

SUMMARY

Nutritional therapy is recognized as a first-line therapeutic intervention in patients with type 2 diabetes (T2D). However, dietary recommendations are ambiguous and no clear consensus exists regarding the macronutrient distribution of the diabetes diet. Currently, the Danish diabetes dietary guidelines recommend a macronutrient distribution of 45-60 energy percent (E%) from carbohydrates, 10-20 E% from protein and <35 E% from fat. Carbohydrate-restriction has been suggested as a viable nutritional treatment to improve glycemic control, although meta-analyses have revealed receding or absent long-term effect. Most feeding studies are, however, influenced by a concomitant weight-loss which makes it difficult to evaluate the effects of an eating pattern unconfounded by the beneficial effects of a weight-loss. Therefore, we investigated the effects of a conventional diabetes (CD) diet and an iso-energetic carbohydrate-reduced high-protein (CRHP) diet during 6 weeks of full meal provision aiming at weight stability in patients with type 2 diabetes. Whereas the macronutrient distribution of the CD diet was in accordance with the current Danish diabetes guidelines (carbohydrates 50 E%/proteins 17 E%/fat 33 E%), the CRHP diet was reduced in carbohydrates to 30 E% and increased in proteins and fat to 30 E% and 40 E%, respectively.

After 6 weeks of treatment, the CRHP diet improved glycemic control by reducing HbA_{1c} by 6.2 (\pm 0.8) mmol/mol whereas the CD diet reduced HbA_{1c} by 0.8 (\pm 1.0) mmol/mol. After 6 weeks of treatment, carbohydrate-restriction reduced 24-hour mean glucose by 13% and a mixed meal test revealed that postprandial glucose and insulin excursions were lower on the CRHP diet, as compared to the CD diet. We also found a significant difference between diets in terms of hepatic fat fraction. Hepatic fat fraction was reduced by 2.4 (-7.8 to -1.0) % following 6 weeks of CRHP dietary treatment. The CRHP diet also reduced fasting triglycerides, total cholesterol and non-HDL-cholesterol but increased urinary excretion of 8-oxoGuo, a marker of oxidative RNA modifications. Collectively, a CRHP diet, compared to a CD diet, improved metabolic control and lipid profiles but increased a marker of oxidative stress in patients with T2D receiving 6 weeks of full food provision.

In conclusion, carbohydrate-restriction is an efficient short-term nutritional strategy in the management of T2D, but the long-term efficacy, safety and feasibility of the diet merit further investigation.

SUMMARY IN DANISH

Kostvejledning anbefales som en del af den initiale behandling af patienter med type 2 sukkersyge. Kostanbefalingerne er dog ikke ensartede, og på nuværende tidspunkt er der ikke enighed om, hvilken makronæringsstofsammensætning der er den optimale i diabeteskosten. De nuværende danske kostanbefalinger anbefaler følgende makronæringsstoffordeling; 45-60 energiprocent (E%) kulhydrat, 10-20 E% protein og <35 E% fedt. Kulhydrat-restriktion er foreslået som en behandlingsmetode til at forbedre den glykæmiske kontrol, men meta-analyser har vist aftagende eller manglende effekt på længere sigt. De fleste kostinterventioner ledsages af et vægttab, hvilket gør det vanskeligt at bedømme kostens effekt på den glykæmiske kontrol uafhængigt af vægttabets gavnlige virkninger.

Vi undersøgte derfor effekterne af en konventionel diabetes (CD) kost og en iso-energetisk kulhydrat-reduceret høj-protein (CRHP) kost i forbindelse med 6 ugers kostudlevering og vægtstabilitet i patienter med type 2 sukkersyge. Makronæringsstoffordelingen i den konventionelle diabetes-kost var i overensstemmelse med de nuværende danske anbefalinger (kulhydrater 50 E%/proteiner 17 E%/fedt 33 E%), hvorimod CRHP-kostens andel af kulhydrater var reduceret til 30 E% og protein og fedt var øget til henholdsvis 30 E% og 50 E%.

