Press release

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Basic information

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Department of: Public Health

Main supervisor: Niels Møller

Title of dissertation: Human metabolism during combined inflammation, fast and bedrest and in response to oral protein and ketone supplementation

Date for defence: 4/11-2020 at (time of day): 13.30 Place: Aarhus Universitetshospital, lokale J115-139 (og via Zoom)

Press release (Danish)

Indtag af protein og ketonstof har muskelbevarende effekter under eksperimentiel febersygdom.

Et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Maike Mose, der forsvarer det d. 4/11.

Muskeltab er hyppigt under sygdom og skyldes kombinationen af en lang række faktorer, hvoraf inflammation, sengeleje og underernæring er vigtige faktorer. Muskeltab er stærkt associeret med øget dødelighed. Indtag af protein og indgift af ketonstof har begge vist muskelbevarende effekter, men effekterne hver for sig eller i kombination under sygdom, er ikke velbelyste. Ultimativt vil forebyggelse af muskeltab potentielt kunne forbedre patienters helbred og livskvalitet og dermed sænke de samfundsøkonomiske udgifter.

Denne ph.d. afhandling belyser forskellige ernæringsprodukters muskelbevarende effekter under eksperimentiel sygdom i tre forskellige studier. I Studie A inducerede vi en tilstand, som imiterede sygdom. Sygdomsmodellen bestod af kortvarig feber (lipopolysaccharide(LPS)-induceret inflammation) kombineret med 36 timers faste og sengeleje. Vi fandt at sygdomsmodellen øgede energiforbruget og forårsagede et skift i brændstof, således at kroppen frisatte og forbrændte mere fedt sammenlignet med den raske kontrol situation (CTR). Desuden blev kroppen mindre følsom for hormonet insulin under sygdom.

Studie B var et randomiseret, dobbeltblindet overkrydsningsforsøg på raske unge mænd, hvor vi brugte sygdomsmodellen til at undersøge de muskelbevarende effekter af 3 forskellige mælkeproteiner med forskelligt leucinindhold (kasein ~10%, valle ~12% og β-lactoglobulin ~16%). Vi fandt sammenlignelige muskelbevarende effekter efter indtag af de 3 proteiner. β-lactoglobulin øgede insulin niveauerne betragteligt sammenlignet med de andre 2 proteiner. Vi fandt desuden, at β-lactoglobulin øgede hormonet GIP (gastric inhibitory polypeptide).

I studie C kombinerede vi 36 timers faste og sengeleje med 2 x LPS, hvilket imiterede forlængede det inflammatoriske respons. Her undersøgte vi de metaboliske effekter af eksperimentiel sygdom sammenlignet med en rask kontrol situation med og uden protein tilskud i et randomiseret overkrydsningsforsøg. Desuden undersøgte vi om det muskelbevarende respons kunne forbedres ved at tilføje ketonstof til protein sammenlignet med protein (+isokalorisk fedt) alene. Vi fandt at sygdomsmodellen inducerede en inflammatorisk, katabol tilstand med øget energi forbrug, samt øgede frie fede syrer, kortisol og glukagon niveauer i blodet. Muskel protein syntesen var nedsat (men uændret netbalance), og vi så hæmmet fosforylering af mTOR og 4EBP1 i sygdomsmodellen sammenlignet med den raske kontrol situation. Under protein indtag øgedes muskelopbygningen og aktiviteten af mTOR og 4EBP1 mere under sygdom end i den raske kontrol situation, således at

identiske absolutte niveauer blev opnået. Dette tyder på, at muskler kan kompensere for den nedsatte basale muskelopbygning under experimentel sygdom. Vi fandt at protein+keton og isoleret protein havde sammenlignelige muskelbevarende effekter (muskel netbalance), dog gennem forskellige mekanismer: protein+keton nedsatte primært proteinnedbrydningen, hvorimod isoleret protein primært øgede proteinopbygningen. Faktisk så det ud til at muskelaminosyreomsætningen blev betragteligt nedsat når keton blev tilsat proteinet.
Vi konkluderer, at vi succesfuldt inducerede en eksperimentiel inflammatorisk tilstand som minder om klinisk inflammatorisk sygdom, og som kan være værdifuld i fremtidig muskelbevarende forskning. Om det insulinotrope β-lactoglobulin respons har glukosesænkende effekter i f.eks. diabetes patienter, kunne være interessant at undersøge. At keton ser ud til at hæmme den ellers velkendte protein-stimulerende effekt på muskelopbygningen, rejser mange spørgsmål omkring potentielle langtidseffekter af BHB – Særligt i atleter hvor indtag af keton aktuelt er særlig udbredt.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 4/11 kl. 13.30 i auditorium J115-139, Aarhus Universitets Hospital, Palle Juul Jensens Boulevard 99, Aarhus N (Og via Zoom). Titlen på projektet er ”Human metabolism during combined inflammation, fast and bedrest and in response to oral protein and ketone supplementation”. Yderligere oplysninger: Ph.d.-studerende Maike Mose, e-mail: maikmose@rm.dk, tlf. 28189854.

