SLUTRAPPORT/FINAL REPORT
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Kjeld Hermansen:

Effekten af et præ-måltid af valle-protein på postprandiel stofskifte hos personer med metabolisk syndrom og type 2 diabetes.

Effect of a pre-meal of whey protein on postprandial metabolism in persons with the metabolic syndrome and type 2 diabetes

Mejeribrugets
ForskningsFond

Juli 2019

Final report

for collaborative projects funded via the Danish Dairy Research Foundation (DDRF)

1. Title of the project

In Danish: Effekten af et præ-måltid af valleprotein på postprandiel stofskifte hos personer med metabolisk syndrom og type 2 diabetes.

In English: Effect of a pre-meal of whey protein on postprandial metabolism in persons with the metabolic syndrome and type 2 diabetes

2. Project manager

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3. Other project staff

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Associate Professor Christian Würtz Heegaard, Aarhus University, Department of Molecular Biology and Genetics, Gustav Wieds Vej 10C, DK – 8000 Aarhus C. E-mail: cwh@mbg.au.dk. Was scheduled to perform the amino acid analyses. However, the task was taken over by Trine K. Dalsgaard due to apparatus failure.

Associate professor Trine Kastrup Dalsgaard, Aarhus University, Department of Food Science, Blichers Allé 20, building D20, DK – 8830 Tjele. E-mail: trine.dalsgaard@food.au.dk and Post doc, PhD Bashar Amer, now employed at Chr. Hansen's A/S, Copenhagen.

MSc Trine Nygaard Johansen, Department of Clinical Medicine – Endocrinology and Diabetes, Aarhus University Hospital, Tage-Hansens Gade 2, DK – 8000 Aarhus C. until September 2015. Present work place: BKI Foods A/S, Aarhus.

4. Sources of funding

DDRF has contributed with financial support to 1/3 PhD scholarship + costs of analytical tests; Danish Diabetes Academy provided 1/3 PhD scholarship and Aarhus University provided the remaining 1/3 of Ann Bjørnshave's PhD scholarship. Furthermore, the partners have received funding from Danish InnovationFund to the project MERITS (grant number 4105-00002B), for analyses of bone markers and other analyses, not covered by DDRF.

5. Project period

Project period with DDRF funding:	1 March 2014 – 28 February 2017
Revised, if necessary:	1 March 2014 – 30 June 2018

6. Project summary

In Danish:

Formålet med dette projekt er at klarlægge om en simpel kostintervention med et valleprotein præ-måltid forud for et fedtrigt måltid hos personer med præ-diabetes dvs. metabolisk syndrom (MeS) samt med type 2 diabetes (T2D) kan forbedre den metaboliske regulering, dvs. lipid-, kulhydrat- og inflammationsmetabolismen. Mere specifikt vil vi teste effekten af proteindosis og -kvalitet, tidsfaktoren samt sygdomsgraden.

Resultaterne viste, at et præ-måltid bestående af valleprotein før et fedtrigt måltid stimulerede insulin og glukagonsekretionen og reducerede blodglukose ved MeS, mens lipidmetabolismen vurderet som postprandiel triglycerid-, ApoB-48 og FFA-responserne ikke blev ændret. Både timingen af hvornår præmåltidet blev spist og proteinkvaliteten påvirkede hormonsekretionen og mavens tømningshastighed. Ved type 2 diabetes gav et valleprotein-præ-måltid øget insulin, glukagon og GIP-responser samt en forsinket mavetømningshastighed, men påvirkede ikke blodglukose eller lipidresponserne. Forskellene mellem T2D og MeS kan måske henføres til det lave antal deltagere med T2D. Resultaterne stammer alene fra akutte undersøgelser.

In English:

The aim of the project is to clarify if a simple dietary change in the diet with a whey protein pre-meal before a fat-rich meal to subjects with the pre-diabetes i.e. metabolic syndrome (MeS) and with type 2 diabetes (T2D) can improve the metabolic profile (lipid-, carbohydrate metabolism and inflammation). More specifically, the effect of protein-dose and -quality, time factor and degree-of-illness are tested.

In conclusion, a pre-meal of whey protein before a fat-rich meal stimulated insulin and glucagon secretion and reduced blood glucose in subjects with metabolic syndrome, whereas there was no impact on lipid metabolism assessed as postprandial triglyceride responses, ApoB-48 or free fatty acids. Both timing and protein quality affected hormone secretion (insulin and glucagon) and gastric emptying. In type 2 diabetes the whey protein pre-meal enhanced insulin,

glucagon, and GIP responses and delayed gastric emptying, but did not influence lipid or glucose responses. The difference from observations in subjects with metabolic syndrome may be ascribed to the low number of diabetic participants i.e. being underpowered. The results above are all from acute experiments.

7. Project aim

In Danish:

Formålet med dette projekt er at klarlægge, om en simpel kostintervention med en snack (præ-måltid) hos personer med præ-diabetes dvs. metabolisk syndrom (MeS) samt med type 2 diabetes (T2D) kan forbedre den metaboliske regulering dvs. lipidmetabolisme, kulhydratmetabolisme og inflammation. En komponent som valleprotein har en positive indvirkning på risikofaktorer for MeS og besidder en stærk insulinotropisk effekt og kan påvirke inflammationsmarkører. Fokus har indtil nu primært været rettet mod effekter af valleprotein på kulhydratmetabolismen og tarmhormoner som inkretiner fx i relation til et efterfølgende måltid (second meal effect). I dette studie vil vi tillige fokusere på et uudforsket område, nemlig hvorvidt valleprotein indtaget som et præ-måltid har en fordelagtig effekt på postprandiel lipæmi (PPL). Vi ønsker, i tre akutte, randomiserede, overkrydsningsstudier, at undersøge effekten af valleprotein som præ-måltid forud for et standardiseret, fedt-rigt måltid hos personer med MeS og T2D. Mere specifikt vil vi teste effekten af proteindosis og -kvalitet, tidsfaktoren samt sygdomsgraden.

