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Original article

Rational and design of an overfeeding protocol in constitutional thinness: Understanding the physiology, metabolism and genetic background of resistance to weight gain[☆]

Protocole de surnutrition chez les maigreurs constitutionnelles : comprendre la physiologie, le métabolisme et la génétique de la résistance à la prise de poids

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Abstract

Background. – Constitutional thinness (CT) is a natural state of underweight (13–17.5 kg/m²) without the presence of any eating disorders and abnormal hormonal profile, and with preserved menses in women. We previously conducted a four-week fat overfeeding study showing weight gain resistance in CT women and one of our main results was the identification of an energy gap: a positive energy balance (higher energy intake than energy expenditure). **Objective.** – This new overfeeding study is designed to confirm the energy gap and propose mechanistic hypothesis. **Design.** – A 2-week overfeeding (daily consumption of one bottle of Renuityl[®] Booster (600 kcal, 30 g protein, 72 g carbohydrate, 21 g fat) on top of the dietary intake) is performed to compare 15 women and men in each CT group (Body Mass Index [BMI] < 18.5 kg/m²) to their controls (BMI 20–25 kg/m²). Bodyweight, food intake, energy expenditure (canopy, calorimetric chamber and Actiheart), body composition (DXA), appetite regulatory hormone profiles after a test meal, proteomics, metabolomics, urinary metabolic profiles, stool microbiome and lipids, fat and muscle transcriptomics are monitored before and after overfeeding. **Results and conclusions.** – Data inter-linking will be able to be established with results of this study. The findings could possibly open to therapeutic approaches to help CT patients to gain weight as well as provide a better understanding of energy regulation with regard to treat obesity (resistance to weight loss), a mirror image of CT (resistance to weight gain).

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Keywords: Overfeeding; Constitutional thinness; Appetite regulatory hormone; Energy expenditure; Metabolomics; Proteomics

[☆] This study is registered in Clinical Trial.gov, no. NCT02004821 (<https://clinicaltrials.gov/ct2/show/NCT02004821?term=thinness&rank=3>).

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Résumé

Contexte. – La maigreur constitutionnelle (MC) est un état physiologique de maigreur (13–17,5 kg/m²) sans trouble du comportement alimentaire, avec des marqueurs biologiques de dénutrition et la conservation de l'axe gonadotrope. Dans un travail préliminaire de 4 semaines de surnutrition lipidique, nous avons montré une résistance à la prise de poids chez la MC malgré un gap énergétique positif (apports supérieurs aux dépenses). **But.** – Ce nouveau protocole de surnutrition doit confirmer ce gap énergétique et proposer des hypothèses mécanistiques. **Protocole.** – Quinze hommes et femmes dans chaque groupe MC (indice masse corporelle [IMC] < 18,5 kg/m²) ou témoins (IMC 20–25 kg/m²) seront soumis à une surnutrition pendant 2 semaines avec du Rentryl® Booster, oral (600 kcal, protéines 30 g, glucides 72 g, lipides 21 g) en plus de l'apport alimentaire habituel, l'apport alimentaire, la dépense énergétique (canopi, chambre calorimétrique et Actiheart), la composition corporelle (DXA), les hormones régulatrices de l'appétit après un repas test, le métabolome urinaire, le microbiote des selles, la transcriptomique du tissu adipeux et musculaire seront évaluées avant et après la surnutrition. **Résultats et conclusions.** – La confirmation du gap énergétique dans la MC femme et homme sera mis en relations avec les résultats des explorations réalisées. Les hypothèses pourraient être appliquées à l'obésité une résistance à la perte de poids, image en miroir de la MC résistance à la prise de poids.

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Mots clés : Surnutrition ; Maigreur constitutionnelle ; Hormone régulatrice de l'appétit ; Dépense énergétique ; Métabolomiques ; Protéomiques

1. Abbreviations

AEE	activity energy expenditure
AN	anorexia nervosa
BMI	body mass index
CO ₂	Carbon Dioxide
CT	constitutional thinness
DEBQ	Dutch Eating Behavior Questionnaire
DNA	Deoxyribonucleic Acid
DRI	Dietary Reference Intake
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - 4th Edition
DXA	Dual-energy X-ray absorptiometry
DPX-L	Lunar Prodigy Dual-Energy X-ray absorptiometry
EDE	Eating Disorder Examination Questionnaire
EDI	Eating Disorder Inventory
EE	energy expenditure
EI	energy intake
FFA	free fatty acids
FFM	free fat mass
FM	fat mass
FT	free triiodothyronine
GLP-1	glucagon-like peptide type 1
HR	heart rate
HR-pQCT	high-resolution peripheral quantitative computed tomography
IGF-1	insulin-like growth factor-1
MOSPA	Monica Optional Study of Physical Activity
O ₂	Oxygen
PAL	physical activity level
PYY	peptide tyrosine tyrosine
REE	resting energy expenditure
RT-qPCR	quantitative reverse transcription polymerase chain reaction
TEE	total energy expenditure
WHO	World Health Organization

2. Introduction

Constitutional thinness (CT) is a natural state of underweight [1,2] according to the WHO's definition (BMI under 16.5 kg/m²) [3]. Despite BMI as low as in anorexia nervosa (AN) patients, CT do not exhibit psychological or biological features commonly seen in AN [4,5] and often consult for bodyweight gain desire. CT women display normal menstruation indicating a normal nutritional status [2]. Growth curves show bodyweights of CTs remain in the lower percentiles for gender and ethnicity throughout their lifetime [6]. Family trees analysis shows significant familial aggregation [6].

CT appears to be a mirror image to obesity. Many features in CT, such as gut hormones, important regulators of energy homeostasis [7], have an opposite profile to that seen in obese. The obese have low plasma ghrelin concentration [8] and reduced/blunted Peptide Tyrosine Tyrosine (PYY) and Glucagon-Like Peptide-1 (GLP-1) [9–11]. While in the CT population, ghrelin is in the normal range [12] and PYY is high all along the nictemeral [2]. This anorexigenic/satietyogenic hormones profile could be considered as a physiological factor integrating the underweight steady state of CT [12].

We conducted a preliminary study [13], in which eight CT women and eight control women (BMI between 18.5 and 25 kg/m²) underwent a four-week fat overfeeding (630 kcal/day). Results showed an increased basal anorexigenic tone in CT during the study indicating an adaptation against the enforced overeating process, thus, a resistance to weight gains in CT. The food stress revealed an earlier postprandial peak in anorexigenic PYY, accounting for smaller meals and frequent snacking in CT. Analysis of energy balance demonstrated no increase in physical activity in both CT and controls showing no compensatory behaviors. At the end of the overfeeding, we observed an increase in resting energy expenditure only in CT group, despite a paradoxical positive energy balance of approximately 450 kcal/day during the overfeeding period. The first assumption of this energy gap observed in CT was secondary and/or additional energy expenditure (EE) pathways highly specific to CT, which could be linked to non-exercise

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