## **Research paper**



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#### Keywords

artificial intelligence; eosinophilic oesophagitis; oesophageal total wall thickness; endoscopic sonography

# EUS in children with eosinophilic oesophagitis – a new method of measuring oesophageal total wall thickness area. An artificial intelligence application feasibility study. A pilot study

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### Abstract

Aim: In the study, we aimed to introduce a formula for measuring the oesophageal total wall thickness area, which could be used for developing an artificial intelligence-based algorithm for the detection of patients whose total wall thickness area exceeds the norms. Material and methods: Mathematical formulas for measuring the square area of the oesophageal total wall thickness area were introduced and applied. Children were grouped according to their weight in clusters. For each cluster, the range (minimal and maximal value) were established. The measurements were done by using the formula for the area of the circular ring according to the formula A =  $\pi$  (B2–b2); the product of  $\pi$  and subtraction square b (smaller radius) and square B (bigger radius). The basic data for our calculations were derived from papers published by Dalby et al., 2010 and Loff et al., 2022. Results: The square area (in mm<sup>2</sup>) of the oesophageal wall was calculated and proposed to be introduced for further analysis. This value set could be used for creating an algorithm for computer-aided analysis of patients diagnosed with sonographic examination and isolating patients for surveillance. Our newly introduced approach could be implemented in sonographic, computer tomography, and magnetic resonance examinations in eosinophilic oesophagitis and other oesophageal diseases. Conclusions: Total wall thickness area could be used for monitoring children with eosinophilic oesophagitis and other oesophageal diseases. The method could also be applied for adults. Therefore, it can be a foundation for further progress with applying artificial intelligence algorithms.

# Introduction

Eosinophilic oesophagitis (EoE) is diagnosed worldwide, and susceptibility to the disorder has increased over the last 10 years<sup>(1,2)</sup>. Both children and adults are affected. In Poland, approximately 1 out of 5,000–10,000 individuals suffer from the condition, which gives a figure of approx. 3.8–7.6 thousand all together in Poland. Other authors estimate the incidence and prevalence as 10–57/100,000<sup>(3,4)</sup>. The disease is more often diagnosed in North America, Europe or Australia than on other continents. Consequently, one can extrapolate the number of affected people across the world as circa 800,000–4,560,000. The majority of them are young (20–30 years old) male individuals, and every fifth diagnosis is established in childhood<sup>(5)</sup>.

The number of diagnosed children is growing rapidly<sup>(2)</sup>. The disease usually occurs in patients with a food and/or inhaled allergy<sup>(6,7)</sup> with age-related and atypical symptoms. No singular symptom is characteristic for EoE<sup>(2,6,8)</sup>. No macroscopic changes found in the oesophagus are pathognomic for EoE<sup>(7)</sup>. Extraction of specimens are necessary for establishing the diagnosis. Histologic findings of ≥15 eosinophils per high-power field serve as the diagnostic hallmark<sup>(4)</sup>.

There are no straightforward correlations between patients' symptoms, endoscopic changes, and histologic examination<sup>(8)</sup>. The wall may be thicker in some diseases, among them in EoE. This abnormality can be diagnosed or traced with high-resolution endoscopic sonography (EUS). The oesophageal wall thickness (TWT) or chosen wall layer thickness can be assessed and measured<sup>(8-10)</sup>. No Artificial Intelligence (AI) methods have been applied in diagnosing or treating EoE children so far<sup>(11,12)</sup>.

Our objective was to introduce a formula for measuring the oesophageal total wall thickness area (TWTa) in oesophagitis which can be used as a foundation for developing an AI-based algorithm. The formula can also be applied in patients with other oesophageal diseases – for example scleroderma, oesophageal burns, surgical reconstructions and others.

# Material and methods

# Compliance with ethical standards

This feasibility study was performed without the participation of patients – we analysed the posssibilities of applying a new method. The study was approved by the Institutional Review Board (ZAPUMW 29. 03. 2023/1). The IRB had waived the requirement to obtain informed consent.