Formålet med projektet er at identificere en simpel måde at forbedre metabolismen hos raske og hos personer med prædiabetes (MeS) og T2D. Vi vil ydermere undersøge plasma-responserne af aminosyrer og metaboliske markører, som ændres efter indtagelse af et præ-måltid af protein. *Vores hypotese er, at valleprotein indtaget som et præmåltid forud for et fedtrigt måltid vil forbedre de postprandielle responser af lipider (triglycerider (TG) og ApoB48), glukose og inflammations markører (MCP-1 og RANTES) hos personer samt at protein dosis, protein kvalitet, tidsfaktoren og sygdomsgrad påvirker responserne.*

In English:

The aim of the project is to clarify if a simple dietary change in subjects with the pre-diabetes i.e. metabolic syndrome (MeS) and with type 2 diabetes (T2D) can improve the metabolic profile (lipid metabolism, carbohydrate metabolism and inflammation). A dietary factor such as whey protein exerts positive effects on risk factors for MeS, possesses a potent insulinotropic action, and can modify inflammation markers. Until now the focus has primarily been related to the effect of whey protein on carbohydrate metabolism and incretin hormones e.g. in relation to the subsequent meal (second meal effect). In the present study, we will focus on an unexplored area to clarify if whey protein consumed as a snack (pre-meal) has beneficial effects on postprandiel lipidemia (PPL) and inflammation markers. We want in three acute, randomised, cross-over studies to study the effect of whey protein as pre-meal prior to a standardised, fat-rich meal in subjects with MeS and T2D. More specific the effect of protein dose and protein quality, time factor and degree-of-illness will be tested.

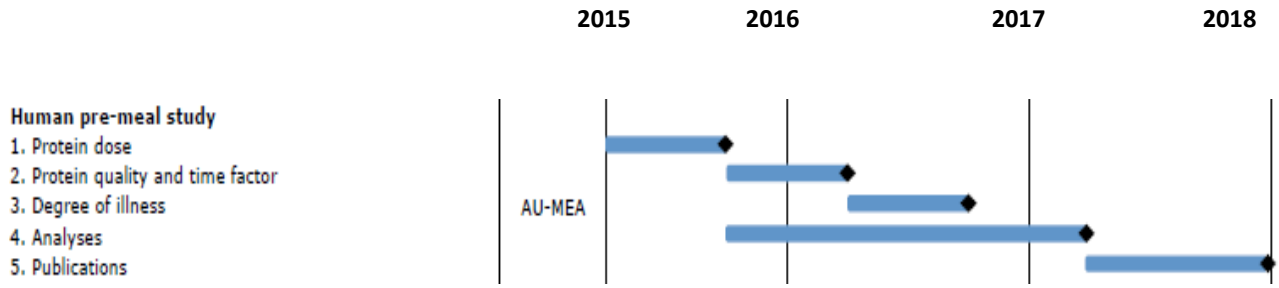
Hence, *the aim of this project is to identify a simple way to improve the metabolism in healthy, subjects with pre-diabetes (MeS) and T2D*. Secondly, the aim is to study the plasma responses of amino acids and metabolic markers that will change when consuming a pre-meal of protein. *We hypothesize that whey protein consumed as a pre-meal prior to a fat-rich meal will improve postprandial responses of lipids (triglycerides (TG) and ApoB48), glucose and inflammatory markers (MCP-1 and RANTES) in humans and that protein dose, protein quality, time factor and degree-of-illness will affect the response.*

8. Background for the project

The prevalence of obesity is increasing with epidemic proportions worldwide. Obesity leads to metabolic disturbances and amplifies the risk of pre-diabetes (i.e. MeS) and T2D. Obesity-related comorbidities include risk factor such as insulin resistance, hypertension and dyslipidaemia. Dyslipidaemia related to obesity and type 2 diabetes is characterised by low levels of high-density lipoprotein (HDL) particles, small and dense low-density lipoproteins and hypertriglyceridemia. Postprandial hypertriglyceridemia (PPL) is a distinct component of dyslipidaemia in T2D. The diet is one of the most important modifiable factors to PPL. The quality of dietary protein and fat influence the magnitude of PPL both in persons with or without T2D. Interestingly, consumption of whey protein from milk together with a fat-rich meal causes an acute reduction of PPL in people with or without T2D compared to casein, cod or gluten protein (Holmer-Jensen et al., Nutr. Res 2013 Jan; 33(1): 34-40; Mortensen et al., Am. J. Clin. Nutri. 2009 Jul; 90(1): 41-48). The observation, that a single dose of whey protein decreases the acute arterial exposure of small TG-rich lipoprotein particles and therefore potential reduce the risk of arteriosclerosis, is new and important.

