



Letter to the Editor

Invited Letter to Editor in response to: Constitutional thinness: body fat metabolism and skeletal muscle are important factors

Our research group recently published a systematic review discussing the criteria actually used in the definition and diagnosis of constitutional thinness (CT)⁽¹⁾. Our main aim was to systematically identify the inclusion criteria used in any available clinical trial that enrolled participants with CT. Despite the heterogeneity of the criteria and thresholds used in the thirty-five reviewed studies, the following points were frequently identified: no eating disorder, no associated disease, no over-exercising, no amenorrhoea, weight gain resistance and stable body weight. As also pointed out by our analysis, most of the included clinical trials defined a threshold of thinness in their inclusion criteria using BMI cut-offs and less frequently the percentage of body fat. In his recent and relevant letter to the Editor, Dr Maffetone⁽²⁾ highlighted the quality and pertinence of our work, suggesting, however, to reinforce the consideration of both body fat metabolism (pointing moreover the limitation induced by the use of BMI only) and skeletal muscle strength that might be of importance when it comes to individuals with CT.

We would like here to thank Dr Maffetone for his encouraging and constructive comment and collectively agree that body fat is a highly important criterion to consider in CT, especially given the recent study that showed smaller adipocytes but higher mitochondrial respiratory capacities in adipose tissue of CT participants⁽³⁾. Our systematic review, which exclusively focused on the inclusion criteria used in available publications, identified only two studies that considered body fat percentage in their inclusion criteria – enrolling participants with a body fat below 20%. While few studies included participants with CT on the basis of body fat, many have used this criterion as an outcome and showed that individuals with CT present non-blunted values, unlike anorectic people^(4,5). These results therefore suggest that people with CT would be underweight, but not underfat. If this were to be confirmed, CT diagnosis could be supported by a state of underweight not associated with underfat, but rather, on the contrary, with ‘non-blunted’ fat. In accordance with the comment and publications of Dr Maffetone⁽⁶⁾, the non-blunted fat mass percentage in CT could account for the relatively healthy state observed in this population.

Similarly, we definitely agree that skeletal muscle is an important factor that can influence an appearance of thinness – for instance in the case of cachexia or sarcopenia, as rightly pointed out by Dr Maffetone. CT is not pathology induced and does not specifically concern elderly people (the mean ages of CT participants ranged from 19.4 to 42.4 years in the reviewed articles) but may still be linked to skeletal muscle issues. This hypothesis might be further supported by the high resting metabolic rate

to fat-free mass ratio of CT participants observed in some studies^(4,7). Our group recently performed histochemical analyses from muscle biopsies collected in CT volunteers, in order to characterise their muscle phenotype and assess potential adaptations^(8,9). According to our results, individuals with CT, in agreement with their lower muscle mass^(4,7-9), showed smaller fibre cross-sectional areas of all muscle fibre types compared with normal-weight participants^(8,9). They also have a lower oxidative profile with a lower capillary supply, a lower proportion of type I slow oxidative fibres in favour of a high proportion of type IIX fast glycolytic fibres, a lower citrate synthase enzyme activity and a down-regulation of genes involved in the metabolism of TAG – fat storage-inducing transmembrane 1 (FITM1) and 2 (FITM2)^(8,9). Muscle fibres of CT individuals also presented lower intramuscular TAG and lower glycogen content⁽⁹⁾. CT individuals seem to present an untypical muscle phenotype, and these recent results reinforce the need for further explorations of muscle physiology but also functionality in such individuals. This is, once more, absolutely in line with the comment from Dr Maffetone and definitely raises the need for the evaluation of physical capacities in this population. It might be of particular interest to assess parameters such as strength, aerobic capacity or metabolic flexibility, in the light of our histological observations. Despite the importance of considering muscle tissue in the context of CT, this was, to the best of our knowledge, only explored in our two previous studies so far^(8,9). It therefore seems essential to achieve greater scientific and statistical power before integrating some criteria relative to muscle function in the diagnosis of CT.

While our review aimed at systematically reporting the criteria used so far in the inclusion of participants with CT⁽¹⁾, it also pointed out that body fat and skeletal muscle were generally not considered in these criteria and were evaluated in few studies only. Our conclusions and the constructive comment from Dr Maffetone call for further physiological and functional investigations of both adipose and muscle tissues in individuals with CT, to better understand and diagnose this condition and hopefully propose appropriate and effective intervention strategies favouring weight gain in this population.

Méline Bailly^{1,2}, Natacha Germain^{2,3}, Bogdan Galusca^{2,3},
 Daniel Courteix¹, David Thivel¹ and Julien Verney¹

¹Université Clermont Auvergne, CRNH, AME2P, 63000
 Clermont-Ferrand, France

²*Eating Disorders, Addictions and Extreme Bodyweight Research Group (TAPE) EA 7423, Jean Monnet University, 42000 Saint-Étienne, France*

³*Division of Endocrinology, Diabetes, Metabolism and Eating Disorders, CHU Saint-Étienne, 42000 Saint-Étienne, France*
email melina.bailly@uca.fr

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