The basic data for our calculations were taken from papers published by Dalby *et al.*, 2010 and Loff *et al.*,  $2022^{(8,13)}$ .

During EUS, the circular sonographic scan of the oesophageal wall could be taken in the thoracic part of the oesophagus at the level of the Th3–Th7 vertebrae. The lumen and wall could be observed and analysed (Fig. 1).

### Statistical analysis

In this pilot study, we did not perform any statistical analysis. The reason for this was the study design. We introduced a new method of measuring TWTa in patients with EoE.

When dilated, the oesophagus looks like a tube. When the US transducer is situated inside the oesophagus, its lumen is dilated, as shown in Fig. 2.

The oesophageal lumen area can be calculated according to the following formula describing the square area of the circle as 'multiplication  $\pi$  by square radius of the circle':

AL. =  $\pi$ · r<sup>2</sup>

Where:  $A_L$  – oesophageal lumen area;  $\pi$  = 3.14; r – oesophageal lumen radius.

The area of the oesophageal lumen plus TWT can be calculated according the same formula. The calculated value is the product of  $\pi$  and the square sum of adding the oesophageal lumen radius and TWT.

 $A_w = \pi^{\cdot} (Z)^2$ 

Where:  $A_w$  = the surface area of the circle composed of the oesophageal lumen and TWT;  $\pi$  = 3.14; Z = the radius of the lumen plus TWT.



Fig. 1. Oesophagus. Transverse section: lumen enclosed by oesophageal wall composed of mucosa, submucosa, muscular layer, and appendage. Histological specimen (animal; WMU museum collection). Courtesy of Prof. Piotr Dziegiel and dr. Aleksandra Piotrowska from the Department of Human Morphology and Embryology, Wroclaw Medical University



Fig. 2. Oesophagus, EUS scan. Radial probe with balloon filled with water. 1. Mucosa, 2. Muscularis mucosae, 3. Submucosa, 4. Muscularis propria, 5. Adventitia. Courtesy of dr. Abdulhabib Annabhani from the Department and Clinic of Gastroenterology and Hepatology, Wroclaw Medical University

The measurements may be simplified by using the formula for the area of the circular ring  $A = \pi$  (B<sup>2</sup>–b<sup>2</sup>); the product of  $\pi$  and subtraction square b (smaller radius) and square B (bigger radius).

The final formula for the oesophagus measurements can be shown as:

$$A_{TWTa} = \pi (Z^2 - r^2)$$

Where:  $A_{TWTa}$  – the surface area of TWT;  $\pi$  = 3.14; Z – the sum of lumen radius and TWT; r – oesophageal lumen radius.

The radius should be measured three times in four different points, and the mean should be calculated. The measurement points should be determined according to the clock rule: at 1, 3, 6 and 9, and here established. The measurement positions are shown as \* in Fig. 3.

Loff *et al.*, (study method: X-ray contrast imaging; 108 children) reported the normal oesophageal diameters as the upper measurement (level of Th 3 vertebra – superior border) or lower measurement (Th 7 vertebra upper edge) average out at 7–8.8 mm (upper – lower part, respectively) in children weighing 3 kg, 8–9.8 mm by 10 kg, 9–10.8 mm by 17 kg, 9.4–11.2 mm by 20 kg, 10.8–12.6 mm by



Fig. 3. Oesophageal lumen and its wall in horizontal section (homocentric circles<sup>\*\*</sup>). 1 (r) – radius of oesophageal L – 2 TWTa; Z – 1+2.
\* measuring points; \*\* two circles created homocentric (concentric or concentrical) circles with a common centre

30 kg, 12.2–14.1 mm by 40 kg, 13.6–15.5 mm by 50 kg, 15–17 mm by 60 kg, and 16.4–18.4 mm by 70 kg<sup>(13)</sup>. The oesophageal diameter values measured by Loff at al. were used by us for calculating the square area of the oesophageal lumen (in  $mm^2$ ). Our calculations are presented in Tab. 1.