Whey protein has a positive impact on MeS risk factors. It is well documented that whey protein triggers a pronounced insulin response, which has great importance for the postprandial blood glucose response. Previously, focus has been on the impact of the meal on blood glucose and insulin responses of the following meal, the so-called 'second-meal effect'. Based on the classic Staub-Traugott phenomenon, where glucose consumed prior to a meal improves the tolerance of carbohydrates in the following meal, we hypothesize that proteins profitably can be consumed as a pre-meal. Thus, proteins consumed as a pre-meal prior to a carbohydrate-rich meal increase the secretion of insulin, incretins (GLP-1, GIP and CCK) and reduce gastric emptying more than, if they are a part of the main meal. More recently, it was found that a small amount of whey protein and specific amino acids (Iso, Leu, Val, Lys, Thr) consumed as a pre-meal trigger a pronounced increase in the early postprandial insulin response. However, the importance of PPL for the risk of CVD of postprandial surpasses the role of hyperglycaemia.

9. Sub-activities in the entire project period



10. Project results

The overall aim of this project is to identify a simple way to improve the metabolism in healthy, subjects with pre-diabetes (MeS) and T2D. Secondly, the aim is to study the plasma responses of amino acids and metabolic markers that will change when consuming a pre-meal of protein. We hypothesize that whey protein consumed as a pre-meal prior

to a fat-rich meal will improve postprandial responses of lipids (triglycerides (TG) and ApoB48), glucose and inflammatory markers (MCP-1 and RANTES) in humans and that protein dose, protein quality, time factor and degree-of-illness will affect the response.

Study 1. The dose-response effect of a pre-meal of whey protein on postprandial lipaemia, glucose and hormone responses (Eur J Nutr. 2019 Mar;58(2):755-764. doi: 10.1007/s00394-018-1684-3)

We hypothesized that a pre-meal of whey protein (WP) consumed 15 min prior to a fat-rich meal reduces the postprandial

TG and chylomicron (ApoB-48) responses as well as glucose in a dose-dependent manner in subjects with MeS.

We tested the effects of three doses (0, 10 and 20 g) of WP on the postprandial responses of TG and ApoB-48 and concomitantly measured glucose, free fatty acids (FFA), insulin, glucagon, GLP-1, and GIP responses as well as appetite assessed using a Visual Analog Scale (VAS).

As seen below in Fig 1, we found that consumption of a WP pre-meal prior to a fat-rich meal did not affect TG and chylomicron (ApoB-48) responses. In contrast, the WP pre-meal stimulates insulin and glucagon secretion and reduces blood glucose as expected (Fig 2) and delays gastric emptying. Consequently, our study points to a differential impact of a WP pre-meal on lipid and glucose metabolism to a fat-rich meal in subjects with MeS. The differential effect on glucose and lipid metabolism of a pre-meal of whey protein is new and original. The positive effect of the whey pre-meal on blood glucose may at least in part be caused by the delayed gastric emptying.

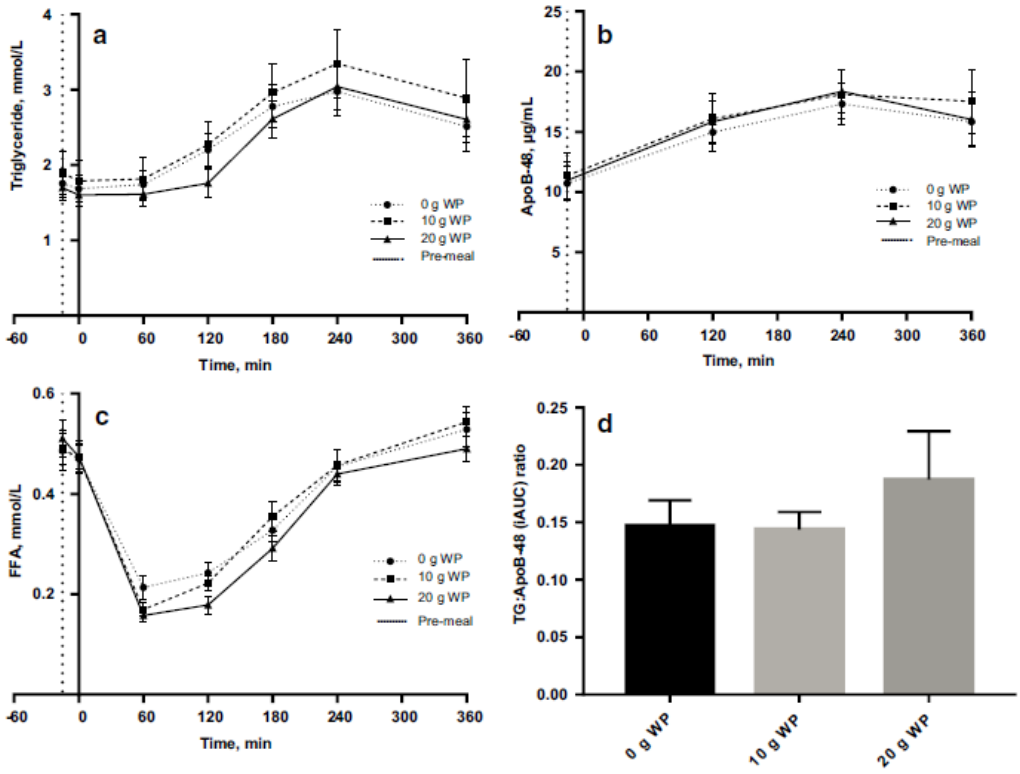


Fig 1. Postprandial plasma responses of **a** triglycerides (TG), **b** apolipoprotein B-48 (ApoB-48), **c** free fatty acids (FFA) after ingestion of pre-meal of 0, 10 or 20 g of whey proteins (WP), and **d** ratio between incremental area under the curve (iAUC) of TG and ApoB-48. Dotted vertical line (y= -15) indicates pre-meal consumption. Data are presented as mean +/- SEM, *n*=20. Data were analysed using analysis of variance (ANOVA) for repeated measurement. The hypothesis was to test if the response curves for the three interventions (0, 10 and 20 g WP) during the postprandial period were parallel. *ApoB-48* apolipoprotein B-48, *FFA* free fatty acids, *TG* triglycerides, *WP* whey proteins.

