Body composition in adults with neurofibromatosis type 1

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SUMMARY

Objective: To evaluate the body composition and nutritional status of neurofibromatosis type 1 (NF1) adult patients.

Method: A cross-sectional study of 60 NF1 patients (29 men, 31 women) aged ≥ 18 years who were evaluated from September 2012 to September 2013 in a Neurofibromatosis Outpatient Reference Center. Patients underwent nutritional assessment including measurements of weight, stature, waist circumference (WC), upper-arm circumference (UAC), and skinfolds (biceps, triceps, subscapular, suprailiac). Body mass index (BMI), upper-arm total area (UATA), upper-arm muscle area (UAMA), upper-arm fat area (UAFA), body fat percentage (BFP), fat mass, fat-free mass, fat mass index, and fat-free mass index were also calculated.

Results: The mean age of the study population was 34.48±10.33 years. The prevalence of short stature was 28.3%. Low weight was present in 10% of the sample and 31.7% of patients had a BMI ≥ 25 kg/m². Reduced UAMA (<5th percentile) was present in 43.3% and no difference was found in UAFA between the sexes. The BFP was considered high in 30% and 17 (28.3%) patients had a WC above the World Health Organization cutoffs.

Conclusion: In this study, NF1 patients had a high prevalence of underweight, short stature, and reduced UAMA, with no difference between the sexes. Reduced UAMA was more prevalent in underweight patients; however, this was also observed in the normal and overweight patients. Further studies should investigate the distribution of body tissues in NF1 patients, including differences between men and women, and the influence of diet and nutrition on clinical features in NF1.

Keywords: neurofibromatosis type 1, nutritional status, anthropometry, body composition, adult.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is the most prevalent form in a group of three genetic diseases called neurofibromatoses, and is caused by inherited or *de novo* mutations on chromosome 17, resulting in reduced neurofibromin synthesis, which subsequently reduces tumor suppression.[1] The diagnostic criteria for NF1 are almost exclusively clinical, and were established by the National Institutes of Health (NIH) Consensus.[2] The most common clinical features of NF1 are *café au lait* spots, dermal neurofibromas, plexiform neurofibromas, axillary and/or inguinal freckling, Lisch nodules, and bone dysplasia. However, NF1 can also exhibit multisystemic involvement including musculoskeletal, cardiovascular, endocrine, ophthalmic, central and peripheral neural system, learning deficits and speech disorders.[3-5]

Recently, the first study of nutrient intake in NF1 patients was published,[6] and, although the clinical manifestations of NF1 are well established, data on body composition are scarce[4,7-10] and not well known. Low weight, short stature, and reduced body mass index (BMI) were found previously in NF1 patients and can be used as nutritional status indicators. However, these characteristics had different prevalence rates in the small number of studies available.[4,7-10] Most of these studies were conducted in children only, or included children and adults in the same sample.

Body composition is related to health.[11] Altered body composition, or excess fat, can greatly increase the risk of cardiovascular disease, diabetes, hypertension, and cancer.[11] In other hand, muscle plays a central role in whole-body protein metabolism and altered muscle metabolism plays a key role in the genesis and prevention of many common pathologic conditions and chronic diseases.[12] Epidemiological and clinical studies use the anthropometry by measuring circumferences and skinfolds. The upper-arm composition is also used as an indicator of fat and muscle distribution. Several studies have shown the direct association of disease, biochemical changes, and nutritional status with upper-arm composition.[13,14]

The NF1 nutritional status assessment is relevant, because features of this disease as underweight or short height can influence patients' health and quality of life. Therefore, the present study aimed to assess the body composition of NF1 adult patients.

METHOD

Sample

The present cross-sectional study included all NF1 patients aged ≥ 18 years from a Brazilian Neurofibromatosis Outpatient Reference Center (NORC) evaluated between September 2012 and September 2013. The study was approved by the Ethics Committee of the Federal University of Minas Gerais. All patients provided their written informed consent. Patients were excluded based on musculoskeletal limitations, presence of a neurofibroma at the measurement site, or the use of medications that might compromise the nutritional assessment.

