

# Predicting pediatric esophageal wall thickness: An EUS study

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## ABSTRACT

**Background and Objective:** EUS has been shown in two small series to be capable of documenting increases in the total esophageal wall thickness (TWT) in children and adults with eosinophilic esophagitis (EoE). To apply EUS-derived TWT in clinical situations or in scientific investigations in pediatric EoE, measurements of esophageal TWT in children of differing ages and heights are required. **Materials and Methods:** Thirty patients (18M: 12F, 7 months to 20 years and 10 months) with a history of esophageal symptoms, but no endoscopic or histologic criteria of EoE were studied using a through the scope 20 MHZ Olympus Ultrasound miniprobe UM-3R (Olympus America, Center Valley Pa 18034) through a GIF Q180 or 160 (Olympus) standard pediatric upper endoscope. The mucosa, the mucosa plus submucosa, and the TWT were measured in the mid- and distal esophagus immediately before taking diagnostic biopsies. **Results:** Measurements from both sites showed a statistically significant increase in TWT as a function of age ( $P < 0.001$ ) and height ( $P < 0.001$ ), as did the individual layers. The width of the mucosa and the submucosa were equivalent and together, they contributed more than half of the entire TWT. There were no significant differences between the means of the mid- and distal esophageal measurements. A multiple regression equation that can predict TWT based on age, with 95% confidence limits, is presented. **Conclusions:** EUS has demonstrated that esophageal TWT in a cohort of control children correlates with height and with age and has provided insights into the organization of the esophageal wall. Esophageal TWT values obtained by EUS can now be interpreted to recognize esophageal wall thickening throughout childhood.

**Key words:** EUS, esophagus, pediatrics

## INTRODUCTION

Endosonographers are beginning to evaluate diagnostic high-resolution EUS as a tool to characterize transmural gastrointestinal (GI) pathology. EUS has been suggested as an easy, safe, and economical tool to differentiate

and measure individual layers of the GI tract without subjecting patients to the dangers of radiation. Small studies have provided data proposing that EUS can distinguish Ulcerative Colitis from Crohn disease,

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by identifying the extent of bowel wall thickening as well as other submucosal features limited to Crohn disease.<sup>[1,2]</sup> Two groups have also reported increased EUS measurements in total esophageal wall thickness (TWT) in 11 children (2.1 *vs.* 1.5 mm)<sup>[3]</sup> and in 28 adults (3.05 *vs.* 2.18 mm)<sup>[4]</sup> with eosinophilic esophagitis (EoE), compared to controls. Review articles have hypothesized that these EUS measurements reflect the pathophysiologic esophageal wall remodeling attributed to EoE.<sup>[5,6]</sup>

Several radiographic series employing different approaches to measure esophageal TWT highlight the challenges in obtaining reproducible, quantitative data. Computed tomography (CT) scans from 110 consecutive adults revealed that the esophageal TWT varied greatly between contracted (4.7 mm) and dilated (2.1 mm) segments.<sup>[7]</sup> Esophageal CT demonstrated an increase in thickness between adults with esophageal cancer (6.4 mm) compared to controls (6.0 mm) and to highlighted differences between adults with esophagitis (4.7 mm) and controls (2.9 mm).<sup>[8,9]</sup> External sonography performed in 93 children aged 1–15 years determined that the cervical esophagus TWT was 2.8 mm at all ages<sup>[10]</sup> and in another group of 124 healthy children 2 days to 12 years the gastroesophageal junction TWT ranged from 2.4 to 5.7 mm.<sup>[11]</sup> A previous EUS study of 24 EoE patients, available only as an abstract, has also noted an increased TWT compared to gastroesophageal reflux (GERD) patients (3.86 *vs.* 3.18 mm).<sup>[12]</sup>

In adults, anatomic relations are conventionally defined by comparing individual patients to universal standards, which are often divided by gender. However, in growing children, there are ranges of normal reflecting the dramatic changes in their developing bodies. This includes the diameter of their esophageal wall, as scant data exist on normal TWT measurements in children. If esophageal TWT is proven to be a reliable marker for esophageal remodeling in pediatric EoE, baseline values in children without EoE are necessary. The present study describes a subset of a larger group of patients enrolled in a prospective, IRB approved study to investigate children with symptoms suggestive of EoE. The aim of the present article is to present and interpret the EUS measurements from the mid- and distal esophagus in a cohort of children with no endoscopic or histologic evidence of EoE. EUS measurements from these controls are plotted as a function of age and of height. The equations derived from this pilot study can guide

evaluation of esophageal TWT measurements in any child having an endoscopy to evaluate for EoE.