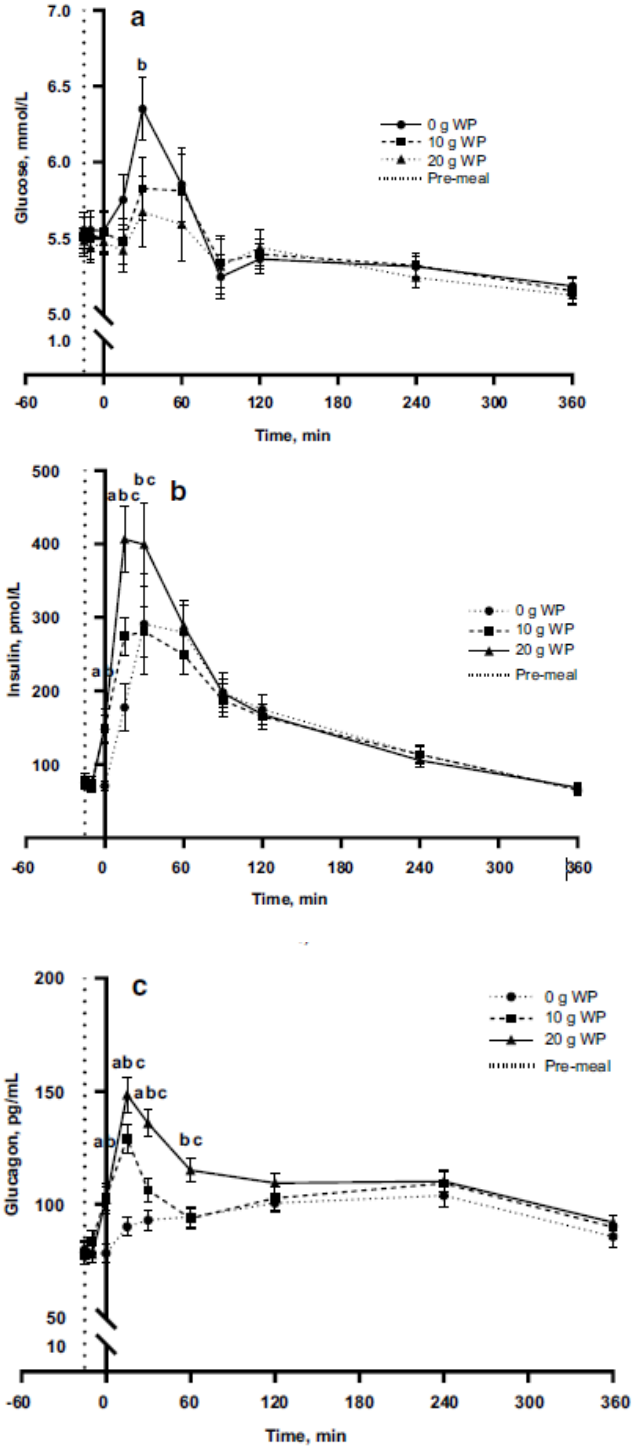


Fig 2. Postprandial responses of **a** insulin, **b** glucagon, and **c** glucose after ingestion of pre-meal of 0, 10 or 20 g of whey proteins (WP). Dotted vertical line (y=-15) indicates pre-meal consumption. Data are presented as mean +/- SEM, *n*=20. Data were analysed using analysis of variance (ANOVA) for repeated measurement. The hypothesis was to test if the response curves for the three interventions (0, 10 and 20 g WP) during the postprandial period were parallel. Differences between individual time points were analysed only if there was a significant interaction between intervention and time. [a] 0 vs 10 g WP; [b] 0 vs 20 g WP, [c] 10 vs. 20 g WP. *WP* whey protein.

Study 2. The protein quality of the pre-meal and the timing of the pre-meal (Br J Nutrition 2019, 121(3), pp. 312-321; DOI: 10.1017/S0007114518003264).

We hypothesised that a WP pre-meal (17.6 g protein) consumed 15 vs 30 min before a fat-rich meal reduces the post-prandial lipid response (PPL) in subjects with metabolic syndrome and that a WP pre-meal has more potent effects than casein and gluten pre-meals. Sixteen subjects with MeS completed an acute, randomised, crossover trial. WP pre-meals were consumed 15 and 30 min, and casein and gluten 15 min before a fat-rich meal. Blood samples were drawn 360 min postprandially to determine metabolite and hormone responses, S-paracetamol (for assessment of gastric emptying) and amino acids.

The amino acid composition is shown in Table 1.

We found, that insulin and glucagon responses were affected by both timing and protein type (for all $P<0.01$), with significantly higher concentrations for WP given at -15 min than at -30 min and higher responses compared to gluten for the first 30 min after pre-meal consumption (for all $P<0.05$). The PPL responses were changed neither by timing nor by protein type. Glucose-dependent insulinotropic peptide (GIP) but not glucagon-like peptide 1 (GLP-1) responses differed between the three protein types. S-paracetamol concentration was higher for WP (-30 min) than for WP (-15 min) 15 min after the main meal ($P=0.028$), and higher for casein and gluten than for WP at time point 30 min (for all $P<0.05$).

