

## RESEARCH ARTICLE

## Testicular Volumes Measurement Comparison by Ultrasound and Orchidometer and Its Relationship with Nutritional Status in Transfusion-dependent Thalassemia

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### Abstract

**BACKGROUND:** One type of thalassemia known as transfusion-dependent thalassemia (TDT) requires a lifelong blood transfusion. Iron overload from prolonged blood transfusions causes nutritional disorders and several organs impairment, including the testicles. In contrast to an orchidometer, ultrasound shows more details of the testicles. This study aimed to compare testicular volumes based on ultrasound and orchidometer measurements and correlate testicular volume with nutritional status in TDT patients.

**METHODS:** A cross-sectional study including 27 male thalassemia subjects who underwent routine check-ups was conducted. Measurements of testicular volume using an orchidometer and ultrasound, and body mass index (BMI) was performed. Ultrasound measurement of testicular volume was calculated using the Lambert Formula, while the orchidometer was performed by matching the bead next to the testicle.

**RESULTS:** Most subjects were underweight (63%) or normal weight (37%). However, no significant correlation between BMI and testicular volume was found. As measured using an orchidometer, the mean volume of the right and left testes were  $9.22 \pm 4.92$  mL and  $8.67 \pm 4.45$  mL, respectively. Ultrasound measurement showed the mean values of the right and left testicles were  $7.68 \pm 3.96$  mL and  $7.09 \pm 4.03$  mL, respectively. Testicular measurements obtained using ultrasound showed a significant difference ( $p < 0.05$ ) when compared with the orchidometer. The testicle measured by ultrasound was smaller, which was more accurate. However, the comparison between the right and the left testicular volumes showed no significance.

**CONCLUSION:** Thalassemia patients are mainly underweight, and their nutritional status have no relationship with testicular volume. Ultrasound, as compared to an orchidometer, is better for measuring testicular volume.

**KEYWORDS:** thalassemia, testicle, orchidometer, ultrasound, body mass index

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### Introduction

Thalassemia is a hereditary blood disorder caused by impaired synthesis of hemoglobin chains.(1) It is one of the

most common autosomal recessive disorders worldwide. (2) Almost 10% of Indonesians are thalassemia carriers; however, the national prevention program is still limited due to the country's limited facilities.(3) The Indonesian Health Ministry in 2012 predicted that 3,000 babies with thalassemia

and 200,000 infant thalassemia carriers would be born each year.(4) Thalassemia is classified based on the need for blood transfusions, namely transfusion- and non-transfusion thalassemia (TDT and NTDT, respectively). TDT requires lifelong blood transfusion.(1) Routine blood transfusions may increase the risk of iron overload. Excess iron will accumulate in various organs and lead to the overproduction of free radicals that cause damage to the organs.(5) Iron overload may result in patients' impaired growth, including inadequate body mass index (BMI) and short stature.(6) Iron accumulation in the pituitary causes hypogonadism and is one of the most frequent complications experienced by TDT patients. It is known that 70-80% of TDT patients who experience hypogonadism may have pubertal failure, sexual dysfunction, and infertility.(7,8) Elevated serum iron and ferritin levels commonly manifest decreased testicular size (6-8 mL).(9) This is primarily due to iron load affecting the Growth Hormone–Insulin-like Growth Factor (GH–IGF) axis and the hypothalamic–pituitary–gonadal (HPG) axis. (10) A study in Growth Hormone (GH) deficient children showed an increase in testicular growth in children treated with GH. This study suggests that GH may have a role in testicular size, and assessing testicular growth and function will help prevent male infertility.(11)

Ultrasound is an imaging modality that is often used and is important for evaluating various testicular abnormalities. An ultrasound image can show the testes' and surrounding organs' anatomical and structural details.(12) The homogeneous granular echo texture of the normal adult testis is made up of uniformly distributed medium-level echoes, similar to the echogenicity of the normal thyroid gland.(13) Patients with secondary hypogonadism, such as hypogonadotropic hypogonadism (HH), have the testicular parenchyma appears less homogeneous.(13)

Testicular volume examination can also be performed via a Prader orchidometer.(14) This equipment is easy to use and low cost, making it the first choice for measuring testicular volume, especially in clinical situations.(15) However, the results are not accurate.(16) Therefore, this study aimed to find the difference in testicular volume between using ultrasound with an orchidometer and determining the correlation of testicular volume based on these measurements with nutritional status in TDT patients. This study provides practical information for doctors treating thalassemia patients. Such information may be helpful for a better understanding of tool selection for measuring testicular volume, diagnostic workup, and interventional options to ensure maximum reproductive health in thalassemia patients.

