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Body composition and bone mineral density in Huntington's disease

Renata Costa de Miranda Ph.D. [a,b], Nicola Di Lorenzo M.D. [c,*], Angela Andreoli M.D., Ph.D. [d], Lorenzo Romano M.D. [e], Gemma Lou De Santis M.D. [e], Paola Gualtieri Ph.D. [a], Antonino De Lorenzo M.D., Prof. [f,g,*]

[a] PhD School of Applied Medical-Surgical Sciences, University of Rome Tor Vergata, Rome, Italy
[b] CAPES Foundation, Ministry of Education of Brazil, Brasília, Brazil
[c] Department of Surgical Sciences, University of Tor Vergata, Policlinico Tor Vergata, Rome, Italy
[d] Department of System Medicine, Human Physiology and Nutrition Unit, University of Rome Tor Vergata, Rome, Italy
[e] Specialisation School of Food Science, University of Rome Tor Vergata, Rome, Italy
[f] Section of Clinical Nutrition and Nutrigenomic, Department of Biomedicine and prevention, University of Rome Tor Vergata, Rome, Italy
[g] Casa di Cura Madonna dello Scoglio, Cotronei, Italy

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ABSTRACT

Objective: Understanding the body composition (BC) of patients with Huntington's disease (HD) could help to delay disease progression and improve treatment efficacy. The aim of this study was to assess BC parameters, including bone mineral density (BMD), and to find new biomarkers that can be early indicators for weight loss in patients with HD.

Methods: Twenty-one age- and sex-matched patients with HD and 29 healthy controls (CT) were enrolled. For each patient, body weight (BW), height, and body mass index (BMI) were evaluated. BC and BMD were measured by dual-energy x-ray absorptiometry. Subsamples were created according to sex and percent fat mass (FM) (obese and nonobese). All analyses were carried out using SPSS version 23.

Results: In all comparisons, BMD and T-score were lower in the HD group, but were not correlated with lean body mass (LBM) or FM. In the HD group, LBM and truncal fat were mostly reduced, except in women with HD whose BC appeared to be less affected by the disease than men. Furthermore, LBM ($r = 0.80$) and truncal fat ($r = 0.68$) were better correlated with BW than BMI ($r = 0.56$).

Conclusion: Complete BC assessment can be crucial for preventive interventions and prognosis definition in patients with HD. New biomarkers such as BMD, LBM, and truncal fat can be early indicators of weight loss in patients with HD.

Introduction

Huntington's disease (HD) is a neurodegenerative disorder, autosomal dominant triplet-repeat that is due to expansion of the *IT-15* gene on chromosome 4 coding for the huntingtin protein [1]. HD is clinically characterized by motor, neuropsychiatric, and systemic symptoms. Some characteristic features are impairment of involuntary (chorea) and voluntary movements, dysarthria, and balance problems. Cognitive functions are progressively compromised—initially only a few skills of thought, but later the decay becomes general. Depression and obsessive-compulsive disorder are commonly seen in patients with HD. Moreover, mania, apathy, and social withdrawal are present, but less common [2]. HD does not only affect the nervous system; in fact, the production of huntingtin protein is ubiquitous throughout the body, affecting all organs and systems of humans and mammals [3,4].

To our knowledge, the exact role of huntingtin has not been established, but its presence is detected in many cellular mechanisms such as vesicle trafficking and transcription [5]. The non-neuronal abnormalities of advanced HD are cardiac failure and infertility [6–8]. Among the peripheral alterations in the digestive tract and metabolism are xerostomia, which affects adverse swallowing and mastication [9]; reduced production of ghrelin after disease evolution [10]; reduced secretion of insulin owing to pancreatic β-cells atrophy; and liver damage, breaking down urea and increasing ammonia levels in the blood [11–15]. A common non-neural manifestation of HD is weight loss, typically progressive, that begins as a minor sign of the disease and can lead to a malnutrition or cachexia, which are frequently seen in neurodegenerative disorders [16,17]. Studies have indicated hyperactivity and anorexia [18] as the main causes of weight loss; however, the early onset of weight loss makes it doubtful that these are the causes.

