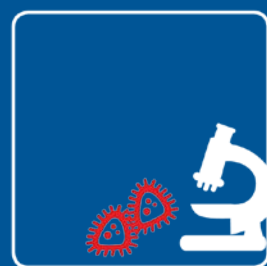


CutDM Pheno – Paradigmeskift i kostbehandling af diabetes. Reduktion af kulhydrat i diabeteskosten – mekanismer bag effekt behandling af type 2 diabetes via selektivt valg af makronæringsstoffer



Slutrapport

for samarbejdsprojekter under Mejeribrugets ForskningsFond (MFF)

1. Projektets titel

Paradigmeskift i kostbehandling af diabetes; Reduktion af kulhydrat i diabeteskosten – mekanismer bag effektiv behandling af type 2 diabetes via selektivt valg af makroernæringsstoffer

CutDM - Cut down on carbohydrate usage in the diet of type 2 diabetes - mechanisms of effective therapy of diabetes by selective choice of macronutrients – The phenotype study

2. Projektleder

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4. Finansieringskilder

Mejeribrugets ForskningsFond
The Novo Nordisk Foundation Center for Basic Metabolic Research
The Department of Biomedical Sciences of University of Copenhagen
Endokrinologisk Forskningsenhed, Bispebjerg Hospital

5. Projektperiode

Projektperiode med MFF finansiering: Januar 2015 – Januar 2018

6. Projektresumé

Diabetes er et voksende samfundsproblem med store konsekvenser for de, der rammes af sygdommen. International Diabetes Federation anslår at 500 millioner mennesker er ramt af sygdommen om mindre end 20 år. En stor del af behandlingen af type 2 diabetes, især i de tidlige stadier, baserer sig på kostændringer. Den videnskabelige evidens bag de nuværende kostråd til diabetikere er dog stadig begrænset. I forskningsprojektet 'Reduktion af kulhydrat i diabeteskosten – mekanismer bag effektiv behandling af type 2 diabetes via selektivt valg af makronæringsstoffer - Fænotypestudiet' støttet af Mejeribrugets Forskningsfond, har vi nærmere undersøgt betydningen af kulhydratindholdet i kosten for type 2 diabetes.

Forsøget er blevet udført på type 2 diabetikere, helt raske og personer i risiko for udvikling af diabetes, såkaldte prædiabetikere. Vi har undersøgt de akutte forskelle mellem effekten af den nuværende anbefalede kost og en kost med et reduceret kulhydratindhold. Hermed kan vi få en mere fuldstændig forståelse for de processer i stofskiftet, der påvirkes af vores kost. Udover insulinfølsomheden har vi målt fedtstofskiftet, mæthedshormoner, hormoner forbundet med betændelsesreaktion mm. for at undersøge, om en anderledes kostsammensætning også har gunstig indvirkning på disse faktorer hos både raske og diabetikere.

Vi har vist, at man sænker det måltidsrelaterede blodsukker ved at spise færre kulhydrater hos både type 2 diabetikere og non-diabetikere. Desuden øger man mæthedshormoner og subjektiv mæthedsfølelse hos type 2 diabetikere. Vi har ydermere vist, at udsving i blodsukker, den såkaldte glukosevariabilitet, sænkes.

Total dietary carbohydrate intake is an important determinant of postprandial glucose increase. We hypothesized that a moderate reduction in carbohydrates will reduce postprandial glucose, insulin response and diurnal glucose in subjects with type 2 diabetes mellitus (T2DM).

We studied 16 patients with T2DM, 14 males, median age 64 years, HbA1c 49.5±9 mmol/mol (mean±SD), treated with metformin. An isoenergetic carbohydrate-reduced intervention diet was compared to a control diet (carbohydrate 30/55 E%, protein 30/15 E%, fat 40/30 E%, respectively). Patients consumed each diet for two consecutive days in a randomized order separated by a washout period of 2-8 weeks. Meal testing was undertaken at breakfast (time 0 - 270 min) and at lunch (270 - 450 min) each test day. Furthermore, diurnal glucose was measured by 48-hrs continuous glucose monitoring (CGM)

Compared to the control diet, the intervention diet significantly reduced postprandial plasma glucose AUC by 14% ($p<0.01$) (student's paired t-test), postprandial serum insulin AUC by 22% ($p<0.01$), postprandial serum C-peptide AUC by 19% ($p<0.01$) and diurnal blood glucose AUC measured by CGM by 11% ($p<0.01$). Furthermore, the intervention diet significantly increased postprandial plasma cholecystokinin AUC by 23% ($p<0.01$) and postprandial plasma ($p<0.01$).

