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Research Paper

ASSESSMENT OF SPIROMETRIC VALUES IN OSTEOGENESIS IMPERFECTA

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ABSTRACT

Purpose: Life expectancy in osteogenesis imperfecta (OI) can vary depending on the degree of compromise, and can lead to death in childhood or even at birth in severe cases. In the literature, the most cited causes of death in OI patients are pulmonary compromise and accidental trauma. The objective of this study was to assess pulmonary function of OI patients using spirometry. **Methods:** A total of 43 patients diagnosed with OI, aged 10 or older, were assessed by spirometry to collect FVC, FEV_1 and FEV_1/FVC ratio; predicted for age, height and gender. **Results:** Behavior on spirometry observed in this study diverged greatly from expected patterns, where patients with the most severe form of the disease and greater deformities had higher values of FVC and FEV_1 than predicted values. In order to minimize interpretation errors, especially overestimation of values, it is suggested that only raw values in liters be used, without comparison using a prediction equation, since this prediction is performed in anthropometrically similar individuals, whereas the population studied was highly heterogeneous in these aspects. **Conclusions:** In conclusion the assessment of pulmonary function in individuals with OI revealed higher mean absolute spirometry values in individuals with the type I form.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disease caused by a defect in the synthesis of type I collagen [1-3]. Clinical presentation is heterogeneous and variable, but besides brittle bones, its main features include ligament capsule laxity, bluish sclera and early deafness [4, 5].

OI is a rare condition, with the occurrence of one case in every 15,000-20,000 births and a prevalence of 1 in 200,000 individuals, displaying no racial or ethnic predilection [4].

Diagnosis is confirmed by clinical, radiographic and genetic examination. The classification of Silence, published in 1979, and reviewed in 2014 [5], has been used for grouping these patients.

OI is probably the most common genetic alteration predisposing to fractures [6]. To date, there are 17 confirmed genetic causes of the disease, where OI is a single nomenclature for a heterogeneous group of connective tissue syndromes, characterized primarily by greater susceptibility to fractures throughout life [5].

The prognosis of the disease is highly variable, depending on the number and severity of symptoms; where degree of bone brittleness, quantity of fractures and deformities are determinants in this respect [7]. Life expectancy of individuals with milder symptoms is normally unaffected, whereas in more severe cases this may lead to death in childhood or even at birth [8, 9].

Studies on the cause of death in OI patients show that pulmonary compromise, followed by accidental trauma, are the leading causes of death in adults with osteogenesis imperfecta [10, 11].

The main respiratory issue affecting individuals with OI is loss of pulmonary function. This loss affects individuals of all ages across all OI types, but appears to be more severe in those with type III, due to the severity of bone brittleness and major deformities in the spine and rib cage [8, 12, 13].

The Referral Center for Osteogenesis Imperfecta (CROI) is located within the Department of Orthopedics and Traumatology of the institution where the work was conducted. This center provides a specific service for the management of individuals with imperfecta osteogenesis, via a multidisciplinary out-patient unit. The work of these professionals involves the assessment, diagnosis and treatment of clinical and functional symptoms of OI [14].

One of the focuses of the team is the early detection and correction of more severe symptoms of the disease in order to preserve functioning in individuals as far as possible. Low respiratory capacity has been reported in the literature as a main factor, serving as an indicator of poor prognosis and the leading cause of death in this patient group [10, 11, 13].

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No classification or standardization correlating spirometric parameters with different OI types is available in the literature.

Some studies have been conducted, but none of these directly associated the main classification for OI with pulmonary function. Moreover, no consensus was found on the use of prediction formulas for patients with abnormal anthropometric measurements.

This calls for a tool for recognizing these changes, in an effort to standardize the assessment of pulmonary function. This can allow early identification of functional losses in OI and the devising of assessment and intervention protocols for these and patients and their many types.

The objective of the present study was to assess pulmonary function using spirometry in patients with osteogenesis imperfecta.

PATIENTS AND METHODS

A cross-sectional study was performed assessing 43 patients diagnosed with osteogenesis imperfecta, of both genders and aged 10 years or older, or able to carry out the procedures proposed, who were being followed by the referral center for osteogenesis imperfecta (CROI) of the Pediatrics sector.