* Corresponding author. Tel.: +39 067 259 6856; Fax: 00390672596853.
E-mail address: Delorenzo@uniroma2.it (A. De Lorenzo).

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Other authors have identified the progressive weight loss as the result of increasing energy expenditure [10], but the causes remain unclear. It has been observed that patients with a high body mass index (BMI) in early stage of HD have presented a slower progression of disease. Consequently, weight loss could work as a potential prognostic index to prevent complications [19]. Behind the weight loss there are hidden changes in the body compartments: In the late phase of HD, obvious reduction of muscle mass, such as sarcopenia [20–22], and reduction of bone demineralization, such as osteoporosis [23], are present. Beginning phases of bone and muscle wasting are important clinical signs that allow a timely, effective treatment to prevent disability and fragility fractures. The early detection of body compartment changes and organic wasting is possible through the assessment of the patient's body composition (BC) and nutritional status. Indeed, BC assessment has many clinical uses, such as assessing disease progression or treatment efficacy. However, in clinical routine practice, with the exception of specialized centers, weight and height measurements are more frequently used. BC and its relationship with changes at the onset of disease, during treatment, and in the long-term follow-up are far more important in the management of diseases. The aim of this study was to assess bone, lean body mass (LBM), and fat mass (FM) in early HD.

Materials and methods

Participants

Fifty individuals, 18 to 65 y of age, were enrolled in this study. Of these, 21 had early-stage HD (10 men and 11 women), according to Gaba et al. [24], and were institutionalized at Nova Salus (Aquila, Italy). Twenty-nine age- and sex-matched healthy adults (15 men and 14 women) served as the control (CT) group. They were recruited from the patients' families or were without genetic mutation to minimize the effects of environmental conditions. Subsamples were generated according to dual-energy x-ray absorptiometry (DXA) FM (%) and classified as non-obese and obese. Comparisons between age- and sex-matched CT and patients with HD for the same parameters were carried out in each new sample. In the non-obese subsample, there were 11 patients with HD and 15 healthy controls. The obese subsample consisted of 10 patients with HD and 14 healthy controls. Exclusion criteria were presence of diabetes mellitus or treatment with a neuroleptic, oral hypoglycemic drug or insulin; thyroiditis; other neurodegenerative, heart, pulmonary, or skeletomuscular diseases; pregnancy or breastfeeding; active cancer and medication known to affect metabolism or endocrine function. Before participation, all participants signed an informed consent form that outlined the experimental procedures for this study, which were approved by the ethical committee of the Fondazione Nova Salus.

Body weight and height

Body weight (BW) was measured, without clothing except underwear, to the nearest 0.1 kg on a calibrated scale (Invernizzi, Rome, Italy). Height (H) was measured, without shoes, to the nearest 0.5 cm using a stadiometer (Invernizzi). BMI was calculated as BW (kg) divided by H squared (m^2).

DXA measurement

Total body mineral density (BMD; g/cm^2), FM (kg), and LBM (kg), in addition to segmental compartments, were measured using DXA (Model DPX, Lunar, Madison, WI, USA; software revision 12.6). DXA uses a constant potential x-ray source at 12.5 fJ and a K-edge filter to achieve a congruent beam of stable dual-energy content (40 and 70 keV). The coefficient of variation (CV) for bone measurements is <1%; CV on this instrument for five participants scanned six times over a 9-mo period were 2.2% for FM and 1.1% for LBM [25]. DXA quality control and calibration measures were performed before each testing session and radiation exposure was <8 μSv. From DXA FM (%), participants were divided in two groups—non-obese (men: FM <25% and women: FM <30%) and obese (men: FM >25% and women: FM >30%, according to De Lorenzo et al. [26,27].