Data collection

The anthropometric measurements used in this study followed the protocol provided by the World Health Organization (WHO).[15] Weight was measured to the nearest 100 g with a mechanical scale (Welmy®), which was checked regularly before each investigation, and height was measured using a vertical stadiometer (Welmy®). Weight and height were used to calculate patients' BMI.[15] The BMI categories used in this study were normal weight (BMI 18.5-25 kg/m²), underweight (BMI < 18.5 kg/m²), and overweight (BMI ≥ 25.0 kg/m²).[15] Fat mass index (FMI) and fat-free mass index (FFMI) were also calculated using the equations according to VanItallie et al.:[16]

$$FMI = \text{fat mass (kg) / height (m)}^2$$
$$FFMI = \text{fat-free mass (kg) / height (m)}^2$$

Waist circumference (WC) was measured at the midpoint between the iliac crest and the rib cage. According to the WHO,[11] the minimum normal cutoff points for WC are 94 cm and 80 cm in men and women, respectively. To calculate the body fat percentage (BFP), skinfold thickness was measured to the nearest millimeter (mm) using a caliper (Cescorf®). These readings were made at four sites on all subjects: at the biceps (BS), triceps (TS), subscapular (SS), and supra-iliac (SIS) areas. These measurements were taken on the right side of the body with the subject standing in a relaxed position. Body density was calculated using the linear regression equations for men and women according to Durnin and Womersley.[17] These equations do not use plenty of skinfold thickness, which may be of interest in NF1 patients, as the presence of a neurofibroma at the measurement site was an exclusion criterion in this study, as previously stated. The BFP was then calculated using Siri's equation,[18] and classified as normal, high, or low according to Lohman's criteria.[19]

The upper-arm circumference (UAC)[20] was measured at the midway point between the acromion and the olecranon process of the elbow of the right arm using a tape measure to the nearest 0.10 cm. The upper-arm composition was assessed based on anthropometric measurements of UAC and TS utilizing standard equations, with values in percentiles, according to the National Center for Health Statistics (NCHS) reference and classified by Frisancho.[20] The following equations[20,21] for upper-arm total area (UATA), upper-arm muscle area (UAMA), and upper-arm fat area (UAFA) were used:

a. $UATA \ (cm^2) = (UAC)^2 \ / \ (4 \ x \ \pi)$
b. $UAMA \ (cm^2) = \{(UAC - TS \ x \ \pi)^2 \ / \ (4 \ x \ \pi)\} - 10 \rightarrow Male$
c. $UAMA \ (cm^2) = \{(UAC - TS \ x \ \pi)^2 \ / \ (4 \ x \ \pi)\} - 6.5 \rightarrow Female$
d. $UAFA \ (cm^2) = UATA - UAMA$

Statistical analyses

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS®) version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate normality and determine the appropriate statistical test. Qualitative variables were described using absolute and relative (percentage) frequencies. Grouped comparisons of qualitative variables were performed using chi-square tests. Quantitative variables with normal distribution were expressed as mean and standard deviation, and compared using the two-tailed

Student's t-test for independent samples. Quantitative variables that were not normally distributed were presented as median and interquartile range (IQR), or minimum and maximum, and compared using the non-parametric Mann-Whitney U test. P-values < 0.05 were considered statistically significant.

RESULTS

Sixty patients aged 18 to 64 years were included in this study. Twenty-nine patients (48.3%) were men. The mean age was 34.48±10.33 years, and there was no difference between men and women (p=0.980). No patients were excluded based on the exclusion criteria. Anthropometric and body composition data are shown in Table 1.

The distribution of anthropometric data classified in categories of height, BMI, WC, and BFP are also presented in Table 1. Using the BMI categories, 6 of the 60 patients (10%) were classified as underweight,

35 (58.3%) were normal weight, and 19 (31.7%) were overweight. After analyzing the WC categories, 17 of the 60 (28.3%) patients had measurements above the WHO minimum normal cutoff points.[11] After analyzing the BFP categories, 18 of the 60 (30%) patients were classified as having a high BFP. There were no significant differences in the categorization of BMI, WC, and BFP between the sexes.

