Bioimpedance Analysis as a Method to Evaluate the Proportion of Fatty and Muscle Tissues in Progressive Myopathy in Pompe Disease

Agnieszka Rózdzyńska-Świątkowska •
Elżbieta Jurkiewicz • Anna Tylki-Szymańska

Received: 05 August 2014 / Revised: 08 June 2015 / Accepted: 10 June 2015 / Published online: 8 August 2015
© SSIEM and Springer-Verlag Berlin Heidelberg 2015

Abstract During progressive myopathy, the space of atrophic muscle tissue is gradually filled by fatty tissue. The proportion of these two tissue types relative to body mass provides an indication of the extent of muscle tissue destruction, i.e., the progression and severity of the disease.

In this study we use Pompe disease as an example to report the new possibility of using bioimpedance analysis (BIA) to assess the relative proportion of fatty and muscle tissue in diseases associated with muscle atrophy, thus enabling the assessment of disease progression and the effectiveness of treatment. Results from BIA analysis were compared with magnetic resonance images.

The results of muscle magnetic resonance images and BIA analysis were similar, which suggests that BIA may provide valuable diagnostic guidance for the assessment of the progression of the disorder.

Introduction

Bioimpedance analysis (BIA) is a noninvasive testing method allowing for accurate analysis of body composition using electrical resistance of various tissues of the body: so-called impedance (Lewitt et al. 2010). It uses the ability of the muscle tissue to conduct electrical current. The test measures impedance, i.e., electrical resistance and reactance of the tissues through which low-intensity electrical current is passed (≤ 1 mA). The phenomenon of resistance is associated with resistivity of specific tissues, while reactance is mainly due to the electrical capacitance of cell membranes, which, due to their structure, act as capacitors (Lewitt et al. 2010). The body composition assessment method based on electrical bioimpedance analysis is used in medicine, mainly to assess the risk and degree of overweight and obesity, where the fatty tissue to body weight ratio is estimated. Researches which based on the noninvasive measurements of the electrical impedance characteristics in medicine are more frequent: BIA was used in comparison of segmental with whole-body impedance measurements in peritoneal dialysis (Nescolarde et al. 2008). Electrical impedance myography (EIM) is a noninvasive technique for the assessment of neuromuscular health of individual muscles or groups of muscles and was used in the assessment of boys with Duchenne muscular dystrophy (Rutkove et al. 2014).

In diseases such as myopathies, muscle cells die with the progress of the disease, and the atrophic muscle tissue is replaced by the fatty tissue (Mercuri et al. 2002a). Muscle atrophy gradually leads to loss of function of the motor system and the respiratory muscles (Pellegrini et al. 2005; Gaeta et al. 2013). The dynamics of the atrophic process in myopathies is usually assessed on the basis of functional tests. In some cases, magnetic resonance imaging allows an

Communicated by: Jörn Oliver Sass

Competing interests: None declared

A. Rózdzyńska-Świątkowska
Anthropology Laboratory, The Children's Memorial Health Institute,
Al. Dzieci Polskich 20, 04-730 Warsaw, Poland

E. Jurkiewicz
Department of Diagnostic Imaging, The Children's Memorial Health
Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland

A. Tylki-Szymańska (✉)
Department of Pediatric, Nutrition and Metabolic Diseases,
The Children's Memorial Health Institute, Al. Dzieci Polskich 20,
04-730 Warsaw, Poland
e-mail: atylki@op.pl; atylki@czd.pl

approximate evaluation of the relative proportions of the muscle and fatty tissues in the selected segments of the whole body (Pellegrini et al. 2005; Gaeta et al. 2013; Pichiecchio et al. 2004).