Dalby *et al.* (study method: EUS; 78 children) measured mean (min-max) normal vs EoE TWT as 3.2 (1.8–4.7) vs 4.2 (3.7–4.9) mm in the thoracic and 3.4 (2.5–4.8) vs 4.2 (3.6–4.9) mm in the abdominal parts, and the mucosal+submucosal layer 1 (0.6–1.6) vs 1.5 (0.8–2.3) mm and 1.2 (0.7–1.7) vs 1.5 (1.1–1.8) mm, and the muscularis propria thickness 0.9 (0.7–1.3) vs 1.4 (0.9–1.8) and 1 (0.7–1.5) vs 1.4 (0.8–1.6) mm, respectively<sup>(8)</sup>.

Relying on these data (TWT measurements), we calculated the square areas of the thoracic part of the oesophagus according to the formulas described above. Our TWTa calculations are presented in Tab. 2.

<u>Procedure for performing measurements according to the new for-</u><u>mula</u>: during the EUS of the oesophagus, the inner and outer wall contour have to be marked in the middle of the oesophagus – the thoracic part between the Th3–Th7 vertebrae. In the next step, the square areas should be measured and compared with the normal

Tab. 1. Square area of the oesophageal lumen calculated according the formula  $\pi r^2$  (in mm<sup>2</sup>)

Children's age (weight according to our experience)		Square area of the oesophageal lumen (A = $\pi r^2$ ; multiplication) in mm <sup>2</sup>	
		Oesophagus at the 3 <sup>rd</sup> Th vertebral level	Oesophagus at the 7 <sup>th</sup> Th vertebral level
0–3 years (3–18 kg)	Calculations for 3 kg	3.14 and 3.5*2 = <b>38.46</b>	3.14 and 4.4 <sup>2</sup> = <b>60.79</b>
	Calculations for 18 kg	3.14 and 4.55 <sup>2</sup> = <b>65.01</b>	3,14 and 5.45 <sup>2</sup> = <b>93.27</b>
Above 3–6 years (13–29 kg)	Calculations for 13 kg	3.14 and 4.2 <sup>2</sup> = <b>55.39</b>	3.14 and 5.1 <sup>2</sup> = <b>81.67</b>
	Calculations for 29 kg	3.14 and 5.35 <sup>2</sup> = <b>89.87</b>	3.14 and 6.25 <sup>2</sup> = <b>122.66</b>
Above 6–13 years (18–66 kg)	Calculations for 18 kg	3.14 and 4.55 <sup>2</sup> = <b>65.01</b>	3.14 and 5.45 <sup>2</sup> = <b>93.27</b>
	Calculations for 66 kg	3.14 and 7.9 <sup>2</sup> = <b>195.97</b>	3.14 and 8.9 <sup>2</sup> = <b>248.72</b>
Above 13 years (39–70 kg)	Calculations for 39 kg	3.14 and 6.05 <sup>2</sup> = <b>114.93</b>	3.14 and 6.95 <sup>2</sup> = <b>151.67</b>
	Calculations for 70 kg	3.14 and 8.2 <sup>2</sup> = <b>211.13</b>	3.14 and 9.2 <sup>2</sup> = <b>265.77</b>

The normal oesophageal lumen according to Loff *et al.*, 2022 was a base for our calculations. Explanation: how we calculated this value:  $3.14 = \pi$ ; \* 3.5 mm, i.e. half of oesophageal diameter (7 mm) measured by Loff *et al.*, because the lumen radius is a half of the lumen diameter. The formula A =  $\pi$  r<sup>2</sup> was used for calculations. 38.46 = product.