In conclusion, the PPL response was not changed by ingestion of a 17.6 g protein pre-meal – supporting project 1 - whereas both timing and protein quality affected hormone secretion (insulin and glucagon). In addition, WP (-15 min) delayed gastric emptying more than casein, gluten and WP (-30 min).

Study 3. Effects of a pre-meal whey protein on metabolic parameters in subjects with and without type 2 diabetes (Nutrients. 2018 Jan 25;10(2). pii: E122. doi: 10.3390/nu10020122).

The metabolic impact of a WP pre-meal before a fat-rich meal has not previously been studied in T2D. We know that the PPL is exaggerated in T2D, and that WP is a potent insulinotropic substance. Therefore, we hypothesized that a WP pre-meal before a fat-rich meal reduces TG and ApoB-48 responses more pronouncedly in subjects with T2D than in subjects without T2D. We also suggested that WP as a pre-meal is more advantageous in this respect than as part of the main meal. We tested our hypothesis by evaluating postprandial responses of TG, ApoB-48, non-esterified fatty acids (NEFA), insulin, glucagon, glucose, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and S-paracetamol, and by assessing appetite regulation (using a visual analogue scale (VAS)).

As seen in Fig 3, a WP pre-meal significantly increased mean postprandial concentrations of insulin ($P<0.0001$), glucagon ($P<0.0001$), and glucose-dependent insulinotropic peptide (GIP) ($P<0.0001$) in subjects with and without T2D. ApoB-48 iAUC was significantly higher ($P=0.0034$) and TG tended to be higher (NS) in T2D than in non-diabetic subjects. However, we detected no effects of the WP pre-meal on TG, ApoB-48, or non-esterified fatty acids responses to the fat-rich meal in either group. Paracetamol absorption i.e. gastric emptying was delayed by the WP pre-meal ($P=0.039$). In conclusion, the WP pre-meal induced similar hormone and lipid responses in subjects with and without T2D. Thus, the WP pre-meal enhanced insulin, glucagon, and GIP responses, but did not influence lipid or glucose responses. In addition, we demonstrated that a WP pre-meal reduced gastric emptying in both groups.

In conclusion, a pre-meal of whey protein before a fat-rich meal stimulated insulin and glucagon secretion and reduced blood glucose in subjects with metabolic syndrome, whereas there was no impact on lipid metabolism assessed as postprandial triglyceride responses, ApoB-48 or free fatty acids. Both timing and protein quality affected hormone secretion (insulin and glucagon) and gastric emptying. In subjects with type 2 diabetes the whey protein pre-meal enhanced insulin, glucagon, and GIP responses and delayed gastric emptying, but did not influence lipid or glucose responses. The difference from observations in subjects with metabolic syndrome may be related to the low number of diabetic participants in the present study. The results above are all from acute experiments. We do not know how the role of a protein pre-meal is in long-term studies and before other types of diets than the fat-rich meal e.g. low carb diet, Healthy Nordic diet and Mediterranean diet which are all promising diets for type 2 diabetic subjects.

Table 1. Nutrient composition and the relative amino acid composition of the three protein powders.

	Protein type		
	Whey	**Casein**	**Gluten**
Nutrient composition[1, 2]			
Amount of protein powder (g)	20	19	21
Total protein (g)	17.6	17.6	17.6
Total fat (g)	0.3	0.1	0.4
Total lactose (g)	<0.02	<0.06	-
Total energy (kJ)	310.6	305.0	314.0
Amino acid composition adjusted to WP (100) (relative (g))[3]			
Alanine	100	45	59
Aspartic acid (asparagine)	100	108	193
Cysteine	100	0	83
Glutamic acid (glutamine)	100	90	174
Glycine	100	52	98
Histidine	100	99	98
Isoleucine	100	49	45
Leucine	100	58	55
Methionine	100	84	66
Phenylalanine	100	106	147
Proline	100	764	908
Serine	100	77	135
Threonine	100	80	79
Tryptophan	100	92	91
Tyrosine	100	108	87
Valine	100	68	62

[1] Data on WP and casein are provided from Arla Foods Ingredients Group P/S, Viby J, Denmark and [2] data on gluten are provided from Reppe Lantmännen, Stockholm, Sweden. [3] We were not able to measure lysine and cystine in the protein samples, due to irregular shapes of gas chromatography mass spectrometry peaks.