Reducing the carbohydrate content in the diet of subjects with T2DM significantly reduces mean plasma glucose concentrations primarily by reducing postprandial glucose excursions.

7. Projektets formål

Nyere forskning peger på, at man kan reducere udsving i blodsukker og insulin ved at sammensætte kosten, så den består af forholdsmæssigt færre kulhydrater. Vores forskningsgruppe fremsætter den hypotese, at man ved at justere kulhydratindholdet i diabeteskosten uden at ændre på mængden af kalorier kan reducere blodsukkerstigningen efter et måltid. Formålet med projektet er at undersøge akutte hormonelle ændringer under indtagelse af måltider med forskelligt indhold af kulhydrater. Vi vil sammenligne den nuværende anbefalede kost (energifordeling på 55% kulhydrater, 15% proteiner og 30% fedt) med en kost lav på kulhydrat (energifordeling på 30% kulhydrater, 30% protein og 40% fedt).

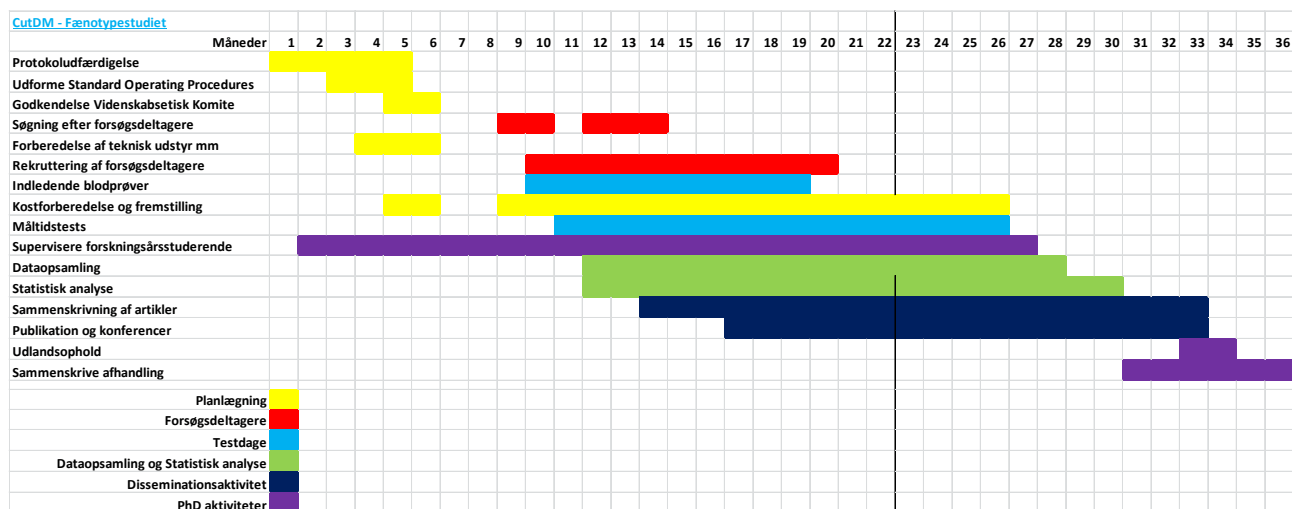
The background for this application is that there is no consensus regarding the choice of diet for patients with Type2 diabetes (T2D). The fundamental hypothesis of this application is that once overt T2D is established, the disease will progress further on a diet high in carbohydrates because of increasing postprandial glucose concentrations.

We hypothesized that a moderate reduction in carbohydrates will reduce postprandial glucose, insulin response and diurnal glucose in subjects with type 2 diabetes mellitus (T2DM).