Tab. 2. Square area of the oesophageal lumen with TWT (in mm<sup>2</sup>)

Children's age (weight according to our experience)		Square area of the oesophageal lumen with TWT (A = $\pi r^2$ ; multiplication) in mm <sup>2</sup>	
		Oesophagus upper level	Oesophagus lower level
0–3 years (3–18 kg)	Calculations for 3 kg	3.14 and (3.5* + 4.2**) <sup>2</sup> = <b>186,17**</b> *	3.14 and (4.4 + 4.2) <sup>2</sup> = <b>232.23</b>
	Calculations for 18 kg	3.14 and (4.55 + 4.2) <sup>2</sup> = <b>240.4</b>	3.14 and (5.45 + 4.2) <sup>2</sup> = <b>292.4</b>
Above 3–6 years (13–29 kg)	Calculations for 13 kg	3.14 and (4.2 + 4.2) <sup>2</sup> = <b>221.56</b>	3.14 and (5.1 + 4.2) <sup>2</sup> = <b>271.58</b>
	Calculations for 29 kg	3.14 and (5.35 + 4.2) <sup>2</sup> = <b>286.38</b>	3.14 and (6.25 + 4.2) <sup>2</sup> = <b>342.89</b>
Above 6–13 years (18–66 kg)	Calculations for 18 kg	3.14 and (4.55 + 4.2) <sup>2</sup> = <b>240.41</b>	3.14 and (5.45 + 4.2) <sup>2</sup> = <b>292.4</b>
	Calculations for 66 kg	3.14 and (7.9 + 4.2) <sup>2</sup> = <b>459.73</b>	3.14 and (8.9 + 4.2) <sup>2</sup> = <b>538.85</b>
Above 13 years (39–70 kg)	Calculations for 39 kg	3.14 and (6.05 + 4.2) <sup>2</sup> = <b>329.9</b>	3.14 and (6.95 + 4.2) <sup>2</sup> = <b>390.37</b>
	Calculations for 70 kg	3.14 and (8.2 + 4.2) <sup>2</sup> = <b>482.8</b>	3.14 and (9.2 + 4.2) <sup>2</sup> = <b>563.82</b>

The normal oesophageal lumen according to Loff *et al.*, 2022 and TWT in EoE patients according to Dalby *et al.*, 2010 were a base for our calculations. Explanation: how we calculated this value: \*\*\* 186.17 (product) = 3.14 and (3.5 + 4.2)<sup>2</sup>.  $3.14 = \pi$ ; \* 3.5 mm, lumen radius – half of oesophageal diameter (7 mm) measured by Loff *et al.*; \*\* 4.2 mm, TWT in EoE patients according to Dalby *et al.* 

Children's age (weight)		Square area of the TWT ring area (in mm <sup>2</sup> )	
		Oesophagus at the 3 <sup>rd</sup> Th vertebral level	Oesophagus at the 7 <sup>th</sup> Th vertebral level
0–3 years (3–18 kg)	Calculations for 3 kg	147.71*	171,44
	Calculations for 18 kg	175.39	199.13
Above 3–6 years (13–29 kg)	Calculations for 13 kg	166.17	189.91
	Calculations for 29 kg	196.51	220.23
Above 6–13 years (18–66 kg)	Calculations for 18 kg	175.39	199.13
	Calculations for 66 kg	263.76	290.13
Above 13 years (39–70 kg)	Calculations for 39 kg	214.97	238.7
	Calculations for 70 kg	271.67	297.85
Explanation: how we calculat and TWT calculated together;	ed these values: * 147.71. Subtraction 38.46 = square area of the lumen	on: 186.17 – 38.46 = 147.71 mm²; where 186	5.71 is the square area of oesophageal lumen

values described above. An important histological aspect is that the measurements have to be performed on the whole oesophageal wall, not on the oesophageal layers (mucosa, submucosa, muscularis, or tunica adventitia). We choose the wall thickness as the most reliable and suitable variable for the measurements.

Results

The predicted TWTa values (in mm<sup>2</sup>) according to age are shown in Tab. 3.