Table 2 shows the classification of body composition variables using upper-arm parameters. Regarding the UAFA, there was no difference between sexes, and only 6.6% of patients had increased UAFA (> 95th percentile). However, in terms of UAMA, 43.3% of patients had values below the 5th percentile, representing 51.7% of men and 35.5% of women with NF1 in this study. When this data was stratified by sex, men showed greater UAMA than women, which was to be expected (p<0.001).

TABLE 1 Anthropometric and body composition data of NF1 patients and its distribution in categories.

Parameters	All patients (N=60)	Men (n=29)	Women (n=31)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Weight (kg)	63.47 (16.98)	70.38 (18.00)	57.00 (13.25)	**0.002**
Height (m)	1.62 (0.10)	1.68 (0.09)	1.57 (0.08)	**<0.001**
BMI (kg/m^2)	23.86 (4.73)	24.79 (5.06)	22.98 (4.30)	0.139
WC (cm)	79.87 (12.18)	85.40 (12.49)	74.70 (9.44)	**<0.001**
Body fat percentage (%)	24.53 (7.75)	19.51 (6.30)	29.23 (5.84)	**<0.001**
Fat mass (kg)	15.86 (7.37)	14.50 (7.91)	17.14 (6.71)	0.168
Fat free mass (kg)	47.60 (12.35)	55.88 (11.12)	39.87 (7.54)	**<0.001**
Fat mass index (kg/m^2)	6.03 (2.71)	5.11 (2.61)	6.90 (2.53)	**0.009**
Fat-free mass index (kg/m^2)	17.82 (2.99)	19.69 (2.67)	16.08 (2.10)	**<0.001**
	n (%)	n (%)	n (%)	
Short stature*[a]	17 (28.3)	9 (31.0)	8 (25.8)	0.653
BMI categories*				0.101
BMI < 18.5 kg/m^2	6 (10.0)	2 (6.9)	4 (12.9)	
BMI ≥ 18.5 and < 25 kg/m^2	35 (58.3)	14 (48.3)	21 (67.7)	
BMI ≥ 25 kg/m^2	19 (31.7)	13 (44.8)	6 (19.4)	
WC categories*				0.351
M: < 94 cm and F: < 80cm	43 (71.7)	21 (72.4)	22 (71.0)	
M: ≥ 94 cm and F: ≥ 80cm	17 (28.3)	8 (27.6)	9 (29.0)	
Body fat percentage categories*				0.128
Normal	42 (70.0)	23 (79.3)	19 (61.3)	
High	18 (30.0)	6 (20.7)	12 (38.7)	
Low	0	0	0	

SD: standard deviation; BMI: body mass index; WC: waist circumference; M: male; F: female; [a]short stature was considered when percentile < 5; *categorical variables were compared using Pearson Chi-square. Means were compared using Student's t-test.

TABLE 2 Classification of body composition variables in percentiles according to the NCHS Standard.[20]

Parameters	All patients (N=60)	Men (n=29)	Women (n=31)	p-value*
UATA (cm²) – Mean ± SD	65.52±20.92	72.78±22.31	58.72±17.24	**0.008**
UATA categories – n (%)				0.505
< p5 (Low)	9 (15.0)	5 (17.2)	4 (12.9)	
p5 – p95 (Normal)	50 (83.3)	23 (79.3)	27 (87.1)	
> p95 (High)	1 (1.7)	1 (3.5)	0	
UAMA (cm²) – Mean ± SD	39.59±14.69	48.01±14.87	31.71±9.24	**<0.001**
UAMA categories – n (%)				0.205
< p5 (Low)	26 (43.3)	15 (51.7)	11 (35.5)	
p5 – p95 (Normal)	34 (56.7)	14 (48.3)	20 (64.5)	
> p95 (High)	0	0	0	
UAFA (cm²) – Mean ± SD	25.93±8.93	24.77±9.08	27.01±8.79	0.337
UAFA categories – n (%)				0.067
< p5 (Low)	1 (1.7)	0	1 (3.2)	
p5 – p95 (Normal)	55 (91.7)	25 (86.1)	30 (96.8)	
> p95 (High)	4 (6.6)	4 (12.9)	0	