8. Projektets baggrund

Nyere forskning tyder på, at vi i Danmark og resten af Verden anbefaler diabetikerne at spise alt for meget kulhydrat. I Danmark vejledes diabetikere eksempelvis med at dække omtrent 55 % af deres daglige energibehov med kulhydrater. Flere nye studier peger på, at man kan forbedre diabetikers blodsukkerkontrol, medicinforbrug og livskvalitet ved at reducere kulhydrat i kosten. Man kan i bedste fald fuldstændig kurere let til moderat type 2 diabetes. Baggrunden for dette er aldrig blevet grundigt undersøgt.

9. Projektets delaktiviteter i hele projektperioden



10. Projektets resultater

ABSTRACT (Accepted in British Journal of Nutrition)

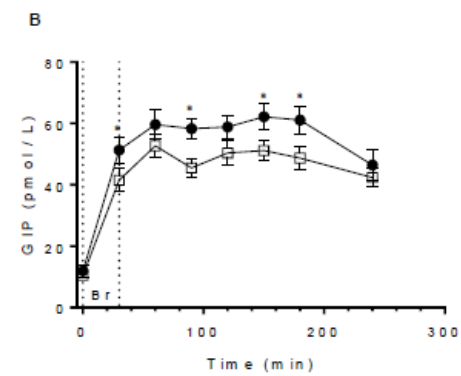
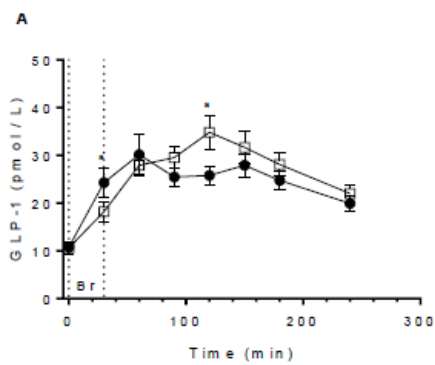
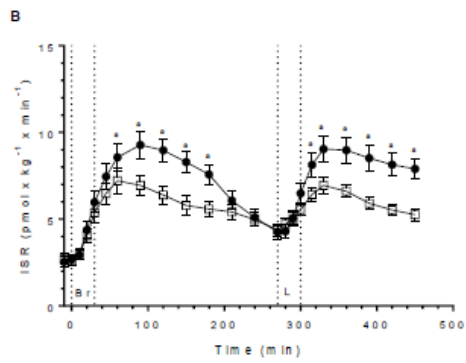
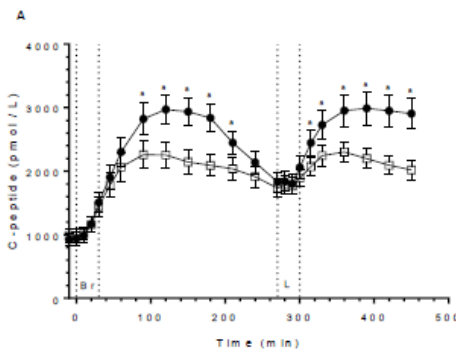
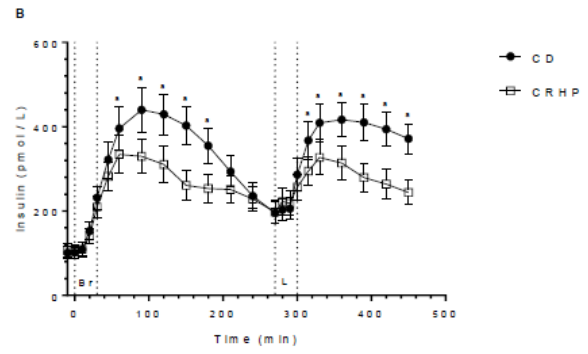
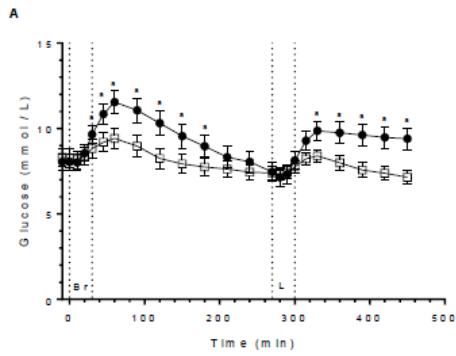
Objective: The aim of the study was to assess whether a simple substitution of carbohydrate in the conventionally recommended diet with protein and fat would result in a clinically meaningful reduction in postprandial hyperglycaemia in subjects with type 2 diabetes mellitus (T2DM).