In this study, BIA was obtained in patients with Pompe disease (glycogen storage disease type II, GSD II). Pompe disease is an autosomal-recessive metabolic myopathy, caused by deficiency of the lysosomal acid α -glucosidase. The deficiency of this enzyme leads to an accumulation of glycogen taking place mainly in muscles and leading to their progressive destruction. The spectrum of clinical phenotypes includes infantile-onset form, juvenile form, and late-onset form. In the classic form (infantile onset), the first symptoms appear in the first months of life with hypotonia, muscle weakness, and cardiomegaly. In juvenile forms, the first symptoms, including progressive proximal and axial muscle weakness, appear between 2 and 5 years of age.

The late-onset form has a slower progression. Skeletal muscle involvement is more prominent with a predilection for the lower limbs. Late-onset features include hypotonia and progressive muscle weakness – mainly in respiratory muscles, leading in advanced stages to ventilator-assisted breathing.

In Pompe disease, the main affected tissue is muscle tissue – as the disease progresses, this tissue becomes atrophic and is replaced by fatty tissue (Del Gaizo et al. 2009; Angelini et al. 2013; Alejaldre et al. 2012).

This study is innovative because BIA was used for the first time to assess the relative proportions of the fatty and muscle tissues in diseases associated with muscle atrophy, thus enabling the assessment of disease progression and the effectiveness of treatment.

Material and Methods

Study Subjects

The study was conducted in The Children's Memorial Health Institute in a group of 20 patients with Pompe disease (10 women and 10 men) aged from 6.7 years to 52 years (mean age: 27.7 years). All the patients had a diagnosis of Pompe disease confirmed by biochemical and molecular analysis (1 infantile-onset form; 8 juvenile form; 11 late-onset form) (Table 1). In 20 patients, body composition analysis by electrical bioimpedance method (BIA) using an InBody J10 (Biospace) device was conducted. Impedance measurements were performed by using 3 different frequencies 5, 50, and 250 kHz at each 5 segments of the body. In 17 patients, MRI images of the thigh muscles were obtained using a 1.5 T scanner (Siemens Sonata Vision) using Axial T1-weighted spin

echo sequences with TR = 300 ms, TE = 10 ms. Slice thickness was equal 10 mm, gap 1 mm and FOV 400 mm.

Study Design

As the disease progresses, the space of atrophic muscle tissue is gradually filled by the fatty tissue. The relative to body mass proportions of these two tissue types are allowed to determine the extent of muscle tissue destruction, i.e., the progression and severity of the disease.

The study objective was to use the BIA analysis method to determine the proportion of the amount of the fatty and muscle tissues in patients with progressive myopathies. This is allowed to evaluate the severity of the disease.

BIA Analysis

The bioimpedance method assesses the tissue components of the body, involving a measurement of electrical resistance in the human body. Resistance varies depending on the composition of the subject's body. The assessment of body composition and the proportion between fatty and muscle tissues is obtained after entering data on age and gender; the device measures body height and weight and performs measurements of resistance and reactance. The test provides information on body composition: body water (l); the amount of protein (kg); the amount of mineral substances (kg); fatty tissue mass (kg); and % of body fat of the whole body weight, skeletal muscle mass (kg), and the distribution of fatty and muscle tissues in various segments of the body. The measurement was performed in a patient in their underwear, according to the instructions of measurement. Criteria of patient inclusion in the study: Pompe disease confirmed by an enzymatic assay, age: min. 3 years, body weight 10–250 kg, height: 95–220 cm. Study exclusion criteria are inability of standing without assistance, implanted pacemaker, pregnancy, or breastfeeding. To observe the changes in the composition of the human body, the analyses should be performed in comparable measurement conditions as far as possible; therefore, the subject should not exercise before the measurement, should not be measured immediately after a meal (min. 2 h), should not take a bath immediately before the measurement, and should be measured after a bowel movement, and the measurements should be performed before noon. The patient assumed a standing position, with the head remaining in the Frankfurt plane. Both hands held the hand electrode rods in such a manner that four fingers were placed on the surface of the electrode, and the thumb was placed on the electrode button. Bare feet were placed on the electrodes in such a way that the heels touched the peripheral electrode, and the sole of each foot remained on the elliptical surface. The results were shown as a graph,

