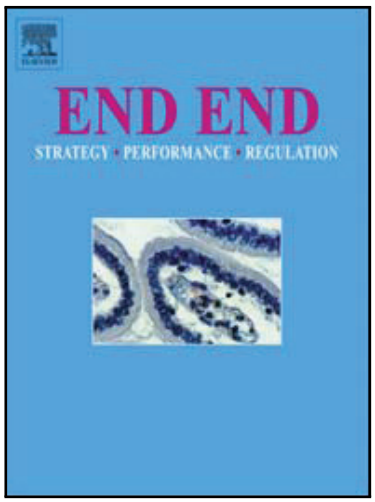

Body Composition and Bone Mineral Density in Huntington's Disease (HD)

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Highlights:

- BMD and T-score were lower in Huntington's Disease patients
- LBM and truncal fat can early indicate weight loss in HD.

Body Composition and Bone Mineral Density in Huntington's Disease (HD)

Running head Body Composition in Huntington's Disease

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AUTHOR'S CONTRIBUTION

CMR and DLA concepted and designed the study, DLN and AA collected data and drafted the article, CMR and GP analyzed data; CMR, DLN, AA, LDSG, GP and DLA interpretated data

and revised it critically for important intellectual content, DLA had primary responsibility for the final content.

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ABSTRACT

Objective: Understanding body composition (BC) of Huntington's disease (HD) patients could help in delaying disease progression and improving treatment efficacy. This study aims to assess BC parameters, including bone mineral density (BMD), and to find new biomarkers that can early reveal a weight loss in HD patients.
Research Methods & Procedures: 21 HD patients and 29 healthy controls (CT), age and gender-matched, were enrolled. For each patient, body weight (BW), height and BMI were evaluated. BC and BMD were measured by Double X-ray Absorptiometry (DXA). Sub-samples were created according to sex and percent fat mass (FM) (obese and non-obese). All analyses were carried out using SPSS 23.0.
Results: In all comparisons, BMD and T-score were lower in HD group, but not correlated with lean body mass (LBM) and FM. In HD group, LBM and truncal fat were mostly reduced, except in HD females, who seem to have their BC less affected by the disease than males. 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 early indicate weight loss in HD.

Keywords Huntington disease, nutrition status, truncal fat, lean body mass, body weight, biomarkers, osteoporosis

Conflict of Interest Statement Declarations of interest: none

INTRODUCTION

Huntington's disease (HD) is a neurodegenerative disorder, autosomal dominant triplet-repeat, due to expansion of 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 become general. Depression and obsessive-compulsive disorder are commonly seen in HD patients. 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].

The exact role of huntingtin has not been established yet, 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 included: xerostomia, which affects adversely swallowing and mastication [9]; reduced production of ghrelin following disease evolution [10]; reduced secretion of insulin due 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 mainly causes of weight loss, but due to the early onset of weight loss these cannot be the causes. Other authors have identified the progressive weight loss in an increasing of energy expenditure [10], but the causes remain unclear. It was observed that patients with a high body mass index (BMI) in early stage of HD have presented a slower progression of disease, consequently, the 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: on 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, which allows a timely effective treatment to prevent disability and fragility fractures. The early detection of body compartments' changes and of organic wasting is possible through the assessment of the body composition (BC) and nutritional status. Indeed, BC assessment has many clinical uses as for assessing diseases progression or treatment efficacy. However, in clinical routine practice, with the exception of specialized centers, only weight and height measurements are more frequently used. BC and their 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 and fat mass in early HD.

MATERIALS AND METHODS

Subjects

Fifty subjects, age 18-65 years, were enrolled in this study, 21 early-stage HD patients (10 males and 11 females), according to Gaba et al. [24], institutionalized at Nova Salus (Aquila, Italy), and 29 healthy subjects (15 males and 14 female), age and sex-matched. Healthy

subjects were recruited from HD patients' family or other subjects without genetic mutation, in order to minimize the effects of environmental conditions. Sub-samples were generated according to DXA FM (%) and classified as non-obese and obese samples. Comparisons between healthy and HD subjects for the same parameters were carried out in each new sample, which had age and gender matching maintained. In the non-obese sub-sample, HD patients were 11, and healthy subjects were 15. The obese sub-sample was made of 10 HD patients and 14 healthy subjects. Exclusion criteria were diabetes mellitus or treatment with neuroleptic, oral hypoglycemic and insulin; thyroiditis; others neurodegenerative, heart, pulmonary or skeletomuscular diseases; pregnancy or breastfeeding; active cancer and medication known to affect metabolism/endocrine function. Prior to participation, all subjects signed an informed consent form that outlined the experimental procedures for this study, which was 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, Rome, Italy). BMI was calculated as BW (kg) divided by H squared (m^2).