Design: Sixteen subjects with T2DM treated with Metformin only, 14 males, median age of 65 [43-70] years, HbA_{1c} 6.5% (47 mmol/l) [5.5-8.3% (37-67mmol/l)] with a BMI of 30 ± 4.4 kg/m² (mean ± SD) participated in the randomized, cross-over study.

Methods: A carbohydrate reduced high protein (CRHP) diet was compared with an iso-energetic conventional diabetes (CD) diet. Macronutrient contents of the CRHP / CD diets consisted of 31% / 54% energy from carbohydrate, 29% / 16% energy from protein and 40% / 30% energy from fat respectively. Each diet was consumed on two consecutive days in a randomized order. Postprandial glycaemia, pancreatic and gut hormones as well as satiety were evaluated at breakfast and lunch.

Results: Compared with CD diet, CRHP diet reduced postprandial area under curve (AUC) of glucose by 14%, insulin by 22% and GIP by 17% (all $p < 0.001$), respectively. Correspondingly, glucagon AUC increased by 33% ($p < 0.001$), CCK by 24% ($p = 0.004$) and satiety scores by 7% ($p = 0.035$) respectively.

Conclusion: A moderate reduction in carbohydrate with an increase in fat and protein in the diet, compared with an energy-matched conventional diabetes diet, greatly reduced postprandial glucose excursions and resulted in increased satiety in patients with well controlled T2DM.



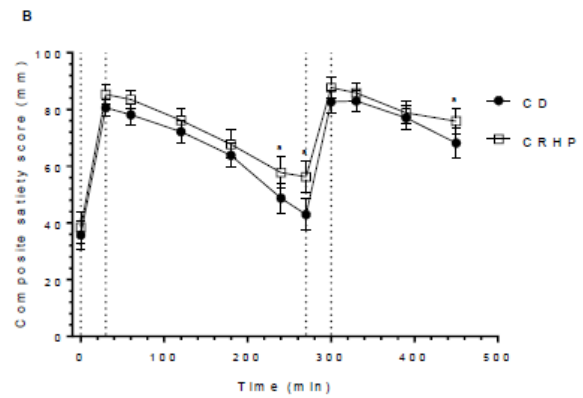
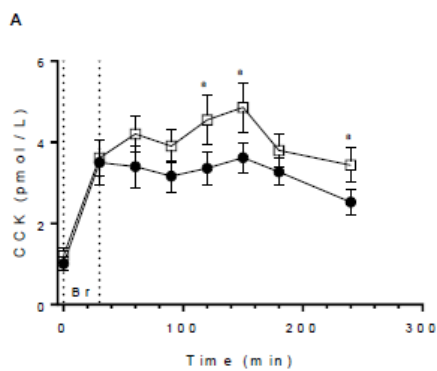
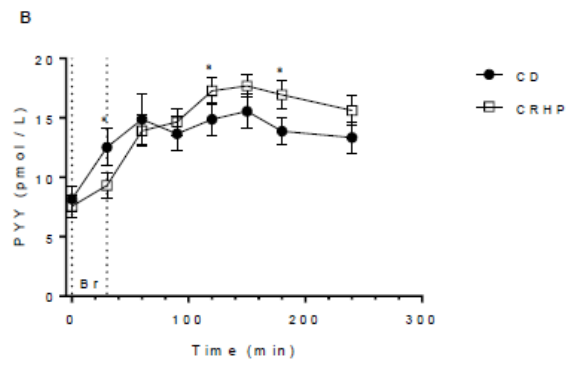
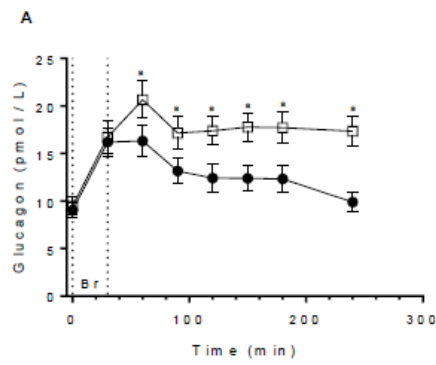