Table 1 Patients characteristics

Patient	Gender	Current age	Age of first symptoms (years)	Age of diagnosis (years)	Mutation	Form
1	M	6.7	No symptoms, family screening	6/12	G377S/c.2495_2496 delCA	Juvenile
2	F	6.8	6/12	2	L291F, 871C>T/R600C, 1798C>T	Infant
3	F	10	No symptoms, family screening	2	IV1-13T>G/c.2662G>T	Juvenile
4	F	13.2	3	4	C1129G>A/c.2495_2496 delCA	Juvenile
5	M	13.7	No symptoms, family screening	6	IVS1-13T>G/c.2662G>T	Juvenile
6	M	14.5	3.5	4	IVS1-13T>G/c.925G>A	Juvenile
7	F	15.9	>1	2.5	IVS1-13T>G/c.307T>G	Juvenile
8	F	16	8	11	IVS1-13T>G/C103G	Juvenile
9	M	23	6	15	IVS1-13T>G/c.2662G>T	Juvenile
10	F	29	7	25	IVS1-13T>C103G	Late onset
11	F	32	16	30	IVS1-13T>G/c.307T>g	Late onset
12	M	33	15	25	IVS1-13T>G/c.307T>G	Late onset
13	M	36	27	29	c.364A>G/c.1796C>T	Late onset
14	F	36	25	34	IVS1-13T>G/C103G, 307T>G	Late onset
15	M	36	18	34	IVS1-13T>G/c.307T>g	Late onset
16	F	38	6	31	c.364A>G/c.1796C>T	Late onset
17	M	45	35	40	IVS1-13T>G/ -	Late onset
18	M	47	35	46	IVS1-13T>G/c.307T>G	Late onset
19	M	51	33	48	IVS1-13T>G/C103G, 307T>G	Late onset
20	F	52	>30	46	IVS1-13T>G/525delT	Late onset

with values given in kilograms and percentages. References used in software are standard range of PBFs which are 10–20% of standard body weight for men and 18–28% of standard body weight for women. For patients under 18 years of age InBody J10 uses standard PBF for appropriate age classes (Heyward and Stolarczyk 1996; Lohman 1992; Tahara et al. 2002; Fomon et al. 1982). In Body J10 software, standard skeletal muscle mass (kg) is estimated with the assumption: 40–47% for boys and men and 40–42% for girls and women of standard body weight (Heymsfield et al. 1990; Ito et al. 2001).

According to the Cole classification of BMI (Cole et al. 2007), two patients had severe thinness, 2 patients were underweight, 13 patients had a normal range of BMI, and 3 patients were overweight. Z-score values were calculated for each patient for the body weight, muscle tissue, and body fat.

For BIA the following scale was used. This scale was invented by the authors for the purposes of this study. “Mild” indicates when body weight (kg) is normal with muscle tissue (kg) and percentage of body fat (PBF %) within normal limits or if body weight is below normal and

both muscle and PBF are below standard charts. “Moderate” indicates when body weight is normal but there is a disproportion between muscle tissue and adipose tissue, for example, muscle tissue is normal and PBF is above the norm or when muscle tissue is below normal and PBF is normal. “Severe” indicates when weight is normal or above normal, muscle tissue is below normal, and fat tissue is above normal.

MRI Analysis

MRI images of the thigh were obtained using a 1.5 T scanner (Siemens Sonata Vision). In Pompe disease, the imbalance between muscle tissue and fatty tissue is mainly visible in the thighs (Alejandre et al. 2012) because the thigh has a simple geometry and tissue composition. Each muscle group was graded according to the degree of degeneration using the scale proposed by Mercuri (Mercuri et al. 2002b): “mild” if only traces of increased signal intensity could be observed in an otherwise well-preserved muscle; “moderate” if less than 50% of the muscle showed an increased signal intensity; and “severe” if at least 50% showed increased signal intensity.