Statistical analyses

All analyses were carried out using SPSS version 23 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was set a priori at $P = 0.05$ level of probability. All values were expressed as median and range (minimum/maximum). To confirm the sex-matched enrollment χ^2 test was conducted to compare sex between groups in sample and subsamples. Mann-Whitney test for nonparametric data was performed for all comparisons between the two groups, including the subsample analysis. BC and BMD parameters in the HD and CT groups were associated by Spearman's correlation.

Results

Anthropometric, BC, and BMD measurements of HD patients and controls were evaluated in the overall sample and also divided by sex (Table 1). In the overall sample, the HD and CT groups were homogeneous for age ($P = 0.31$) and sex ($P = 0.77$). BW and BMI were lower, but not significant, in the HD group ($P > 0.05$). Men with HD presented lower BW and BMI than women with HD. From DXA, FM (kg; $P = 0.04$), truncal fat (kg; $P = 0.01$), and LBM (kg; $P = 0.04$) were significantly lower in the HD group. In women with HD, variables related to fat and lean compartments lost significance. Men with HD, however, maintained the other differences seen in the overall sample. Total BMD and T- and Z-scores were lower in patients with HD ($P < 0.01$). When the overall sample was divided by sex, the same results were seen for BMD. The HD and CT groups were homogenous for age and sex ($P = 0.95$ for the nonobese group and $P = 0.63$ for the obese group), as well as in the subsamples divided according to FM (%). In the nonobese subsample, FM (kg) did not significantly differ between groups, although the patients presented lower values of truncal fat ($P = 0.04$), total BMD, and T-score ($P < 0.01$) than the controls. In the obese subsample, truncal fat ($P = 0.03$), total BMD, and Z- and T-scores were significantly lower in the HD group ($P < 0.01$; Table 2).

In the overall HD group, correlations pointed out a significant association of variables such as LBM (kg; $r = 0.80$; $P < 0.01$), truncal fat (kg; $r = 0.68$; $P < 0.01$), and BMI ($r = 0.56$; $P < 0.01$) with BW. Regarding BC, different results were observed in the overall HD group and all of the healthy controls, as the latter presented significant correlations among bone and BC parameters. The same findings did not apply to the CT group (Table 3).

Discussion

The most significant finding of the present study was that BMD was not correlated with LBM in patients with HD. On the contrary, the same parameters were correlated in the CT group and in fact it is well known that BMD and lean mass are correlated not only in athletes but also in healthy individuals [28]. In addition, the BMD, which was lower in patients with HD [29], did not correlate with any other BC parameters. At the same time, patients with HD have always shown a significant reduction of T-score. LBM also was reduced in patients with HD, but above all, it was positively associated with BW, which was more strongly correlated with LBM with respect to BMI. This fact may undermine the use of BMI as a prognostic index to assess BW changes in patients with HD. Lower truncal fat values in the patient group was an important result that has always been significant in all comparisons.

This study was the first to use DXA for a global and segmental BC assessment in HD patients, focusing the attention on individual characteristics, in agreement with Hood [30].

Several studies have reported BW loss and low BMI in patients with HD in early and advanced stages [31,32]. In this study, men with HD had lower BW and BMI than controls. BMI and BW did not precisely evaluate BC; therefore, in this study it was highlighted that bone, LBM, and FM could be used as early and reliable prognostic indexes, in agreement with other studies [33,34].

Table 1
Comparisons between CT and HD groups in the overall sample and divided by sex