TABLE 1

Macronutrient composition and ingredients of test meals standardized at 10 MJ/day

Breakfast	CRHP ¹ diet	CD ² diet
Energy (kJ)	3000	3000
Carbohydrate (E%)	31	54
Protein (E%)	29	16
Fat (E%)	40	30
Fiber (g/MJ)	2.5	4
Ingredients (g)		
Egg	192.3	39.7
Olive oil	7.5	----
Bread	37.4	69.4
Rye flour yoghurt topping	21.4	49.6
Tomato	85.5	----
Cheese	16.0	19.8
Ham	26.7	----
Skyr (Icelandic yoghurt) with vanilla	160.3	----
Strawberry jam	----	19.7
Apple	----	49.6
Almond	----	11.9
Milk, acidophilus cultured	----	198.3

Lunch		
Energy (kJ)	3000	3000
Carbohydrate (E%)	31	54
Protein (E%)	29	16
Fat (E%)	40	30
Fiber (g/MJ)	3.5	2.7
Ingredients (g)		
Chicken	137.3	38.1
Olive oil	14.7	----
Tomato	147.2	142.8
Spring onion	9.8	19.0
Bell pepper	29.4	47.6
Bread	24.5	47.6
Milk	245.3	142.8
Feta cheese	29.4	----
Chick peas	39.2	----
Pasta	----	66.6
Pesto	----	33.3
Butter	----	9.5

Figure 1. Mean \pm SEM 7.5-hour concentrations of glucose (**A**) and insulin (**B**) in 16 subjects with type 2 diabetes mellitus after intake of a CRHP or CD breakfast and lunch respectively (mean of 2 consecutive days on each diet). ^aSignificant difference ($p < 0.05$) between CD and CRHP diet; CD, conventional diabetes; CRHP, carbohydrate reduced high protein.

Figure 2. Mean \pm SEM 7.5-hour concentrations of C-peptide (**A**) and ISR (**B**) in 16 subjects with type 2 diabetes mellitus after intake of a CRHP or CD breakfast and lunch respectively (mean of 2 consecutive days on each diet). ^aSignificant difference ($p < 0.05$) between CD and CRHP diet; CD, conventional diabetes; CRHP, carbohydrate reduced high protein;ISR, insulin secretion rate.

Figure 3. Mean \pm SEM 4.5-hour concentrations of GLP-1 (**A**) and GIP (**B**) in 16 subjects with type 2 diabetes mellitus after intake of a CRHP or CD breakfast (mean of 2 consecutive days on each diet). ^aSignificant difference ($p < 0.05$) between CD and CRHP diet; CD, conventional diabetes; CRHP, carbohydrate reduced high protein; GLP-1, glucagon-like peptide-1.

Figure 4. Mean \pm SEM 4.5-hour concentrations of glucagon (**A**) and PYY (**B**) in 16 subjects with type 2 diabetes mellitus after intake of a CRHP or CD breakfast (mean of 2 consecutive days on each diet). ^aSignificant difference ($p < 0.05$) between CD and CRHP diet; CD, conventional diabetes; CRHP, carbohydrate reduced high protein; PYY, polypeptide YY;GIP, gastric inhibitory polypeptide.

Figure 5. Mean \pm SEM 4.5-hour concentrations of CCK (**A**) in 16 subjects with type 2 diabetes mellitus after intake of a CRHP or CD breakfast and 7.5-hour composite satiety score on a 100 mm VAS scale (**B**) after intake of a CRHP or CD breakfast and lunch respectively (mean of 2 consecutive days on each diet). ^aSignificant difference ($p < 0.05$) between CD and CRHP diet; CD, conventional diabetes; CRHP, carbohydrate reduced high protein; CCK, cholecystokinin; VAS, visual analogue scale.