Table 2 BIA and MRI results

Patient	Age (years)	Gender	Current age	Body mass (kg) [references]	BIA		BIA (scale)	MRI (scale)
					Muscle tissue (kg) [references]	Percent body fat [references]		
1	6.7	M	6.7	24.1 [21.2–28.6]	9.4 [9.4–11.6]	16.1 [10–20]	Mild	Mild
2	6.8	F	6.8	24.9 [22.2–30.0]	8.7 [9.6–11.8]	25.8 [12–22]	Severe	–
3	10	F	10	36.3 [39.6–53.6]	15.5 [17.9–21.9]	17.7 [16–26]	Mild	Mild
4	13.2	F	13.2	40.5 [45.5–61.5]	15.4 [20.3–24.8]	25.1 [18–28]	Moderate	Mild
5	13.7	M	13.7	58.1 [60.2–81.4]	29 [30.4–37.2]	9.5 [10–20]	Mild	Mild
6	14.5	M	14.5	60.9 [54.6–73.8]	30.4 [27.5–33.5]	11.9 [10–20]	Mild	Mild
7	15.9	F	15.9	51 [48.1–65.1]	19.1 [21.5–26.3]	28 [18–28]	Severe	Severe
8	16	F	16	55.7 [47–63.6]	21.9 [21–25.6]	27.8 [18–28]	Mild	Mild
9	23	M	23	39.4 [54–73]	20.2 [27.1–33.1]	3 [10–20]	Not classified	Moderate
10	29	F	29	56.6 [48.1–65.1]	19.8 [21.5–26.3]	34.4 [18–28]	Severe	–
11	32	F	32	55.4 [53.7–72.7]	20.7 [24.2–29.6]	29.8 [18–28]	Severe	Moderate
12	33	M	33	68.9 [61.3–82.9]	30 [31–37.8]	20.9 [10–20]	Moderate	Severe
13	36	M	36	59.7 [50.6–68.4]	25.9 [22.7–27.7]	20.9 [18–28]	Mild	Mild
14	36	F	36	38.1 [45.9–62.1]	15.3 [20.4–25]	22.3 [18–28]	Not classified	Moderate
15	36	M	36	85.4 [63–85.2]	28.3 [31.9–38.9]	39.1 [10–20]	Severe	Severe
16	38	F	38	73.5 [57–72.2]	28 [25.8–31.6]	29.6 [18–28]	Moderate	Moderate
17	45	M	45	81 [57.2–77.4]	30.8 [28.8–35.2]	30.7 [10–20]	Moderate	Severe
18	47	M	47	71.6 [56.9–76.9]	24.8 [28.6–35]	35.8 [10–20]	Severe	–
19	51	M	51	76.4 [57.7–78.1]	31.5 [29.1–35.5]	27 [10–20]	Moderate	Moderate
20	52	F	52	72.4 [50.4–68.2]	22.8 [22.6–27.6]	42 [18–28]	Severe	Severe

Ethical Consideration

The protocol was approved by the Human Subjects Institutional Review Board at the Children's Memorial Health Institute. Written informed consent had to be provided by the parents or legal guardians. The study was designed and conducted in compliance with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice.

Results

BIA

BIA results including the body mass, the muscle tissue mass, and percentage of adipose tissue together with the reference range (WHO reference charts) for each parameter are shown in Table 2. Six of the 20 patients were classified as “mild” form, five as “moderate” form, and seven as “severe” form. Two patients were not classified in any of the groups due to

low body weight and inconclusive test results (Fig. 1). For example, patient 14 should have put on 16 kg but 12 kg of this was muscle tissue and only 4 kg was adipose tissue. Thus, even at this stage, there was a visible disproportion between adipose tissue and muscle tissue.

MRI

Muscle groups were graded according to the degree of degeneration using the scale proposed by Mercuri (Mercuri et al. 2002b). Figure 2 shows examples of MRI. Seven of 17 patients were classified as “mild” form, five as “moderate” form, and five as “severe” form. Because of equipment malfunction, MRI images were not obtained for three patients.