	Overall sample			Men sample			Women sample		
	CT group	HD group		CT group	HD group		CT group	HD group	
Parameters	(n = 29) Median (min/max)	(n = 21) Median (min/max)	*P*-value	(n = 15) Median (min/max)	(n = 10) Median (min/max)	*P*- value	(n = 14) Median (min/max)	(n = 11) Median (min/max)	*P*- value
Age (y)	53.00 (40.00/64.00)	54.00 (44.00/62.00)	0.30	52.00 (45.00/64.00)	53.00 (46.00/62.00)	0.57	53.00 (40.00/62.00)	55.00 (44.00/60.00)	0.40
BW (kg)	71.80 (50.50/89.20)	62.80 (51.00/78.00)	0.05	79.20 (62.70/89.20)	70.00 (58.00/78.00)	0.01*	57.90 (50.50/85.50)	58.00 (51.00/70.00)	0.57
BMI (kg/m^2)	22.10 (19.40/32.38)	24.45 (19.38/26.81)	0.07	27.00 (20.79/29.80)	24.53 (19.38/26.81)	0.02*	22.85 (19.40/32.38)	23.18 (20.17/25.10)	0.73
DXA									
Lean									
LBM (kg)	46.75 (31.01/67.04)	39.21 (31.03/54.06)	0.04*	55.33 (44.24/67.04)	47.57 (46.00/54.06)	0.02*	38.37 (31.01/58.17)	35.40 (31.03/39.21)	0.05
LBM (%)	67.00 (51.71/80.07)	68.07 (48.47/79.30)	0.91	70.42 (59.70/80.07)	72.46 (64.61/79.30)	0.60	65.19 (51.71/70.65)	60.13 (48.47/69.41)	0.54
Truncal lean (kg)	22.62 (14.37/32.77)	19.53 (15.13/26.37)	0.10	26.30 (19.39/32.77)	23.61 (20.24/26.37)	0.03*	18.35 (14.37/27.84)	18.10 (15.13/19.54)	0.40
Fat									
FM (kg)	18.72 (12.19/36.89)	16.00 (7.52/31.49)	0.04*	19.35 (12.19/32.20)	13.82 (7.52/19.05)	0.01*	17.19 (15.05/36.89)	17.38 (13.95/31.49)	0.57
FM (%)	27.00 (14.90/43.34)	27.60 (12.97/46.30)	0.76	24.89 (14.90/36.40)	24.04 (12.97/29.92)	0.68	29.94 (26.20/43.34)	31.90 (26.83/46.30)	0.50
Truncal fat (kg)	10.10 (4.98/19.66)	8.08 (2.15/14.52)	0.01*	11.44 (4.98/19.66)	8.08 (2.15/13.01)	0.01*	8.27 (6.08/15.98)	7.18 (5.45/14.52)	0.15
Bone									
Total BMD (g/cm^2)	1.19 (0.91/1.37)	1.09 (0.98/1.21)	0.00*	1.23 (1.07/1.37)	1.10 (0.98/1.21)	0.00*	1.14 (0.91/1.31)	1.06 (0.99/1.11)	0.01*
T-score	0.81 (−2.37/2.75)	−0.30 (−1.55/0.96)	0.00*	1.20 (−0.60/2.75)	−0.21 (−1.55/0.96)	0.00*	0.29 (−2.37/2.12)	−0.80 (−1.53/−0.12)	0.01*
Z-score	0.36 (−1.70/2.30)	−0.57 (−1.76/0.19)	0.00*	0.49 (−1.00/2.00)	−0.77 (−1.76/0.19)	0.00*	0.23 (−1.70/2.30)	−0.90 (−0.74/0.11)	0.10

BMI, body mass index; BW, body weight; CT, control; FM, fat mass; HD, Huntington's disease group; LBM, lean body mass
All values are presented as median (minimum/maximum). Parameters were compared between CT group and HD group by Mann–Whitney test
*Statistical significance was attributed as $P < 0.05$.

The reduction of BMD and bone mass has previously been observed in HD [35], and in the examined sample no correlations were found between bone, muscle, and FM. In literature, the cross-talk among muscle, bone, and fat in patients with HD has not been studied. Therefore, based on the present data, it is possible to hypothesize that reduced BMD could be a peripheral manifestation because of an alteration of bone metabolism related to the numbers of CAG repeats [36,37]. Bone mass could be indicated as a clinical marker of peripheral disease because it is independent of BC parameters.