## Methods

### Study Design and Subject Recruitment

A comparative study with a cross-sectional design was conducted from December 2018 to November 2019. Ethical approval for the protocol was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, on December 31, 2018 (Protocol number: 18-12-1447). Informed consent was obtained from the subjects. The sample size was calculated with intraclass correlation sampling to compare the samples using two different measurement tools, and the total sample included in this study was 27 TDT subjects.

The samples were collected by convenient sampling with the target population of male adult patients aged 18 to 40 with major beta-thalassemia who underwent routine check-ups. This age range of subjects was chosen because most patients over 18 had fully developed testes, and patients over 40 had a progressively minimal decline in size.(17) The selected subjects must have graduated at least from junior high school. Subjects with any disease, disorder, or therapy that may affect testicular volume either directly or indirectly; had mental disorders; had been taking drugs, such as antipsychotics, antidepressants, prokinetics, and H2 antagonists that cause hyperprolactinemia; had a history of pituitary gland surgery; had a history of testicular trauma, radiation, or testicular surgery; had pituitary tumors and myelodysplastic syndrome or sickle cell disease; and underwent testosterone therapy in the last two weeks were excluded from the study.

### BMI Measurement

Weight and height information from the subject's medical records were used to calculate the BMI. BMI was calculated as body weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ). The classification of BMI used in this study was based on the Centers for Disease Control and Prevention (CDC). Weight in the range of 18.5 to 24.9  $\text{kg}/\text{m}^2$  was considered as normal weight,  $<18.5 \text{ kg}/\text{m}^2$  for underweight, range of 25 to 29.9  $\text{kg}/\text{m}^2$  for overweight, and  $\geq 30 \text{ kg}/\text{m}^2$  for obesity.(18)

### Ultrasound and Orchidometer Measurement

Each subject underwent testicular examination using a GE Logiq S8 (GE Healthcare, Solingen, Germany) Probe Linear Matrix ML6-15-RS 4 to 13 Hz ultrasound. Subjects were positioned supine with the scrotum and thigh area exposed while the abdomen was covered. Subject was asked to hold

his penis so that it remained positioned superolateral to the abdomen. The area below the scrotum was then covered with a towel/tissue between the thighs. A consultant radiologist then examined each testicle for anatomical structure, homogeneity, and testicular volume with grayscale mode calculated using the empirical formula of Lambert (length x width x height x 0.71). A previous study compared testicular volume calculations in experimental animals with various formulas and found that the empirical formula of Lambert provided the most accurate volume calculation that most closely matched the actual testicular volume.(19) Therefore, in this study, we used the empirical formula of Lambert to measure testicular volume with ultrasound.

After measuring the testicle using ultrasound, each subject underwent testicular measurements using a Prader orchidometer for comparison with the ultrasound results. Orchidometry was performed by placing the bead next to the testicle and matching the testicular volume with the Prader orchidometer beads. The bead that was as large as the testicle would be recorded.

### Statistical Analysis

The collected data were analyzed using SPSS 25.0 for Windows (IBM Corporation, Armonk, NY, USA). Descriptive analysis was done to see the frequency and average BMI of TDT patients. In this study, a comparative analysis was performed using a paired T-test to assess the difference in testicular volume between ultrasound and orchidometer examination.

## Results

Normality tests results for subjects' age and right and left testicular volume-based on ultrasound and orchidometer measurements showed that the data were normally distributed ( $p>0.05$ ). At the same time, the BMI value presented no normal distribution ( $p<0.05$ ). Based on age, most of the subjects were in the age group of 20-29 years old, 70.4% ( $n=19$ ), followed by the age groups of <20 years old and 30-39 years old, with 18.5% ( $n=5$ ) and 11.1% ( $n=3$ ), respectively. The subjects' mean age was  $24.14\pm 5.47$  years old. Furthermore, 63% of subjects ( $n=17$ ) were underweight, 37% ( $n=10$ ) presented normal weight, and no subjects were overweight or obese. Subjects' median BMI was 17.9 (13.0-24.6) (Table 1).