En kulhydrat-reduceret høj-protein kost forbedrede patienters glykæmiske kontrol ved at reducere HbA_{1c} med 6.2 (±0.8) mmol/mol, hvorimod CD-kosten reducerede HbA_{1c} med 0.8 (± 1.0) mmol/mol.

Sammenlignet med CD-kosten, reducerede CRHP-kosten døgn-blodsukkeret med 13% og en måltidstest viste, at postprandielle glukose- og insulin-niveauer var lavere på CRHP-kosten efter 6 ugers behandling. Vi påviste også en signifikant forskel på leverens fedtindhold, når vi sammenlignede de to kosttyper. Seks ugers CRHP-behandling reducerede leverens fedtindhold med 2.4 (-7.8 to -1.0) %. En kulhydrat-reduceret høj-protein kost reducerede også koncentrationen af faste-triglycerider, total-kolesterol og non-HDL-kolesterol men øgede urin-udskillelsen af 8-oxoGuo, som er en markør for oxidative RNA-forandringer. Samlet set forbedrede CRHP-kosten patienternes glykæmiske kontrol og lipid-profil, men øgede en markør for oxidativt stress.

Vi kunne konkludere, at en kulhydrat-reduceret kost er en effektiv kortsigtet behandlingsstrategi mod type 2 diabetes, men at yderligere undersøgelser kræves for at bestemme den langsigtede effekt, sikkerhed og anvendelighed af CRHP-kosten.

PREFACE AND LIST OF PAPERS

This PhD thesis is based on a clinical study performed at Copenhagen University Hospital Bispebjerg and the Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen. The research kitchen at the Department of Nutrition, Exercise and Sport produced and distributed study meals. Data were analyzed in collaboration with the Department of Radiology, Copenhagen University Hospital Herlev, Department of Clinical Pharmacology, Copenhagen University Hospital Bispebjerg, Clinical Research Centre and the Emergency Department, Copenhagen University Hospital Hvidovre, Department of Clinical Biochemistry, University of Copenhagen, Department of Biomedical Sciences and the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen and Department of Nutrition, Exercise and Sports, University of Copenhagen.

The study was initiated in April 2016 and terminated in November 2017.

The present PhD thesis is based on the following manuscripts:

- I. Mads J. Skytte*, Amirsalar Samkani*, Amy D. Petersen, Mads N. Thomsen, Arne Astrup, Elizaveta Chabanova, Jan Frystyk, Jens. J. Holst, Henrik S. Thomsen, Sten Madsbad, Thomas M. Larsen, Steen B. Haugaard, Thure Krarup. A carbohydrate-reduced high-protein diet improves HbA_{1c} and liver fat content in weight stable participants with type 2 diabetes: a randomized controlled trial. *Diabetologia* 2019 Nov;62(11):2066-2078.
- II. Mads J. Skytte, Amirsalar Samkani, Arne Astrup, Jan Frystyk, Jens F. Rehfeld, Jens. J. Holst, Sten Madsbad, Mogens Fenger, Thomas M. Larsen, Thure Krarup, Steen B. Haugaard. Moderate carbohydrate restriction during 6 weeks increases beta-cell responsiveness, satiety and reduces glucose excursions and insulin secretion in type 2 diabetes: a randomized feeding trial. (Ready for submission).
- III. Mads J. Skytte, Amirsalar Samkani, Arne Astrup, Thomas M. Larsen, Jan Frystyk, Henrik E. Poulsen, Trine Henriksen, Jens J. Holst, Ove Andersen, Sten Madsbad, Steen B. Haugaard, Thure Krarup, Emil L. Larsen. Effects of a Highly Controlled Carbohydrate-Reduced High-Protein diet on Markers of Oxidative Nucleic Acid Modifications and Inflammation in Weight Stable Subjects with type 2 diabetes; a Randomized Controlled Trial. Under review by the *Scandinavian Journal of Clinical and Laboratory Investigation*.

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