Patients requiring urgent or elective surgical intervention were excluded, as were those presenting with previous or current pulmonary, cardiac or neurological disease, individuals with rib cage or vertebral fracture within the six month leading up to the study, and those with significant pain in any region on the day of data collection.

The study was approved by the Research Ethics Committee.

Spirometry

Spirometry was performed on a Koko Spirometer device, and forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and the ratio of these two measures (FEV_1/FCV) were assessed; as predicted for age, height and sex according to the equation of Pereira [15].

Individuals were weighed and measured wearing only light clothing with footwear removed. Age was recorded as age at last birthday. Spirometry was performed in a sitting position, using a nasal clip and, when height measurements could not be taken, arm span measurements were used. Arm span was adjusted to Brazilian anthropometric standards [16] by dividing arm span by 1.03 in females and 1.06 in males.

Functional Ability

Functional walking ability was clinically assessed, with individuals classified into one of four groups:

Group 1: Independent walking, without assistance;

Group 2: Independent walking with the aid of crutches;

Group 3: Independent wheelchair user

Group 4: Dependent wheelchair user, i.e. unable to move around unaided by wheelchair.

Data collection and assessments were performed between October 2013 and October 2014.

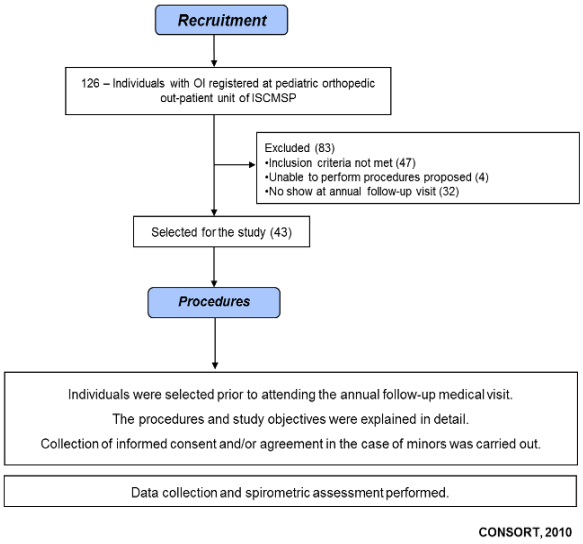
Statistical Analysis

Variables were expressed descriptively as mean and standard deviation and data were tabulated using Microsoft® Excel® for Mac 2011 version 14.4.8 software.

The Statistical Package for Social Sciences, version 13.0 was employed for statistical analysis of the data set with application of the Kruskal-Wallis test for variables of interest. The level of significance adopted was 5%.

The flow chart (Fig 1) was followed for recruitment and data collection.

Figure 1. The flow chart was followed for recruitment and data collection.



RESULTS

A total of 43 patients were assessed, 39.53% male and 60.46% female, with mean and standard deviation for age of 28.37 years (±15.98), height of 145.03cm (±15.6) and weight of 49.7kg(±17.0) (Table 1).

Relationship of Spirometry with OI types (Table 2).

Relationship of Spirometry with functional independence (Table 3).

Table 1. Characterization of sample according to OI type.

	All (n=43) Mean(SD)	Type I (n=20) Mean(SD)	Type III (n=11) Mean(SD)	Type IV (n=12) Mean (SD)
Age (years)	28.37 (15.98)	28.00 (15.20)	28.18 (18.66)	29.17 (16.09)
Height (cm)	145.03 (15.57)	148.40 (13.48)	130.82 (13.59)	145.03 (15.58)
Weight (kg)	49.72 (16.98)	57.60 (17.43)	36.21 (8.84)	49.00 (14.48)
BMI (kg/m²)	23.38 (6.11)	25.92 (6.05)	21.38 (5.40)	23.39 (6.12)
MOBILITY				
Independent	19	15	0	4
crutches	14	5	5	4
Independent wheelchair user	10	0	6	4

Legend: M: male; F: female, OI: osteogenesis imperfecta, BMI: body mass index.

Table 2. Mean and standard deviation for spirometric values attained and percentage (%) of predicted values according to Pereira et al 2007 [15].