Dual-energy X-ray Absorptiometry Measurement

Total body mineral density (BMD) (g/cm^2), Fat Mass (FM) (kg) and Lean Body Mass (LBM) (kg), besides segmental compartments were measured using dual-energy X-ray absorptiometry (DXA; Model DPX, Lunar, Madison, WI, 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 less than 1%; CVs on this instrument for five subjects scanned six times over a nine months' period were 2.2% for fat mass and 1.1% for lean mass [25]. DXA quality control and calibration measures were performed prior to each testing session and radiation exposure was < 8 μSv. From DXA FM (%), subjects were divided in 2 groups, non-obese (males: FM <25% and females: FM <30%) and obese (males: FM >25% and females: FM >30%, according to De Lorenzo [26,27].

Statistical Analyses

All analyses were carried out using the Statistical Program for the Social Sciences (SPSS) version 23.0 for Windows (Armonk, NY: IBM Corp. 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 gender-matched enrollment Chi-square test was conducted in order to compare genders between groups in sample and sub-samples. Mann-Whitney test for non-parametric data was performed to all comparisons between HD group and CT group, including the sub-sample analysis. BC and BMD parameters in HD and CT groups were associated by Spearman's correlation.

RESULTS

Anthropometric, BC and bone mineral measurements of HD patients and controls were evaluated in the overall sample and also divided by gender (Table 1). In the overall sample,

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 HD group (p>0.05). HD males presented lower BW and BMI than HD females. From DXA, FM (kg) (p=0.04), truncal fat (kg) (p=0.01) and LBM (kg) (p=0.04) were significantly lower in HD group. In the HD female group, variables related to fat and lean compartments lost significance. HD males, instead, maintained the other differences seen in the overall sample. Total bone mineral density, T-score and Z-score were lower in HD patients (p<0.01). When the overall sample was divided by gender, the same results were seen to BMD. HD and CT groups were homogenous for age and sex (p=0.95 for non-obese group and p=0.63 for obese group) also in the sub-samples divided according to FM (%). In the non-obese sub-sample, FM (kg) was not significantly different between groups, although HD patients presented lower values of truncal fat (p=0.04), total BMD and T-score (p<0.01). In the obese sub-sample, truncal fat (p=0.03), total BMD, Z-score and T-score were found to be significantly lower in HD patients (p<0.01) (Table 2).

In the overall HD patients, correlations pointed out a significant association of variables as LBM (kg) (r=0.80; p p<0.01), truncal fat (kg) (r=0.68; p<0.01) and BMI (r=0.56; p p<0.01) with BW. Regarding to bone compartment, there was seen different results in overall HD patients and overall healthy subjects, since the latter presented significant correlations among bone and BC parameters, and on the other hand, the same was not seen in CT group (Table 3).

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

	Overall sample			Male sample			Female sample		
Parameters	**CT group n=29 Median (min;max)**	**HD group n=21 Median (min;max)**	***p***	**CT group n=15 Median (min;max)**	**HD group n=10 Median (min;max)**	***p***	**CT group n=14 Median (min;max)**	**HD group n=11 Median (min;max)**	***p***
Age (years)	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

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 $p<0.05$ (*). CT group: Control group; HD group: Huntington's Disease group; BW: Body Weight; BMI: Body Mass Index; LBM: Lean Body Mass; FM: Fat Mass;

Table 2 Comparisons between CT group and HD group in sub-samples divided by FM (%)

	Non-obese sub-sample			Obese sub-sample		
Parameters	**CT group n=15 Median (min;max)**	**HD group n=11 Median (min;max)**	***p***	**CT group n=14 Median (min;max)**	**HD group n=10 Median (min;max)**	***p***
Age (years)	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/m2)	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 *

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 $p<0.05$ (*). CT group: Control group; HD group: Huntington's Disease group; BW: Body Weight; BMI: Body Mass Index; LBM: Lean Body Mass; FM: Fat Mass; BMD: Body Mineral Density;

Table 3 Correlations among 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	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		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			0.00	0.00	0.01	0.12	0.09
BW (kg)	r				0.81*	0.87*	0.46*	0.55*
	p				0.00	0.00	0.01	0.00
BMI (kg/m^2)	r					0.53*	0.77*	0.83*
	p					0.00	0.00	0.00
LBM (kg)	r						0.06	0.18
	p						0.74	0.35
FM (kg)	r							0.94*
	p							0.00