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Press release (English)

The muscle preserving effects of different dairy proteins and ketone bodies in a human model of inflammatory disease.

The project was carried out by Maike Mose, who is defending her dissertation on 4/11.

Disease-induced muscle loss is common, and, most often, caused by a combination of inflammation, bedrest and malnutrition. Loss of muscle mass is strongly associated with increased mortality. Protein and ketone bodies have muscle-preserving effects, but knowledge about their isolated or combined effects during disease is sparse. Ultimatively, preventing muscle loss could improve the prognosis of patients, but also lower the socio-economic costs. This phD dissertation sheds light on the muscle anabolic effects of different nutritional supplements during experimental diseased conditions in 3 different trials.

In Trial A, a disease model comprising lipopolysaccharide (LPS)-induced inflammation combined with a 36-h fast and bedrest, the late phase of clinical inflammatory conditions were mimicked. We found that experimental diseased conditions increased energy expenditure and the utilization of fat compared with control conditions.

Trial B was a randomized, double-blinded crossover design in healthy young men, where the muscle preserving effect of 3 dairy proteins differing in leucine content (casein (CAS) ~10%, whey (WHE) ~12%, β-lactoglobulin (BLG) ~16%) was investigated using the disease model. We found that CAS, WHE and BLG had similar muscle preserving effects. BLG increased insulin concentrations compared with both CAS and WHE. Additionally, BLG increased gastric inhibitory polypeptide (GIP) concentrations compared with CAS and WHE, whereas plasma glucose concentrations changed similarly between interventions.

In Trial C, a similar disease model comprising dual LPS-exposure combined with a 36-h fast and bedrest, mimicking more prolonged and ongoing inflammation, we investigated the metabolic shift compared with control conditions with and without a protein beverage. Additionally, we investigated whether the addition of ketone bodies to protein (ketone+protein) could potentiate the muscle anabolic response compared with isolated protein (+isocaloric fat) during diseased conditions. This disease model markedly increased energy expenditure and free fatty acids, glucagon and cortisol concentrations in the blood and decreased muscle protein synthesis (without alterations in muscle net balance) and decreased mTOR and 4EBP1 phosphorylation compared with CTR. Upon protein ingestion, muscle protein synthesis and phosphorylation of mTOR and 4EBP1 increased more during diseased conditions compared with control reaching similar absolute levels. This indicates that the muscle during "inflammation, fast and bedrest" is able to compensate for the lower muscle synthesis at baseline. We found a similar increase in muscle net balance following ketone+protein and protein intervention, but through distinct mechanisms. Interestingly, when ketone and protein were co-administered, the protein-stimulatory effect on muscle protein synthesis was completely inhibited, together with an overall reduction in muscle amino acid turnover.

In conclusion, we successfully introduced catabolic inflammatory hypermetabolic disease models that mimic important aspects of clinical disease, and that may have implications in future anti-catabolic intervention studies. The BLG-mediated insulinotropic effect may have implications in a hyperglycemic population like, e.g., diabetic patients. Interestingly, we found that addition of ketone to protein completely inhibited the protein-stimulatory effect on muscle protein synthesis. This finding raises questions regarding the effects of long-term ketone use, especially in athletes where induction of exogenous ketosis is currently widespread.

The defence is public and takes place on 4/11 at Aarhus University Hospital in J115-139 , Palle Juul Jensens Boulevard 99, Aarhus N (and via Zoom). The title of the project is "Human metabolism during combined inflammation, fast and bedrest and in response to oral protein and ketone supplementation". For more information, please contact PhD student Maike Mose, email: maikmose@rm.dk, Phone +45 28189854.

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