Predicted TWTa (in mm<sup>2</sup>) as min and max values for children of different weight categories are shown in Fig. 4. The curve is detailed to allow the sonographer to find the correct value at a glance. The calculated TWTa in young patients should be placed between the max and min values to be assessed as normal.

**Interpretation of TWTa** in children weighing 18 kg (as an example). The values for this weight are: min 175.4 mm<sup>2</sup> and max 199.1 mm<sup>2</sup>. If the TWTa is between these values, it should be seen as normal. We calculated 175.4 mm<sup>2</sup> as 240.41 mm<sup>2</sup> – 65.01 mm<sup>2</sup> = 175.4 mm<sup>2</sup>; where 240.41 mm<sup>2</sup> is the square area of the oesophageal lumen with the oesophageal wall, and 65.01 mm<sup>2</sup> is the square area of the oesophageal lumen. We calculated 199.1 mm<sup>2</sup> as 292.4 mm<sup>2</sup> – 93.3 mm<sup>2</sup> = 199.1 mm<sup>2</sup> according to the same method.



Fig. 4. TWTa range in mm<sup>2</sup> (minimal and maximal values) in children grouped according to weight

When TWTa is below 175.39, it shows that the oesophageal wall is too thin, and when it is above 199.13, the oesophageal wall is too thick, and the children should be diagnosed for EoE or other diseases in which the wall may be thickened.

## Discussion

EUS in children is mostly performed to diagnose choledocholithiasis, pancreatic fluid collections, pancreatitis or pancreatic mass<sup>(14)</sup>, so EoE is not the most common cause for performing the examination, but its usefulness has gradually increased<sup>(8,15)</sup>. EUS in children should be performed by paediatric sonographers because of the difference in patients' body size and the need for paediatric anaesthesia<sup>(16)</sup>.

We introduced a new method for tracing fibrosis with oesophageal wall thickening risk, which increases circa 5% a year since establishing the diagnosis. If the disease duration is longer or patients do not respond to treatment, stenoses occur due to chronic inflammation<sup>(13)</sup>. Oesophageal stenoses occurred in 17% patients with less than two years delayed diagnosis, but in circa 70% with a delay of 15–20 years<sup>(17)</sup>. In young children, the anticipated treatment period is very long – even up to several dozen years. The TWTa analysis can disclose oesophageal wall fibrosis during the routine check-ups. This is an additional benefit of our proposal.

There are some specific features that can be observed during endoscopy in EoE patients: mucosal fragility or oedema, white exudate areas, longitudinal groove and circular folds (transient or persistent; so called oesophageal trachealisation)<sup>(7)</sup>. The whole oesophagus appears as a narrow tube. However, these changes can be seen from the inner aspect and, therefore, there is a need for an additional method to support the endoscopic examination. If untreated, the disease leads to oesophageal fibrosis and fibrostenotic strictures<sup>(2,7,18)</sup>.

To establish the diagnosis, tissue specimens are taken by endoscopic biopsy (2–4 specimens should be assessed during gastroscopy). Eosinophilic infiltration in the mucosa (at least 15 eosinophils in the microscopic field; magnification 400x in light microscopy) is obligatory for diagnosis. Eosinophils in the oesophageal mucosa are present in more than one condition, for example in gastroesophageal reflux disease. Moreover, the same eosinophilic infiltration can be observed in coeliac or Crohn diseases or intestinal inflammations (but usually less than 15 cells). The treatment in those conditions is different, so the differentiation is crucial. In our study, we introduced a simple method to support the supervision, namely changes in TWT.

We chose the weight-dependent reference value, because the normal diameter (an important factor in our new method) of the oesophagus is corelated with the child's weight, but not with age<sup>(13)</sup>. We decided to base our measurements on TWT, and not on the mucosal, submucosal or muscular layer thickness, due to its simplicity and reliability. For example, during steroid therapy in EoE patients, changes are mainly observed in the increasing mucosal layer thickness, while the other layers are resistant to therapy<sup>(19)</sup>. We decided to choose TWT as a key parameter as more reliable than others. We decided to measure the thoracic part of the oesophagus at Th3– Th7. The usefulness of the mucular layer thickness instead of TWT should be considered and analysed in further studies.