	All (n=43)	Type I (n=20)	Type III (n=11)	Type IV (n=12)
FVC (%pred)	2.85 (1.01)	2.97 (1.02)	2.42 (1.10)	3.1 (0.88)
	103.88 (33.76)	99.84 (15.09)	117.27 (57.21)	98.58 (27.25)
FVC	2.33 (0.85)	2.42 (0.68)	2.0 (1.13)	2.51 (0.79)
FEV_1 (%pred)	96.51 (33.82)	93.35 (18.48)	108.72 (56.74)	90.58 (25.41)
FEV_1	0.87 (0.29)	0.83 (0.14)	1.01 (0.52)	0.82 (0.09)
FEV_1/FVC (%pred)	2.85 (1.01)	2.97 (1.02)	2.42 (1.10)	3.1 (0.88)

Legend: *FVC= forced vital capacity; FEV_1= forced expiratory volume in first second; FEV_1/FVC=ratio of vital capacity and expiratory volume; % pred = percentage of value predicted by Pereira in 2007 [15].*

Table 3. Mean spirometric values attained and percentage (%) of predicted values according to functional independence.

Functional independence	All	Independent	Crutches	Wheelchair
FVC	2.85 (1.01)	3.24 (0.98)	2.50 (0.81)	2.61 (1.16)
FVC (%pred)	103.88 (33.76)	99.57 (16.11)	99.42 (31.99)	118.3 (54.97)
FEV_1	2.33 (0.85)	2.68 (0.66)	2.00 (0.73)	2.14 (1.12)
FEV_1 (%pred)	96.51 (33.82)	94.47 (16.74)	93.92 (33.57)	104 (55.40)
FEV_1/FVC	0.87 (0.29)	0.85 (0.14)	0.83 (0.08)	0.98 (0.56)
FEV_1/FVC (%pred)	94.25 (13.05)	95.21 (16.13)	96.5 (9.72)	89.3 (10.04)

Legend: FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in First Second; FEV_1/FVC: Ratio of Vital Capacity and Expiratory Volume; % Pred: Percentage of Value Predicted by Pereira in 2007 [15].

DISCUSSION

Pulmonary complications have been reported as the leading cause of death in OI patients [5, 17]. Based on this premise, we identified the need for a method able to guide forms of prevention and treatment of these complications.

Spirometry was identified as a potential approach for systematic assessment of these individuals, without causing discomfort or posing risk of further fractures [8, 12, 13].

Another aspect warranting analysis in OI is the heterogeneous presentation of the disease and its most marked characteristic, brittle bones [18]. This brittleness increasing the incidence of fractures, which in severe cases can cause deformities in the entire skeleton, resulting in temporary or permanent inactivity.

During the regular follow-up visits, a series of common complaints were identified, not always directly linked to complications induced by the disease. These complaints were recurrent in numerous individuals across different age groups. Generally, these patients are spared by their families from domestic tasks, free and protected from any kind of physical effort or activity and are in a constant latent state awaiting the next trauma. This explains the concerns of this study in seeking objective assessment data which may help indicate physical treatment approaches and inclusion of these individuals in social and professional activities.

Fatigue is a common complaint in our group and this is cited in the literature as a major limiting factor for patients, impacting the performance of activities of daily living [19, 20].

Takken [20], raised a hypothesis for the genesis of fatigue in these individuals. The authors´ primary question centered on possible structural changes in the cardiorespiratory system, since this contains type I collagen as an important structural component. Therefore, fatigue complaints might be caused by tissue changes. However, evidence gathered by the authors leads us to believe that hypoactive lifestyle is most likely responsible for fatigue, muscular weakness and low tolerance to physical exercise [21].

In support of this hypoactivity theory, the 2008 study conducted by Van Brussel et al. [21], showed the beneficial effects of a supervised training program, such as improved aerobic capacity, muscle strength and reduced levels of subjective fatigue in children classified as having mild OI types. However, a decline in these gains was noted when the training was discontinued, corroborating the hypoactivity theory in these patients.

In 2011, Montpetit et al. [22], assessed 54 OI patients for mobility, independence and limitations. Greater limitations were found for domestic and working life in young adults with the more severe types of the disease.

In the present study, no statistically significant difference in FCV and FEV_1 values were found for OI type. However, significance was found for FEV_1 values in terms of functional independence, where higher values were identified in individuals with independence for walking. This finding is reinforced by the data of Montpetit et al. [22], showing a higher degree of independence among individuals with less severe forms of the disease.