In the present study, a significant wasting of LBM was seen in patients with HD in general and in the male patients specifically, but no significant difference was observed between the CT and HD groups when divided by subsamples. Published studies regarding changes in LBM in patients with HD are limited and present conflicting results [31–33]. These contrasting findings may be due to an inclusion of unequal stages of disease and a lack of physical activity level assessment, as well as to the limits of bioimpendentiometric (BIA) analysis in evaluating BC. Because it was observed that the reduction of LBM was independent of the anthropometric parameters and that LBM, truncal fat, and BMI were correlated with weight in this order of importance, this data corroborated the hypothesis of using LBM as a prognostic index in HD [31–33].

In the overall sample, total FM (kg) was significantly lower in the patients with HD than in the CT group, and remained lower only in men with HD. Moreover, in all comparisons, only a significant lower truncal fat (kg) was found in the patients with HD. These results, for the first time in literature, allow us to hypothesize that truncal fat reduction is probably due to the higher energy expenditure in patients with HD [31]. Because these results highlighted a significant correlation between truncal fat and BW, which can be monitored through circumference and plicometry, the measurement of truncal fat can be suggested as a useful index in the evaluation of the nutritional status of patients with HD. Cubo et al. [33] found an inverse association between subscapular skinfold thickness and free fat mass.

The results showed the influence of HD on sex BC and, to our knowledge, few studies have investigated differences related to sex [38]. According to Goodman et al., women with HD had significantly lower BMD and Z-score levels than both healthy controls and affected men [35], whereas for LBM, the results showed a significant reduction in men with HD. Other studies have reported lower lean mass in women with HD, although it is necessary to underline that its results have been evaluated through BIA analysis [31–33].

A limitation of the present study was that it did not investigate the food intake of patients. Based on the results and limitations of this study, further investigations are needed on the role of BC and sex regarding HD progression, through increasing the patient sample and gathering more information on the symptoms and number of repeated triplets. Finally, follow-up studies should be conducted to accurately evaluate disease progression and BC. Nevertheless, herein we could testify new findings related to the BC, BMD, LBM, and truncal fat of patients with HD from a reliable evaluation of nutritional status.

Conclusions

The aim of this study was to find reliable and useful indexes in the evaluation of nutritional status in patients with HD. Even in its early stages, HD was seen to deeply influence BC parameters: bone, lean mass, and fat mass. Consequently, in patients with HD and genetically predisposed relatives; it is crucial that an evaluation of the nutritional indexes described here is

Table 2
Comparisons between CT and HD groups in subsamples divided by FM (%)

Parameters	Nonobese subsample			Obese subsample		
	CT group (n = 15) Median (min/max)	HD group (n = 11) Median (min/max)	*P*-value	CT group (n = 14) Median (min/max)	HD group (n = 10) Median (min/max)	*P*- value
Age (y)	53.00 (41.00/64.00)	56.00 (46.00/62.00)	0.10	52.50 (40.00/59.00)	50.50 (44.00/60.00)	0.66
BW (kg)	66.50 (56.00/87.50)	58.00 (51.00/78.00)	0.08	71.95 (50.50/89.20)	62.80 (54.50/73.00)	0.15
BMI (kg/m^2)	23.39 (19.40/27.58)	23.30 (19.38/25.10)	0.33	26.33 (21.57/32.38)	24.53 (22.21/26.81)	0.06
DXA						
Lean						
LBM (kg)	50.85 (36.76/67.04)	45.10 (31.32/54.06)	0.10	45.49 (31.01/57.64)	37.20 (31.03/47.24)	0.19
LBM (%)	70.55 (64.96/80.07)	69.31 (61.41/79.30)	0.51	63.92 (51.71/70.42)	58.53 (48.47/74.08)	0.75
Truncal lean (kg)	23.18 (19.91/32.77)	20.23 (16.87/26.37)	0.13	20.77 (14.37/28.80)	18.09 (15.13/24.44)	0.47
Fat						
FM (kg)	16.46 (12.19/22.49)	13.95 (7.52/17.70)	0.06	21.64 (16.45/36.89)	19.50 (13.70/31.49)	0.28
FM (%)	24.89 (14.90/29.40)	24.79 (12.97/29.45)	0.96	31.53 (26.10/43.34)	32.86 (26.10/46.30)	0.55
Truncal fat (kg)	8.23 (4.98/13.84)	6.66 (2.15/9.78)	0.04*	13.98 (7.74/19.66)	8.41 (6.21/14.52)	0.03*
Bone						
Total BMD (g/cm^2)	1.21 (0.91/1.33)	1.08 (0.98/1.20)	0.01*	1.18 (1.00/1.37)	1.10 (1.03/1.21)	0.00*
T-score	1.01 (−2.37/2.31)	−0.46 (−1.55/0.85)	0.01*	0.71 (−1.38/2.75)	−0.21 (−1.00/0.96)	0.00*
Z-score	0.36 (−1.70/2.30)	−0.73 (−1.76/0.11)	0.08	0.38 (−0.86/2.00)	−0.54 (−0.77/0.19)	0.01*