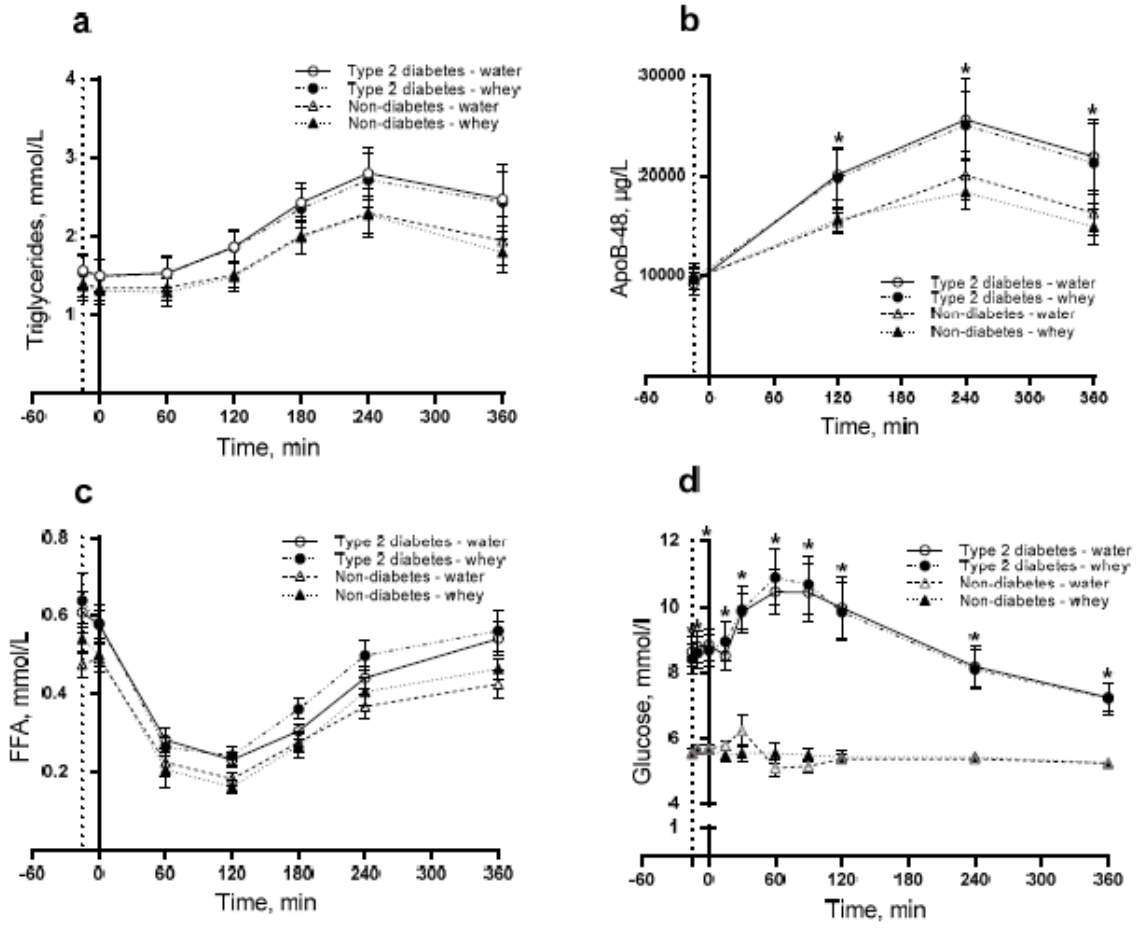


Fig 3. Postprandial responses of triglycerides (TG) (**a**); ApoB-48 (**b**); non-esterified fatty acids (NEFA) (**c**) and glucose (**d**). 12 T2D and 12 non-diabetic subjects were observed after consumption of 20 g whey protein (WP) or water as a pre-meal ingested 15 min prior to a fat-rich meal. Dotted vertical line (y=-15) indicates pre-meal consumption. Data are given as mean +/- standard error of the mean (SEM), *n* = 24. * indicates differences between subjects with and without type 2 diabetes. ANOVA for repeated measurements was used to examine the effect of diabetes, intervention and time on the postprandial responses.

11. Deviations

No scientific or financial deviations. The project was delayed due to Ann Bjørnshave's maternity leave.

12. The relevance of the results, including relevance for the dairy industry

In acute experiments, a pre-meal of whey protein before a fat-rich meal has a positive effect on glucose metabolism and blood glucose levels in subjects with pre-diabetes, whereas it had no impact on lipid metabolism. A pre-meal of whey protein appears more potent than e.g. a pre-meal of gluten protein. It may prove to be a simple way to improve metabolism in healthy, subjects with pre-diabetes (MeS) and T2D. It would be an easy and cheap way to improve health. However, further studies are needed focussing on the impact on people with pre-diabetes and type 2 diabetes being on relevant diets e.g. low card diets, healthy Nordic diets and Mediterranean diets over longer time. Our group is planning to pursue a long-term study with pre-meal whey protein in combination with a low-carb diet. If this turns out positive it would be relevant to continue with a combination with a healthy Nordic diet where we have carried out

a landmark study in a Nordic collaboration – *The SYSDIET Center of Excellence* – showing the positive effects of such a diet on cardiovascular risk markers in prediabetes. It would certainly be favourable if it is possible to reduce the liquid volume needed to dissolve the whey into and make further improvements with respect to the taste. If the experiments outlined turns out positive, there will be a large positive financial potential for the dairy industry.

13. Communication and knowledge sharing about the project

Papers in international journals:

Ann Bjørnshave, Kjeld Hermansen. Effects of Dairy Protein and Fat on the Metabolic Syndrome and Type 2 Diabetes, Rev. Diabet. Stud. 2014;11(2):153-66. doi: 10.1900/RDS.2014.11.153.

Mette Bohl, Ann Bjørnshave, Mette Krogh Larsen, Søren Gregersen, Kjeld Hermansen. The effects of proteins and medium-chain fatty acids from milk on body composition, insulin sensitivity and blood pressure in abdominally obese adults. Eur. J. Clin. Nutr. 2017;71(1):76-82. https://doi.org/10.1038/ejcn.2016.207

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. A pre-meal of whey proteins induces differential effects on glucose and lipid metabolism in subjects with the metabolic syndrome: a randomised cross-over trial. Eur J Nutr. 2019 Mar;58(2):755-764. DOI: 10.1007/s00394-018-1684-3

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. Pre-Meal Effect of Whey Proteins on Metabolic Parameters in Subjects with and without Type 2 Diabetes: A Randomized, Crossover Trial. Nutrients 2018;25;10(2). pii: E122. DOI: 10.3390/nu10020122.