Hypoactivity in conjunction with hyperprotection against trauma tends to lead to physical impairment and restricted social contact. The vast majority of individuals are sedentary, with very few practicing supervised physical activity or taking part in rehabilitation programs. Aerobic conditioning [21], muscle strength [23] and functional independence [22] are compromised, especially in individuals with more severe forms of the disease. In the present study, an approach was sought that can provide early detection of those changes which are factors for poor prognosis. Spirometry constitutes a simple, low-cost method for assessing and assisting ventilatory disturbances.

The first spirometric studies performed exclusively in individuals with OI were described by Falvo et al, in 1973 [12] , where the variability and incoherence of results exhibited a similar pattern to that found in the present study, even though the spirometry method and classification of individuals was not the same as the gold standard employed currently. The highest FCV value attained was in the individual classified as the most severe.

In 2012, Lomauro et al. [8] provided the first detailed description of respiratory function in the two most severe types of non-lethal OI. On spirometry, prediction equations were adapted, using pediatric equations to assess adults with severe deformities, so that results could better reflected reality.

In the present study, similar results were obtained when using the prediction equation of Pereira [16], since this is an estimated value for a normal Brazilian adult population. Raw expiratory values, expressed in liters, showed that more severe individuals had a lower expiratory capacity, yet comparison with predicted values reveals overestimation of these values, clearly indicating that the equation used for the normal population cannot be comparable to the patient group studied. Following the model of Lomauro [8], the equation of Pereira 1996 [16] was replaced by the Crapo [24] equation, but this yielded similarly discrepant values.

When performing spirometry in OI patients, height must be corrected in the presence of severe spinal deformities and, in lower limbs, height is corrected using arm span [25]. This correction was carried out in the present study by measuring between the fingertips of the arms extended horizontally. The arm span measurement can be used as an estimate of biological height in cases of spinal deformity, or whenever height measurements

cannot be taken. In children, arm span serves as an accurate estimate of height.

The study by Takken et al. [20] showed that low height of patients leads to high FVC and FEV_1 values, even in individuals with the milder form of the disease, where these height values are most likely overestimated. During the study it was noted that structural changes and deformities in limbs and trunk can lead to overestimation of values. As an alternative to correcting this error, the authors carried out tests using a height measurement approximated for age of the individuals.

In the present study, there was an evident need to adapt the prediction equations or change the anthropometric measurements used for their construction, perhaps by employing other measurements to adapt this population to comparable spirometry patterns, or even by devising specific equations for each disease type. We believe that using averages or approximations of ideal height of each individual would confer low reliability and limited reproducibility for the exam.

In the study by Wekre et al. [24], the authors correlated pulmonary function test with vertebral deformities, where it was necessary to correct weighted values to allow for the overestimated spirometry values of individuals with more severe deformities. The arm span measurement was used instead of height, as the results were totally distorted when height was used, particularly in type III patients. Switching height for arm span does not lead to significant changes in spirometry values in less severe individuals, yet in more severe cases with greater deformities these values can better reflect reality.

Behavior on spirometry observed in this study diverged greatly from expected patterns for a normal population, where patients with the most severe form of the disease and greater deformities had higher FVC and FEV_1 values than predicted values. With similarly controversial results, wheelchair users showed superior performance to independent walkers.

After data collection and review of the literature, it was noted that spirometry values in these patients need to be assessed by targeted, specific equations, while recognizing that adjusting height based on arm span is not an appropriate measurement for some patients. A relationship of inversion of values was found in individuals with OI when using the predicted measurements established for the general population, leading to overestimation of results of individuals with greater anthropometric abnormalities.

In order to minimize interpretation errors, especially overestimation of expiratory values, it is suggested that only raw values in liters be used, without comparison using a prediction equation for the normal population, since this prediction is performed in anthropometrically similar individuals, whereas the population studied was highly heterogeneous in these aspects.

It was concluded that individuals with type 1 OI had higher mean absolute spirometry values on pulmonary function assessment.

The use of raw spirometry values or specific equations is suggested for these patients, since application of standard prediction equations revealed a problem with anthropometric measurements, which proved unable to predict normal spirometry values for individuals with OI.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of interest: All authors have no conflicts of interest.

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