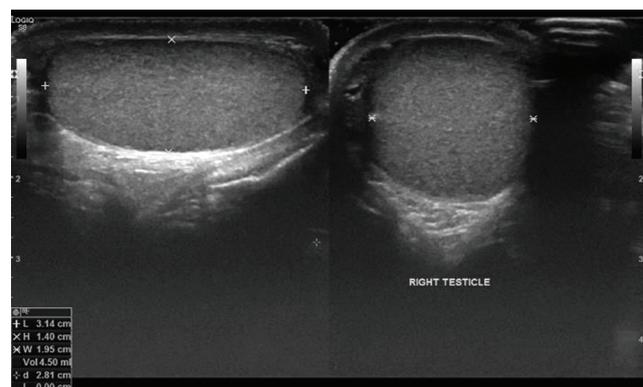
The mean testicular volume obtained using the orchidometer was larger in the right testicle, which was

**Table 1. Characteristics of subjects (n=27).**

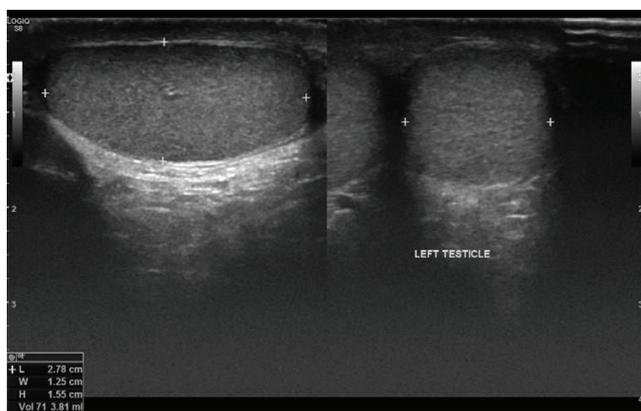
Characteristic of Subjects	Value
Age, n (%)	
<20 year-old	5 (18.5)
20-29 year-old	19 (70.4)
30-39 year-old	3 (11.1)
Age (year-old), mean $\pm$ SD	24.14 $\pm$ 5.47
Nutritional Status, n (%)	
Underweight	17 (63)
Normal	10 (37)
Overweight or Obese	0 (0)
BMI (kg/m <sup>2</sup> ), median (min-max)	17.9 (13.0-24.6)

$9.22\pm 4.92$  mL, while in the left testicle was  $8.67\pm 4.45$  mL. The mean volume of the right testicle measured using ultrasound was  $7.68\pm 3.96$  mL, and the left testicle was  $7.09\pm 4.03$  mL. Figures 1 and 2 showed that the right testicle was larger than the left testicle as measured using ultrasound. Both testicles as measured using the orchidometer were also larger than those measured by ultrasound. Based on the analysis, the volume of both the right and left testicular based on ultrasound was smaller than that obtained by the orchidometer, and the differences were significant ( $p<0.05$ ). The volume of the right testicle, as measured by ultrasound and orchidometer, was larger than the left testicle; however, the difference was not statistically significant ( $p>0.05$ ), as shown in Table 2.

BMI was shown to have no significant correlation with the testicular volume in the right and left testes after measured by ultrasound and orchidometer ( $p<0.05$ ), as shown in Table 3.



**Figure 1. Longitudinal (left image) and transversal (right image) ultrasound images of the right testicle. Length = 3.14 cm, height = 1.40 cm, width = 1.95 cm, and volume = 4.50 mL.**



**Figure 2. Longitudinal (left image) and transversal (right image) ultrasound images of the left testicle.** Length = 2.78 cm, height = 1.55 cm, width = 1.25 cm, and volume = 3.81 mL.

## Discussion

Our results showed that the majority of patients were underweight. Although data on the nutritional status of adult thalassemia patients were sparse, it was speculated that thalassemia patients present an increased risk of nutritional deficiencies due to increased nutritional requirements and/or inadequate intake and absorption of nutrients. Another study in India also reported this result, which mentioned that the majority (48.2%) of TDT patients had a BMI below normal values with a mean BMI of  $13.9 \pm 1.6$  kg/m<sup>2</sup>. The study also found that malnutrition can reduce thalassemia patients' quality of life.(20) Therefore, it is important to assess the nutritional status of thalassemia patients and prescribe the right medicine to prevent malnutrition and their quality of life.

The normal range of testicular volume was >14 mL in Japanese males aged from newborn to 80 years, and >17 mL in in the United States based on measurements obtained from an orchidometer.(21) Another study from Korea, where young adults aged 19-27 years old was evaluated using ultrasonography and the Lambert formula, determined

that the testicular volume cut-off value was 18 mL in young adults.(22) In our research, we found that both testicles, as measured using both an orchidometer and ultrasound, had a smaller volume than the normal value. Another study from Iran investigating young adults aged 18-41 years, reported that the testicular volume in patients with thalassemia ranged between 1.2 and 29 mL. At the same time, the average size of the right and left testis were 11.4 and 11.7 mL, which is lower than the normal value and almost similar to our study. They also reported that age, type of thalassemia, and transfusion dependency did not correlate significantly with the measurement of testicular volume with a  $p > 0.05$ .(23) However, the concept of "normal" testicular size varies based on ethnicity and country, and many variations in testicular volume in infertile and fertile men exist.(24)

Testicular size is affected by the secretion of gonadotropins that increase testosterone, a process that affects secondary sexual development and spermatogenesis. Reduced germ cell mass is correlated with decreased testicular size and consistency of the testicular soft tissue since germ tissue makes up 85% of the testicular size. In thalassemia patients with iron overload, acquired hypogonadotropic hypogonadism (AHH) may occur due to disruption of the H-P-G axis resulting in the inability of the testes to produce normal testosterone levels and spermatozoa production.(8) As a result, thalassemia patients have a decrease in testicular size compared to normal patients.