Ann Bjørnshave, Trine Nygaard Johansen, Bashar Amer, Trine Kastrup Dalsgaard, Jens Juul Holst, Kjeld Hermansen. Pre-meal and postprandial lipaemia in subjects with metabolic syndrome: Effects of timing and protein quality (randomised cross-over trail). Br J Nutrition 2019, 121 (3): 312-321; DOI: 10.1017/S0007114518003264.

Pekmez CT, Bjørnshave A, Pratico G, Hermansen K, Dragsted LO. Pre-meal protein intake alters postprandial plasma metabolome in subjects with metabolic syndrome. Eur J Nutr 2020 ; 59, 1881–1894; https://doi.org/10.1007/s00394-019-02039-9

Easily read papers:

Ann Bjørnshave, Kjeld Hermansen. Kan mælkeprotein forebygge hjertekarsygdom? Mælkeritidende april 2015, 8: 10-11.

Kjeld Hermansen, Ann Bjørnshave Har et præmåltid protein positiv indflydelse på fedtstofskiftet? BestPractice 2017, August, 11(7):26-27 (Danish magazine for General Practitioners).

Ann Bjørnshave, Kjeld Hermansen. Valleproteiner før måltid kan måske hjælpe diabetikere. Mælkeritidende 2019, 16: 14-15.

Student theses:

Trine Nygaard Johansen *The effect of protein quality and time-factor by consumption of a Pre-meal on Postprandial Lipemia in Subjects with the Metabolic Syndrome,* MSc thesis (Molecular Nutrition and Food Technology) defended on 28 September 2018, Faculty of Science and Technology, Aarhus University.

Ann Bjørnshave *Acute effects of a pre-meal of whey proteins on postprandial lipaemia and glucose metabolism in subjects with metabolic syndrome and type 2 diabetes,* PhD thesis defended on 21 September 2018, Faculty of Health, Aarhus University.

Oral presentations at scientific conferences, symposiums etc.:

Mette Bohl, Ann Overgaard, Søren Gregersen, Kjeld Hermansen. *Dairy lipids, proteins and abdominal.* 32th International Symposium on Diabetes and Nutrition (DNSG - Diabetes Nutrition Study Group), Reykjavik, Iceland, June 2014.

Ann Bjørnshave, Christian Würtz Heegaard, Kjeld Hermansen*. Whey protein, postprandial lipidemia and cardiovascular disease: Evaluation of the effect of a pre-meal of whey protein on postprandial lipidemia in persons with the metabolic syndrome and type 2 diabetes.* Summer School on Diabetes and Metabolism, PhD Network on Diabetes and Metabolism, Gl. Avernæs, Denmark, September 2014.

Ann Bjørnshave, Christian Würtz Heegaard, Kjeld Hermansen. *Whey protein, postprandial lipemia and cardiovascular disease: effect of a pre-meal of whey protein on postprandial lipemia in subjects with the metabolic syndrome and type 2 diabetes.* Annual Workshop in Molecular Metabolism and Endocrinology, Aarhus, Denmark, October 2014.

Ann Bjørnshave, Christian Würtz Heegaard, Kjeld Hermansen. *Dose-response effect of whey protein consumed as premeal on postprandial lipemia in persons with the metabolic syndrome*. PhD day, Aarhus University, Denmark, January 2015.

Kjeld Hermansen, Ann Bjørnshave, Mette Bohl. *The effect of milk protein on metabolic parameters.* Symposium: 'Protein, training and weight loss', Center for Sports, Aarhus University, Denmark. 25 November 2015.

Mette Bohl, Ann Bjørnshave, Søren Gregersen, Kjeld Hermansen. *Effects of medium-chain saturated dairy fat on the body composition of abdominal obese subjects (DairyHealth): a 12-week, randomized, double-blinded, intervention study.* Abstract and poster presentations at 51th Annual Meeting, European Association for the Study of Diabetes (EASD), Stockholm, Sweden, 14-18 September 2015.

Ann Bjørnshave, Christian Würtz Heegaard, Kjeld Hermansen. *Dose-response effect of whey protein consumed as premeal on postprandial lipemia in subjects with the metabolic syndrome.* 75th Scientific Sessions, American Diabetes Association, Boston, USA, 5-9 June 2015, Abstract, Diabetes, June 2015, vol. 64, suppl. 1.

Kjeld Hermansen, Søren Gregersen, Mette Krogh Larsen, Ann Bjørnshave, Mette Bohl. *Beneficial effects of medium-chain saturated dairy fat on the body composition of abdominal obese subjects (DairyHealth): A 12-week, randomized, double-blinded, intervention study*. , Abstract, poster presentation and guided tour poster at 75th Scientific Sessions, American Diabetes Association, Boston, USA, 5-9 June 2015.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen*. Pre-meal of whey proteins induces differential effects on glucose and lipid metabolism in subjects with the metabolic syndrome.* Abstract and oral presentation at 34th International Symposium on Diabetes and Nutrition (DNSG - Diabetes Nutrition Study Group), Prague, Czech Republic, 29 June-1 July 2016.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. *Pre-meal of whey protein induces differential effects on glucose and lipid metabolism in subjects with the metabolic syndrome.* Symposium on 'Diet, Diabetes and the Metabolic Syndrome', The Novo Nordisk Foundation, Hellerup, Denmark, 25-26 August 2016.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. *Comparison of metabolic parameters to whey proteins consumed as a pre-meal in subjects with and without type 2 diabetes.* Abstract and oral presentation at Danish Diabetes Academy meeting, 1 November 2016.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. *Effects on metabolic parameters of whey proteins consumed as pre-meal in subjects with type 2 diabetes compared to healthy subjects.* MEA Research Symposium 2016, Aarhus, Denmark, 24 November 2016.