HD group (n=21)		Z-score	T-score	BW (kg)	BMI (kg/m^2)	LBM (kg)	FM (kg)	Truncal Fat (kg)
BMD	*r*	0.44*	1.00*	0.27	0.04	0.31	-0.05	0.19
(g/cm^2)	*p*	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		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			0.23	0.85	0.18	0.81	0.41
BW (kg)	*r*				0.56*	0.80*	0.24	0.68*
	p				0.01	0.00	0.30	0.00
BMI (kg/m^2)	*r*					0.37	046*	0.72*
	p					0.09	0.03	0.00
LBM (kg)	*r*						-0.28	0.24
	p						0.21	0.28
FM (kg)	*r*							0.70*
	p							0.00

Analyses were conducted using Spearman's correlation coefficient (r). Statistical significance was attributed as $p<0.05$ (*). CT group: Control group; HD group: Huntington's Disease group; BW: Body Weight; BMI: Body Mass Index; LBM: Lean Body Mass; FM: Fat Mass.

DISCUSSION

The most significant finding of this study was that BMD was not correlated with LBM in HD patients. 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 normal subjects [28]. Besides that, the BMD, which was lower in HD patients [29], did not correlate with any other BC parameters. At the same time, HD patients have always shown a significant reduction of T-score. LBM was also reduced in HD patients but, above all, it was positively associated to BW. BW was stronger correlated with LBM respect to BMI. This fact may undermine the use of BMI as prognosis index to assess BW changes in HD patients. Lower truncal fat values in HD patients 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 HD patients in early and in advanced stage [31,32]. In this study, HD males were seen to have lower BW and BMI than control subjects. BMI and BW do not evaluate precisely BC, therefore in this work it was highlighted that bone, lean and fat, could be used as early and reliable prognostic indexes, in agreement with other authors [33,34].

The reduction of BMD and bone mass had already been observed in HD [35], and in the examined sample no correlations were found between bone, muscle and fat mass. In literature, the cross-talk among muscle, bone and fat in HD patients has not been studied. Therefore, from this data it is possible to hypothesize that reduced BMD could be a peripheral manifestation due to 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, since it is independent of BC parameters.

In this study a significant wasting of LBM was seen in HD patients of general and men samples. Meanwhile, there was no significant difference between CT and HD groups when divided by sub-samples. Published studies regarding changes in LBM in HD subjects are limited and present conflicting conclusions [31-33]. Probably, these contrasting findings are due to: an inclusion of unequal stages of disease and a lack of physical activity level assessment and the limits of bioimpendentiometric analysis to evaluate BC. Since 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 corroborate the hypothesis of using LBM as a prognostic index in HD [31-33].

In overall subjects, total FM (kg) was significantly lower in HD patients compared to CT subjects, and remained lower only in HD men group. Moreover, in all comparisons only a significant lower truncal fat (kg) was found in HD patients. These results, for the first time in literature, allow to hypothesize that truncal fat reduction is probably due to the higher energy expenditure in HD patients [31]. Since 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 in HD patients. Also, Cubo et al. [33] have found an inverse association between subscapular skinfold thickness and free fat mass.

The results showed the influence of HD on gender BC and up to now few studies have investigated differences related to gender. [38] According to Goodman et al., females HD had

significantly lower BMD and Z-score levels than both healthy controls and affected males [35], while for LBM the results showed a significant reduction in HD males. Other studies have reported lower lean mass in female HD, although it is necessary to underline that its results have been evaluated through bioimpendentiometric analysis. [31-33]
The limit of the study was that it did not investigate food intake of patients.
Based on the results and limits of this study, further investigations are needed on the role of BC and gender regarding HD progression, through increasing patient sample and gathering more information on the symptoms and number of repeated triplets. Finally, follow-up studies should also be conducted to accurately evaluate the disease progression and BC. Nevertheless, herein we could testify new findings related to BC, BMD, LBM and truncal fat of HD patients 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 HD patients. HD, even in early-stage, was seen to deeply influence BC parameters: bone, lean, and fat masses. Consequently, in HD patients and genetically predisposed relatives, it is crucial an evaluation of the nutritional indexes inhere described 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 utilized as body weight prognoses factors in the early HD patients. A clearer understanding of BC in neurological chronic disease may help improve nutrition therapy and can be a useful tool in clinical practice for the assessment of patient status.

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