BIA vs. MRI

In 12 cases the results of BIA analysis and MRI image were accordance and were classified to the same grade; only in 3 cases the results were not accordance and were graded into different classes of severity of the disease. In 2 cases analysis for BIA was not unequivocal, the

Fig. 1 Relation between muscle tissue, body mass and body fat in z-score values

Fig. 2 Examples of MRI. (a) Mild; (b) moderate; (c) severe

body weight was considerably below the standard charts, analysis showed both the scarcity of fat tissue and muscle tissue, and therefore, it was difficult to classify these patients to one of the groups. MRI was not performed in 3 patients.

Discussion

In recent years, several studies have reported the use of muscle MRI as a useful noninvasive technique for the assessment of neuromuscular disorders (Mercuri et al. 2002a;

De Jager et al. 1998; Paradas et al. 2010; Fisher et al. 2005; Wattjes et al. 2010). In this study, the authors introduce a completely new, simple to perform, and reliable diagnostic method to assess the progress of the muscle atrophy process in myopathies. The accuracy of BIA is comparable with magnetic resonance (Salinari et al. 2002). BIA is much cheaper, faster, and easier to perform. The use of BIA to assess the relative proportions of fatty and muscle tissues in diseases associated with muscle atrophy is an innovative method not previously used in myopathies. The results of our study show that there is a correlation between the percentage of body fat by segment and the degree of replacement of the muscle tissue with fatty tissue, as shown in MRI. As the disease progresses, the percentage of body fat increases and reduces the percentage of muscle tissue. Furthermore, it correlates with the age of the patients and the severity of the disease evaluated clinically. The results prove the high sensitivity of the BIA method and suggest great potential for using electric bioimpedance analysis as a cognitive tool enabling the assessment of the proportion of fatty and muscle tissues in progressive myopathies as well as the potential for using the device in diagnostics. Notwithstanding this, a detailed study is required involving a larger group of subjects with progressive myopathies. The device for bioimpedance measurement used in this study allowed for measurements only in the standing position, but there are devices available that can perform measurements in the supine position. This could be useful in patients with severe muscle atrophy preventing them from moving without assistance. BIA devices allow for accurate measurement of bioimpedance for five body segments, four limbs and the trunk; they are based on the technology of the 8-point tactile electrode system, ensuring accuracy and reproducibility of measurements using eight different points of measurement: the thumb and fingers of both hands and the front and back parts of the soles of both feet (Kaido et al. 2013).

The scale developed by the authors needs to be verified with more tests. An interpretation of the results of analysis for patients with body weight significantly below the reference charts appears to be problematic. In cases where a body weight was considerably below the standard charts, analysis showed both the scarcity of fat tissue and muscle tissue, and therefore, it was difficult to classify patients into one of the groups.

Conclusions

Loss of muscle tissue in progressive myopathies is associated with an increased fat amount in the muscles.

Measurement of the proportion of these two tissues allows to specify the degree of atrophy of skeletal muscles and thus the degree of severity of the disease. Sensitive and reliable tool for this purpose is the BIA as it was demonstrated on the example of testing patients with varying degrees of severity of Pompe diseases. BIA because of their sensitivity, simplicity, and cheapness can be used to assess muscle atrophy in other myopathies.

Acknowledgments We thank Maniac Gym for lending us an InBody J10 device to perform this study. We are also grateful to the subjects and their families who gave their time and participated in this study.