Ann Bjørnshave. *Whey Pre-meal: Does it have beneficial effects on metabolism?* Oral presentation at Arla Foods Ingredients Research Seminar, Aarhus, Denmark, 12-13 December 2016.

Kjeld Hermansen. *Impact of milk protein on metabolic parameters in Metabolic Syndrome and Type 2 Diabetes*. Oral presentation at Arla Foods Ingredients Research Seminar, Aarhus, Denmark, 12-13 December 2016.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. *Whey proteins consumed as a pre-meal - comparison of metabolic parameters in subjects with and without type 2 diabetes.* Poster presentation at PhD day 2017, Aarhus University, Denmark, 27 January 2017.

Kjeld Hermansen, Jens Juul Holst, Ann Bjørnshave. *Metabolic effects of a pre-meal of whey proteins in subjects with and without type 2 diabetes.* Poster presentation at American Diabetes Association's 77th scientific sessions, San Diego, California, USA 9-13 June 2017.

Ann Bjørnshave, Jens Juul Holst, Kjeld Hermansen. *Comparison of metabolic effects of a pre-meal of whey proteins in subjects with and without type 2 diabetes.* Oral presentation at Diabetes Nutrition Study Group (DNSG), Skagen, Denmark, 18-21 June 2017.

Kjeld Hermansen. *Can we prevent the Metabolic Syndrome with dairy products?* Invited lecturer at Diabetes Nutrition Study Group (DNSG), Skagen, Denmark, 18-21 June 2017.

Ceyda Tugba Pekmez, Ann Bjørnshave, Giulia Pratico, Kjeld Hermansen, Lars Ove Dragsted. *Differential response in postprandial plasma metabolomics with pre-meal whey protein intervention in subjects with metabolic syndrome – PREMEAL-1 STUDY.* Poster presentation, 10th MetaboMeeting, University of Birmingham, UK, 11-13 December 2017.

Oral presentations at meetings:

Kjeld Hermansen. *Mælkefedt, mælkeprotein og Metabolisk Syndrom.* Invited speaker at Mejeriforskningens dag 2015. Billund, Denmark, 23 April 2015.

Ann Bjørnshave, Kjeld Hermansen. *Effect of a pre-meal of whey protein on postprandial metabolism in persons with the metabolic syndrome and type 2 diabetes.* Danish Dairy Research Foundation, Health and Nutrition Group, Viby J, Denmark, 5 December 2016.

Kjeld Hermansen. *Forebyggelse af Metabolisk Syndrom ved hjælp af mejeriprodukter.* Invited speaker at Mejeriforskningens dag 2017, Billund, Denmark, 2 March 2017.

Ann Bjørnshave. *Whey protein containing pre-meals for patients with metabolic syndrome and type 2 diabetes.* Invited speaker at Mejeriforskningens dag 2019, Billund, Denmark, 27 March 2019.

Other:

Kjeld Hermansen. Videnskab .dk - *Tre fede mejeriprodukter om dagen kædes sammen med sænket dødelighed.* 12 September 2018. https://videnskab.dk/krop-sundhed/tre-fede-mejeriprodukter-om-dagen-kaedes-sammen-med-saenket-doedelighed

Kjeld Hermansen commentary *Mælk og yoghurt ser ud til at beskytte mod hjerte-kar-sygdomme.* UFL Videnskab nyt week 43, 18/10-2018. http://ugeskriftet.dk/videnskab/maelk-og-yoghurt-ser-ud-til-beskytte-mod-hjerte-kar-sygdomme

14. Contribution to master and PhD education

Trine Nygaard Johansen defended her Master thesis (Molecular Nutrition and Food Technology) *The effect of protein quality and time-factor by consumption of a Pre-meal on Postprandial Lipemia in Subjects with the Metabolic Syndrome* on 28 September 2018, Faculty of Science and Technology, Aarhus University.

Ann Bjørnshave defended her PhD thesis *Acute effects of a pre-meal of whey proteins on postprandial lipaemia and glucose metabolism in subjects with metabolic syndrome and type 2 diabetes* on 21 September 2018 at Faculty of Health, Aarhus University. As part of Ann Bjørnshave's trained, she stayed 4 months (March – June 2016) at Department of Analytical Pharmaceutical Chemistry, Uppsala University, Sweden. During the stay, Ann was introduced to metabolomics, to include a thorough theoretical and practical introduction to LC-MS and metabolomics analyses of samples from study 3.

15. New contacts/projects

Collaboration established with Professor Curt Pettersson and members of his staff: Jakob Haglöf; Mikael Engskog and Torbjörn Arvidsson, Department of Analytical Pharmaceutical Chemistry, Uppsala University, Sweden, where Anne Bjørnshave spent 4 months in 2016.

A collaboration has been established with Professor Steen Haugaard and Chief Physician Thure Krarup (CutDM) – both from Bispebjerg Hospital – the aim is to combine pre-meal whey protein and low-carbohydrate diets. The project is planned to be carried out in collaboration with Professor Emma Stevenson and Post doc Dan West from Newcastle University, with a special focus on the long-term effects of providing a pre-meal.

16. Signature and date

The project is formally finalised when the project manager and DDRF-representative (e.g. steering committee leader) have signed this final report.

Date: 15 July 2019, Signature, Project manager:

Date: 15 July 2019 Signature, DDRF-representative: