkt relaterat till typ 2-diabetes. Andra faktorer som har betydelse för sjukdomen är bland andra grad av fysisk aktivitet, ärftlighet och kosthållning.

Diabetes är en kronisk sjukdom som innebär en ökad risk för framtida sjuklighet. Komplikationer till sjukdomen kan ses i en rad inre organ där åderförkalkningen, aterosklerosen, oftast är en orsakande faktor. Behandlingen av typ 2-diabetes har länge varit inriktad mot att förbättra livsstilsfaktorer och kosthållning samt att ge läkemedel avsedda att gynnsamt påverka blodsockerkontrollen samt andra riskfaktorer såsom blodtryck och blodfetter.

Lämplig kost vid diabetes har länge ansetts vara det vi i Sverige kallar tallriksmodellen. Råden har varit att energiintaget av kolhydrater bör vara 50-60 energiprocent, av protein 10-15 energiprocent och av fett 30 energiprocent. En livlig debatt har pågått om lämpligheten av att äta så pass mycket kolhydrater, som omvandlas till socker i blodet, när man har diabetes och när förmågan att ta hand om blodsockret är nedsatt. Många patienter med diabetes har också noterat att blodsockret snabbt sjunker om kolhydraterna i kosten minskas. Den så kallade lågkolhydratkosten, LCHF, har därför anammats av många patienter och fått många förespråkare. En del kostexperter har dock varnat för den höga fetthalten i lågkolhydratkosten, som man menat ökar risken för höga blodfetter och åderförkalkning.

Denna avhandlings syfte har varit att utröna kortsiktiga och långsiktiga effekter av koster med högt eller lågt kolhydrat/fett-innehåll. Ett lägre kolhydratinnehåll innebär i praktiken ett högre fettinnehåll om man vill ha samma totala energiinnehåll. Tre av arbetena är baserade på en två-årig klinisk studie med deltagande av 61 patienter med typ 2-diabetes. I en annan klinisk studie studerades effekter efter måltid på blodsocker, blodfetter och hormoner av tre olika kosttyper.

Delarbete I beskriver en jämförelse mellan lågkolhydratkost och lågfettkost hos de 61 deltagande diabetespatienterna. Dessa lottades till en rådgivning med syfte att äta lågkolhydratkost alternativt lågfettkost under den två-åriga studietiden. Studien visade att lågkolhydratgruppen fick bättre blodsockerkontroll och kunde sänka sina insulindoser i större grad än lågfettgruppen. Några negativa effekter på blodfetterna kunde inte ses trots det högre fettintaget. Viktnedgången var likvärdig i de båda grupperna under hela studietiden. Trots god viktnedgång i lågfettgruppen sågs ingen förbättring av blodfetterna. I delarbete II beskrivs kosttypernas inverkan på olika markörer för inflammation. Lågkolhydratkosten uppvisar tecken till att ge minskad inflammation jämfört med lågfettkosten, genom minskade värden på markörer för inflammation (IL-6, IL-1Ra). Hur patienterna mådde under studietiden registrerades genom enkäter (SF-36). I delarbete III redogörs för resultaten, som påvisar positiva effekter på välbefinnandet för lågkolhydratgruppen.

I delarbete IV beskrivs effekterna efter frukost och lunch på blodsocker, blodfetter och hormoner, av tre olika kosttyper. De kosttyper som studerades var lågkolhydratkost och lågfettkost av samma typ som använts i den ovan beskrivna två-åriga studien. En tredje kosttyp som studerades var en typ av medelhavskost, där frukost endast bestod av en kopp kaffe och där hela energiintaget intogs till lunch tillsammans med ett glas vin. Resultaten visade att vid jämförelse mellan lågfett- och lågkolhydratkost sågs lägre blodsocker och lägre nivå av insöndrat insulin vid intag av lågkolhydratkost. Vid samma jämförelse sågs också att lågkolhydratkost gav en tendens till högre triglyceridnivå. Intressant var att medelhavskosten med hela energiintaget till lunch inte gav högre blodsockernivå än lågfettkosten vid lunch, trots stor skillnad i energiintag. En förklaring tros vara den höga insöndring av ett hormon, glucose-dependent insulinotropic peptide (GIP), vid intag av medelhavskosten till lunch. GIP är ett hormon som stimulerar insulininsöndringen vilket kan hålla nere blodsockernivån.

Sammanfattningsvis visar resultaten av jämförelser i två kliniska studier mellan lågkolhydratkost och lågfettkost ett flertal positiva effekter för lågkolhydratkost. Man ser framförallt en bättre sockerkontroll. Data talar också för inflammationsdämpande effekter av lågkolhydratkost liksom positiva effekter på välmående. Efter fettrik måltid ansamlas fett i blodet i form av triglyceridinnehållande kylomikroner. Fastevärden av fettet triglycerider torde dock inte påverkas negativt. Medelhavskost i form av koncentrerat energiintag med rikligt med fleromättade fetter kan ha gynnsamma effekter på blodsockerkontroll. Ytterligare forskning behövs dock, framförallt vad gäller de riktigt långsiktiga effekterna.

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