A moderate reduction in carbohydrate with an increase in fat and protein in the diet, compared with an energy-matched conventional diabetes diet, greatly reduced postprandial glucose excursions and resulted in increased satiety in patients with well controlled T2DM.

11. Afvigelser

11.1 Fagligt

Ingen

11.2 Økonomisk

Ingen

11.3 Tidsplan

6-9 måneders forsinkelse grundet engagement i andet sideløbende kostprojekt samt forsinkelse i analyse af blodprøver hos eksterne laboratorier.

12. Resultaternes betydning, herunder for mejeribrug

De indledende resultater tyder på, at man kan nedsætte type 2 diabetikers blodsukkerstigning efter et måltid samt sænke blodsukkerudsving og øge mæthed ved at udskifte nogle af kulhydraterne i maden med protein og fedt. Mejeriprodukter har generelt et lavt indhold af kulhydrater og er samtidig en god kilde til protein og fedt.

Resultaterne er opnået i et akutstudie på 2 x 2 dage, hvorfor der er behov for længerevarende undersøgelser for at vurdere effekten af en længerevarende kostomlægning med indtag af færre kulhydrater, flere proteiner og mere fedt.

13. Formidling og vidensdeling vedr. projektet

Artikler i internationale tidsskrifter:

2018 feb: 1. manuskript antaget og afventer publikation i peer reviewed tidsskrift: British Journal of Nutrition; Samkani et al. 'A carbohydrate reduced high protein diet acutely decreases postprandial and diurnal glucose excursions in type 2 diabetes patients'

Populærvidenskabelige artikler:

'Revurdering af kosten til diabetikere', Mælkeritidende Nov 13 2015

Studenteropgaver:

Kandidatopgave forsvaret februar 2018: 'The Acute Effects of a Carbohydrate Reduced High Protein Diet on Glycaemia and Glycaemic Variability in Well Controlled Type 2 Diabetes Mellitus: A Randomized Controlled Study', Mads Norvin Thomsen

Indlæg ved faglige kongresser, symposier etc.:

2016 juni: American Diabetes Association, posterpræsentation
2016 september: Ernæringsfokus, Landbrug & Fødevarer, oral præsentation
2016 november: LASSEN dagen Bispebjerg Hospital, posterpræsentation
2017 januar: Dansk Endokrinologisk Selskabs årsmøde, oral præsentation
2017 maj: North Europe Young Diabetologists meeting, oral præsentation
2017 juni: juni: American Diabetes Association, posterpræsentation
2017 november: LASSEN dagen Bispebjerg Hospital, high speed præsentation, modtager af LASSEN prisen

14. Bidrag til kandidat og forskeruddannelse

Kandidatopgave: 'The Acute Effects of a Carbohydrate Reduced High Protein Diet on Glycaemia and Glycaemic Variability in Well Controlled Type 2 Diabetes Mellitus: A Randomized Controlled Study', Mads Norvin Thomsen

15. Nye kontakter/projekter

Nyt projekt under gennemførelse:

CutDM-iso, ph.d.-studerende Mads Juul Skytte.

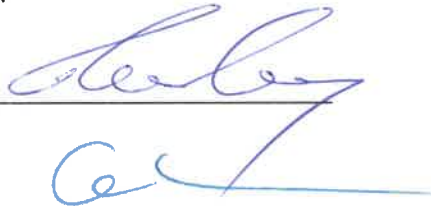
Nyt projekt planlagt:

CutDM-hypo, ph.d.-studerende Mads Norvin Thomsen

16. Underskrift og dato

Projektet er formeldt afsluttet, når projektleder og MFF-repræsentant (fx styregruppeformanden for den respektive styregruppe) har underskrevet slutrapporten.

Dato: 4. 4. 2018 Projektleders underskrift:



Dato: 27. marts 2018 MFF-repræsentants underskrift: Grith Mortensen