SD: standard deviation; NCHS: National Center for Health Statistics; UATA: upper-arm total area; UAMA: upper-arm muscle area; UAFA: upper-arm fat area; < p5: percentile under 5; p5-p95: percentile between 5 and 95; > p95: percentile above 95. *Means were compared using Student's t-test and categorical variables were compared using Pearson Chi-square test.

Comparing patients with normal or reduced UAMA (< 5th percentile), there was no difference in height between groups (p=0.316), but comparing sexes, there was no difference for height between men with normal or reduced UAMA (p=0.526), and it was significantly lower in women with UAMA under 5th percentile (p=0.022). NF1 patients with reduced UAMA showed lower weight (p<0.001), BMI (p<0.001), fat mass (p<0.001) and fat-free mass (p=0.024), for both men and women, but FMI were lower only for women (0.013).

Discussion

In our study, compared to the non-NF1 population, NF1 patients were found to be underweight and present short stature, as well as reduced UAMA, with no sex differences for categories of these variables. Reduced muscle mass (as indicated by UAMA) was more prevalent in underweight patients (83.3%); however, this was also observed in normal (54.3%) and overweight (11.8%) patients. A small number of patients (1.7%) had low adipose tissue.

With regard to anthropometric characteristics, the prevalence of underweight adults in the Brazilian population is 2.7% (1.8% in men and 3.6% in women).[22] In this study, the prevalence of underweight is above the 5% mark that the WHO uses to identify malnutrition in a population.[22] In addition, 13 of the 29 men (44.8%) and 6 of the 31 women (19.4%) were overweight, while in the Brazilian adult population, this prevalence is 49% (50.1% in men and 48% in women).[22]

Short stature was present in 28.3% of the sample, which was higher than seen in a study by Petramala et al.,[7] and lower than seen in the studies of Souza et al.[4] and Trovo-Marques et al.[8] These studies were conducted in different age groups, and also included children in the analyses. In the Brazilian population survey,[22] the average height (in centimeters) of adults living at the same region in Brazil was high compared to patients with NF1 of this study.

The body composition analysis showed that women had a higher BFP compared to men with NF1, although in absolute values of fat (in kilograms), there was no difference between the sexes. This may be due to the lower weight and lower fat-free mass shown by women with NF1.

Men with NF1 had a larger UATA, UAC, and UAMA compared with women, while UAFA was similar between the sexes. This difference may be caused primarily by muscle mass, as there was no difference in UAFA and the bone gap difference between the sexes was already considered in the equations used.[21] The UAMA was considered low in 43.3% of patients in this study, representing 51.7% of men and 35.5% of women. The average values of UAMA have been shown to be higher in men than in women in other studies; however, the absolute values of this research were lower than the values found in other national and international studies.[23-26]

Stevenson et al.[10] used quantitative peripheral computed tomography to compare the bones and skeletal

muscle of NF1 patients and volunteers not affected by the disease. This study demonstrated that children with NF1 have lower muscle cross-sectional area than their controls, but this did not lead to major advances in the pathophysiology of this finding. Furthermore, reduced muscle strength is a feature described in NF1 patients by Souza et al.[27] also recruited from NORC. According to Pompeu et al.,[23] the UAMA has good correlation with the maximal voluntary strength.

This study found anthropometric differences between men and women with NF1. Although changes in weight and fat accumulation are expected comparing sexes, it seems that this difference is larger than the commonly found in people without NF1 and should receive attention in further studies. Probably, men and women are affected by NF1 in different ways in their body compartments, which can be related to situations like AMB greater in men and/or fat accumulation greater in women. Other studies[28,29] have also found differences between men and women for variables such as BMI, reinforcing the need to assess the impact of NF1 in each sex.