According to current research, the right and left testis' volume, measured by orchidometer, was significantly larger than their corresponding ultrasound-measured testes. The findings were comparable to those of a prior study in which it was demonstrated that a substantial correlation between testicular volume as assessed by ultrasonography and intraoperative caliper measurement and testicular measurement using an orchidometer was found. The testicular volume in this research as determined by the orchidometer, was greater than that determined by ultrasonography. Due to the inclusion of the testicular skin,

**Table 2. Testicular volume differences with orchidometer and ultrasound.**

Testicles	Testicular Volumes Measurements		Orchidometer vs. Ultrasound <i>p</i> -value*
	Orchidometer (Mean±SD)	Ultrasound (Mean±SD)	
Right testes**	9.22±4.92	7.68±3.96	0.021
Left testes**	8.67±4.45	7.09±4.03	0.013
Right vs. Left Testes <i>p</i> -value*	0.244	0.094	

\*Paired T-test, significant if  $p < 0.05$ ; \*\*Normal testicular volume value: 18.13±3.85 mL (right testis) and 18.37±3.62 mL (left testis).

**Table 3. Testicular volume correlation with BMI.**

	Testicular volumes measurements			
	Orchidometer		Ultrasound	
	r value	p-value*	r value	p-value*
Right testes	-0.335	0.088	-0.329	0.094
Left testes	-0.295	0.135	-0.343	0.08

\*Spearman correlation test, significant if  $p < 0.05$ .

epididymis, and other per testicular tissues, the volume of the testicles may have been overestimated.(15) Furthermore, although the volume of the right testis as measured by the orchidometer and ultrasound, was larger than the left testes, we did not find any statistically significant difference between these measurements. This result was similar to a previously reported study with healthy children in which it was shown the left testes had a more prominent pampiniform plexus and slower venous drainage (as venous drainage in the left testis is relatively perpendicular to the left renal vein anatomically), thus, the left testis was generally warmer and smaller.(15)

We also analyzed the correlation between the testicular volume of TDT patients measured by ultrasound and orchidometer with their BMI and there was no significant correlation between them. However, other studies showed that testicular volume and BMI in healthy patients had a significant but weak correlation.(22,25)

A study on 65 boys aged 7 to 24 years comparing the sensitivity of the orchidometer and ultrasound to detect differences in the testicular volume found that ultrasound was more accurate than the orchidometer. The study also showed that the sensitivity of the orchidometer was 50% (weak).(26) Limitations regarding testicular volume using an orchidometer were found as it also measured the skin and subcutaneous tissue, particularly in patients with smaller testes and thicker skin and subcutaneous tissue and with different testicular tissue shapes, such as not uniformed or ellipsoid testes shape.(27)

Recent study showed that ultrasound is still more beneficial for assessing the testis because it is more accurate than an orchidometer. A study addressing thalassemia men in Iran showed that small testicular volume had a significant correlation with low sperm parameters, a factor that affects patient fertility.(28) By assessing testicular volume in thalassemia men using ultrasound, a method that yields more information about the size and structure of the testis, we can prescribe appropriate medication to help reduce the risk of infertility in men with thalassemia.

Since this study has a small sample size and did not compare the testicular volume between TDT and normal Indonesian patients, further studies with a bigger sample size and a better study design should be conducted to show that more benefits could be obtained through the use of ultrasound in assessing testicular volume in thalassemia patients.

## Conclusion

The majority of TDT subjects were underweight, followed by normal weight, and no TDT subjects were overweight or obese. However, the nutritional status showed no significant correlation with testicular volume. As measured by ultrasound, testicular volumes were significantly smaller than those measured by orchidometer. Ultrasound yields more detailed information about the testis, which can help clinicians assess the testis in thalassemia patients.

## Authors Contribution

RM, JP, and EY were involved in the conception and planning of the research. RM, DAL, and REY performed the data acquisition/collection. JP and EY calculated the experimental data and performed the analysis. RM, JP, and REY aided in interpreting the results. RM and DAL drafted the manuscript. DAL and REY designed the figures and tables. All authors took part in giving critical revision of the manuscript.

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