BMD, bone mineral density; BMI, body mass index; BW, body weight; CT, control; FM, fat mass; HD, Huntington's disease group; LBM, lean body mass
All values are presented as median (minimum/maximum). Parameters were compared between CT group and HD group by Mann–Whitney test
*Statistical significance was attributed as $P < 0.05$.

Table 3
Correlations between BC and BMD parameters in CT and HD groups

CT group (n = 29)		Z-score	T-score	BW (kg)	BMI (kg/m^2)	LBM (kg)	FM (kg)	Truncal fat (kg)
BMD (g/cm^2)	*r*	0.88*	1.00*	0.56*	0.53*	0.46*	0.29	0.32
	P-value	0.00	0.00	0.00	0.00	0.01	0.12	0.09
Z-score	*r*		0.88*	0.26	0.34	0.09	0.28	0.23
	P-value		0.00	0.16	0.07	0.64	0.14	0.23
T-score	*r*			0.56*	0.53*	0.46*	0.29	0.32
	P-value			0.00	0.00	0.01	0.12	0.09
BW (kg)	*r*				0.81*	0.87*	0.46*	0.55*
	P-value				0.00	0.00	0.01	0.00
BMI (kg/m^2)	*r*					0.53*	0.77*	0.83*
	P-value					0.00	0.00	0.00
LBM (kg)	*r*						0.06	0.18
	P-value						0.74	0.35
FM (kg)	*r*							0.94*
	P-value							0.00
HD group (n = 21)								
BMD	*r*	0.44*	1.00*	0.27	0.04	0.31	−0.05	0.19
(g/cm^2)	*P*-value	0.04	0.00	0.23	0.85	0.18	0.81	0.41
Z-score	*r*		0.44*	−0.26	−0.08	−0.42	0.43	0.10
	P-value		0.04	0.25	0.74	0.06	0.05	0.67
T-score	*r*			0.27	0.04	0.31	−0.05	0.19
	P-value			0.23	0.85	0.18	0.81	0.41
BW (kg)	*r*				0.56*	0.80*	0.24	0.68*
	P-value				0.01	0.00	0.30	0.00
BMI (kg/m^2)	*r*					0.37	046*	0.72*
	P-value					0.09	0.03	0.00
LBM (kg)	*r*						−0.28	0.24
	P-value						0.21	0.28
FM (kg)	*r*							0.70*
	P-value							0.00

BMD, bone mineral density; BMI, body mass index; BW, body weight; CT, control; FM, fat mass; HD, Huntington's disease group; LBM, lean body mass
Analyses were conducted using Spearman's correlation coefficient (*r*)
*Statistical significance was attributed as $P < 0.05$.

conducted to provide preventive interventions and disease prognosis. A potential biomarker of HD could be BMD, which was reduced independently of BC parameters. Moreover, LBM and truncal FM could be used as body weight prognoses factors in patients with early disease. A clearer understanding of the role of BC in neurologic chronic diseases may help improve nutrition therapy and can be a useful tool in clinical practice for the assessment of patient status.

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