Compliance with Ethics Guidelines

Conflict of Interest

Agnieszka Rózdzyńska-Świątkowska, Elżbieta Jurkiewicz, and Anna Tylki-Szymańska declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

References

- Alejaldre A, Diaz-Manera J, Ravaglia S et al (2012) Trunk muscle involvement in late-onset Pompe disease: study of thirty patients. *Neuromuscul Disord* 22:148–154
- Angelini C, Nascimbeni AC, Semplicini C (2013) Therapeutic advances in the management of Pompe disease and other metabolic myopathies. *Ther Adv Neurol Disord* 6:311–321
- Cole TJ, Flegal KM, Nicholls D et al (2007) Body mass index cut off to define thinness in children and adolescents: international survey. *BMJ* 335:194
- De Jager AEJ, van der Vliet TM, van der Ree TC et al (1998) Muscle Computed Tomography in adult-onset acid maltase deficiency. *Muscle Nerve* 21:398–400
- Del Gaizo A, Banerjee S, Terk M (2009) Adult onset glycogen storage disease type II (adult onset Pompe disease): report and magnetic resonance images of two cases. *Skeletal Radio* 38:1205–1208
- Fisher D, Walter MC, Kesper K et al (2005) Diagnostic value of muscle MRI in differentiating LGMD2I from other LGMDs. *J Neurol* 252:538–547
- Fomon SJ, Haschke F, Ziegler EE (1982) Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 35: 1169–1175
- Gaeta M, Barca E, Ruggeri P et al (2013) Late-onset Pompe disease (LOPD): correlations between respiratory muscles CT and MRI features and pulmonary function. *Mol Genet Metab* 110:290–296
- Heymsfield SB, Smith R, Aulet M (1990) Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr* 52:214–218

- Heyward VH, Stolarczyk LM (1996) Applied body composition assessment. Human kinetics, Campaign, p 82
- Ito H, Ohshima A, Ohto N et al (2001) Relation between body composition and age in healthy Japanese subjects. *Eur J Clin Nutr* 55:462–470
- Kaido T, Ogawa K, Fujimoto Y (2013) Impact of Sarcopenia on survival in patients undergoing living donor liver transplantation. *Am J Transplant* 20:1–8
- Lewitt A, Mądro E, Krupienicz A (2010) Podstawy teoretyczne i zastosowania analizy impedancji bioelektrycznej (BIA). *Endokrynologia, Otyłość, Zaburzenia Przemiany Materii* 3:79–84
- Lohman TG (1992) Advanced in body composition assessment – current issues in exercise science series. Human Kinetics, Champaign, p 80
- Mercuri E, Cini C, Counsell S et al (2002a) Muscle MRI findings in a 3 generation family affected by Bethlem myopathy. *Eur J Paediatr Neurol* 6:309–314
- Mercuri E, Picchietto A, Counsell S et al (2002b) A short protocol for muscle MRI in children with muscular dystrophies. *Eur J Paediatr Neurol* 6:305–307
- Nescolarde L, Doñate T, Piccoli A, Rosell J (2008) Comparison of segmental with whole-body impedance measurements in peritoneal dialysis patients. *Med Eng Phys* 30(7):817–824
- Paradas C, Llauger J, Diaz-Manera J et al (2010) Redefining dysferlinopathy phenotypes based on clinical findings and muscle imaging studies. *Neurology* 75:316–323
- Pellegrini N, Laforet P, Orlikowski D, Pellegrini M et al (2005) Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *Eur Respir J* 26:1024–1031
- Pichiechio A, Uggetti C, Ravaglia S et al (2004) Muscle MRI in adult-onset acid maltase deficiency. *Neuromuscul Disord* 14: 51–55
- Rutkove SB, Geisbush TR, Mijailovic A et al (2014) Cross-sectional evaluation of electrical impedance myography and quantitative ultrasound for the assessment of Duchenne muscular dystrophy in a clinical trial setting. *Pediatr Neurol* 51(1):88–92
- Salinari S, Bertuzzi A, Mingrone G et al (2002) New bioimpedance model accurately predicts lower limb muscle volume: validation by magnetic resonance imaging. *Am J Physiol Endocrinol Metab* 282:960–966
- Tahara Y, Moji K, Aoyagi K et al (2002) Age-related pattern of body density and body composition of Japanese men and women 18–59 years of age. *Am J Hum Biol* 14:743–752
- Wattjes MP, Klay RA, Fisher D (2010) Neuromuscular imaging in inherited muscle diseases. *Eur Radiol* 20:2447–2460