In our study, body composition was inadequate in terms of muscle mass. Low muscle mass is usually associated with low weight and malnutrition,[15] which was also found in this study. However, we also found low muscle mass in normal weight and overweight patients, suggesting that the BMI values should be interpreted with caution when assessing the nutritional status in NF1 patients, or that the BMI cutoff points must be adapted to changes in body composition. The reduced muscle mass can indicate an early sarcopenia in NF1 patients. It may have multiple causes that should be investigated in further studies, as poor blood flow to muscle, mitochondrial dysfunction, decreased caloric intake, a decline in anabolic hormones, or an increase in proinflammatory citokines.[30] Souza et al.[6] showed a decreased caloric intake in NF1 patients, but the authors discussed a possible overestimation of the daily energy expenditure when using the predictive equations.

Nutritional status can influence patients' quality of life.[31,32] Previous studies have shown that the clinical severity and social representations of NF1 are correlated with quality of life, as reported by NF1 patients and their families.[33,34] The importance of nutritional care in NF1 patients and their clinical features must be investigated further in future studies.

This study has limitations, such as convenience sampling and selection bias, that may have been caused by selecting patients with nutritional conditions including obesity and diabetes. All patients who had previously been treated in the outpatient center were invited to participate in this study to minimize this error. Randomization and the inclusion of a control group (with unaffected patients) would be useful in improving the external validity of similar studies. Additionally, UAMA is not the gold standard method for assessing muscle mass, and further studies should use better parameters to investigate the muscle mass in NF1 patients.

Conclusion

NF1 patients in this study had a high prevalence of underweight, short stature, and reduced UAMA, with no difference between the sexes. Reduced UAMA was more prevalent in underweight patients; however, it was also observed in the normal and overweight patients. Further studies should investigate the distribution of body tissues in NF1 patients with standard methods and investigate the possible correlation and impact of the nutritional status on the clinical features of the disease.

Resumo

Composição corporal em adultos com neurofibromatose tipo 1

Objetivo: avaliar a composição corporal e o estado nutricional de adultos com neurofibromatose tipo 1 (NF1).
Método: estudo transversal com 60 pacientes com NF1 (29 homens, 31 mulheres) com idade ≥ 18 anos que foram avaliados de setembro de 2012 a setembro de 2013 em um Centro de Referência em Neurofibromatoses. Pacientes foram submetidos à avaliação nutricional, incluindo medidas de peso, estatura, circunferência da cintura (CC), circunferência do braço e dobras cutâneas (bíceps, tríceps, subescapular, suprailíaca). Índice de massa corpórea (IMC), área total do braço (ATB), área muscular do braço (AMB), área adiposa do braço (AAB), percentual de gordura, massa gorda, massa livre de gordura, índice de massa gorda e índice de massa livre de gordura foram calculados.
Resultados: a idade média da amostra foi de 34,48±10,33 anos. A prevalência de baixa estatura foi 28,3%. Baixo peso esteve presente em 10% da amostra e 31,7% apresentaram IMC ≥ 25 kg/m2. A AMB reduzida esteve presente em 43,3% e não foram encontradas diferenças na AAB entre os sexos. O percentual de gordura foi considerado alto em 30% da amostra, e 28,3% apresentaram CC acima dos pontos de corte da Organização Mundial de Saúde.
Conclusão: neste estudo, pacientes com NF1 apresentaram alta prevalência de baixo peso, baixa estatura e AMB reduzida, sem diferenças entre os sexos. AMB reduzida

foi mais prevalente em pacientes com baixo peso, no entanto também foi observada em pacientes com peso normal ou sobrepeso. Estudos futuros devem investigar a distribuição de tecidos corporais na NF1, incluindo diferenças entre sexos, e a influência da nutrição nas manifestações clínicas da doença.

Palavras-chave: neurofibromatose tipo 1, estado nutricional, antropometria, composição corporal, adulto.

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