EUS wall measurements may present challenges due to its specific anatomical morphology. When empty, the oesophagus looks like typical tubular viscera (Fig. 1). The folds could be a potential pitfall<sup>(20)</sup>. To exclude these problems, we postulate performing the examination in a standardised oesophageal lumen established previously <sup>(13)</sup>, for example by using the balloon enclosed the US transducer proposed by Rabinowitz<sup>(20)</sup>.

Lastly, we postulate to rely on the square oesophageal wall according to the formula for measuring the square area of the ring/circular belt. The formula for the square area is a product of multiplication  $\pi$ and subtraction of square radiuses of oesophagus lumen and TWT (calculated together) and lumen radius;  $A = \pi$  ( $Z^2$ - $r^2$ ). The square area measurements are more reliable, because the risk of mistake is smaller, with four measurements and extraction of the mean value. We hope that this method for measuring the square area of the wall as a ring could be developed and introduced in other radiological examinations, including X-ray, CT and/or MRI, in which the oesophageal wall thickness could be measured.

We agree with Min *et al.* in that the adoption of AI in gastroenterology is expected in the near future<sup>(21)</sup>. AI methods are slowly being implemented both in children and in adult patients, for example for inflammatory bowel disease treatment<sup>(22,23)</sup>. We introduced a method that is easy to apply in AI examinations of EoE children.

AI is still in its early stage, but it is being rapidly put into use. Machine learning is an AI method in which data analysis is focused on the recognition of different patterns. So, in the simplest terms, the AI uses input data to predict the real visceral status, for example oesophageal wall thickness. Deep learning methods provide computer-aided detection of mucosal ulcers on capsule endoscopy images<sup>(24)</sup>. Convolutional neural networks could be used in the analysis of the oesophageal wall status on post-examination images<sup>(25)</sup>. We proposed a set of data to initiate this analysis. An AI algorithm may be created with the proposed data set and further applied for different oesophagus examination methods, among them X-ray, Computer Tomography, Magnetic Resonance Imaging, and US examination. We think that the oesophageal wall thickness could be analysed during routine thoracic cavity examination<sup>(26)</sup>.

Moreover, the newly introduced TWTa method could be introduced for monitoring children after oesophageal burns, surgical reconstructions, connective tissue diseases, and scleroderma. We see a potential benefit of TWTa measurements in the treatment of patients with oesophageal wall injuries after foreign body swallowing and in oesophageal reflux disease resistant to treatment (for example in children with congenital or acquired central nervous system disorders). TWTa could also support the diagnosis of oesophageal motor activity disorders. Lastly, it can be used to support the diagnosis of bone-marrow transplant patients with dysphagia in GRAFT evaluation.

## Conclusions

1. We introduced a simple set of minimal and maximal values of the oesophageal wall thickness square area in children of different weight.

2. We find TWTa measurements useful in monitoring patients with diagnosed EoE to isolate those with fibrosis risk.

#### Limitations of the study

It is difficult to conduct studies in children due to the lack of publications. Also, it is challenging to use the same methods due to variety of methods and perspectives presented in paediatric populations. There are no reliable measurements of applied parameters in children. The oesophageal lumen radius landmark values must be regarded with a tolerable variation of circa 2 mm rather than absolutes (natural fluctuation at a given weight).

#### **Conflict of interest**

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

#### Author contributions

Original concept of study: SW. Writing of manuscript: SW. Analysis and interpretation of data: SW, RK, KA, TP, UZD. Final approval of manuscript: SW, RK, KA, TP, UZD. Collection, recording and/or compilation of data: SW, RK, TP, UZD. Critical review of manuscript: RK, KA, TP, UZD.

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