## MATERIALS AND METHODS

### *Patients*

The 30 patients described in this study were part of the first 98 patients recruited to participate in a SUNY Downstate Institutional Review Board approved protocol between April 1, 2012, and September 1, 2018. The present study investigates children with symptoms of esophageal dysfunction requiring endoscopy. For younger children symptoms included, vomiting, food aversion, food refusal, and failure to thrive. For older children, they included heartburn and dysphagia, and for adolescents' food impaction was occasionally noted. The present study inclusion criteria required patients with <15 eosinophils per high-power field (eos/hpf) who had EUS data obtained at the time of endoscopy. The study cohort were subsequently further screened with additional methods, as described below to eliminate any patient with endoscopic or histologic features of EoE, and are referred to as controls. The majority (25/30) of the presented cohort were found on their initial endoscopy to not meet the criteria for EoE. Five participants with an initial diagnosis of EoE had measurements obtained after they received therapy, which yielded a prolonged clinical, endoscopic, and histologic remission. Informed consent was obtained from the parents of children under 18 and directly from the patients who were over 18 years. Assents were obtained from all children 7–18 years of age.

All study participants were screened with objective quantitative scoring systems designed to identify and characterize patients with EoE. None had either endoscopic or histologic quantitative scores associated with EoE. EoE Endoscopic Reference Score (EREFS) is a validated esophageal endoscopic score based on features observed in adult EoE<sup>[13]</sup> that has recently been successfully applied to children.<sup>[14]</sup> A quantitative histopathology score was also determined by two pathologists (BL, RG) based on a recently published EoE histologic scoring system (EoEHSS) developed by ML Collins *et al.*<sup>[15]</sup> The scoring system rates multiple histologic features commonly noted in EoE to yield both a grade (intensity) and a stage (distribution) score.

### *Methodology*

EUS was performed utilizing a 20 MHZ Olympus ultrasound miniprobe UM-3R (Olympus America, Center Valley Pa 18034) and an Olympus M305 Stream US

processor. Two endoscopists (EG, SSR) performed the first 20 cases described in this manuscript jointly and the latter performed every subsequent investigation. The probe was passed through a 2.8 mm channel in a standard Olympus pediatric upper endoscope (Olympus America, Center Valley Pa 18034) under general anesthesia. The identification of the individual anatomic layers of the esophageal wall followed the approach previously employed by Fox *et al.*<sup>[3]</sup> Ultrasound measurements were obtained after completing an endoscopic inspection of the esophagus, stomach, and duodenum and before esophageal biopsies. To measure distal esophageal thickness, the probe was positioned 2–3 cm above the lower esophageal sphincter. The head of the bed was raised (to minimize the risk of aspiration), and water was infused to create an acoustic interface. After allowing the esophagus to be fully distended, images showing clear demarcation of the layers were frozen, and measurements were obtained from two images using the electronic calipers that are included in the Olympus processor and their proprietary NS software (Olympus America, Center Valley Pa 18034). The measurements were derived from unique images in most cases corresponding to different sites from the same region and were then averaged. If measurements varied by >20%, the procedure was repeated until reproducible values were obtained, which were then averaged. Measurements were made at least twice to avoid the potential confounding effect of esophageal contractions and asymmetry. The mucosa, the mucosa plus submucosa, and the TWT were measured. The same procedure was repeated for the mid-esophagus based on the endoscopic determination of the upper and lower esophageal sphincters. Values are presented as means with standard deviation. The stomach was then emptied of added water and biopsies were obtained from the same sites as the EUS measurements. Figure 1 illustrates the endoscopic images and the measurements obtained.

### Data analysis and statistics

EUS measurements of TWT at the mid- and distal esophagus were plotted *versus* the independent variables (age, height, and body mass index [BMI]). Linear regression lines were generated from the data in Figures 2 and 3 and were calculated along with coefficients of determination ( $R^2$ ) through Excel. All of the analyses of the individual layers in Supplementary Table 1, as well as the other *P* values, were derived through Excel. When provided, values are means  $\pm$  standard deviations.

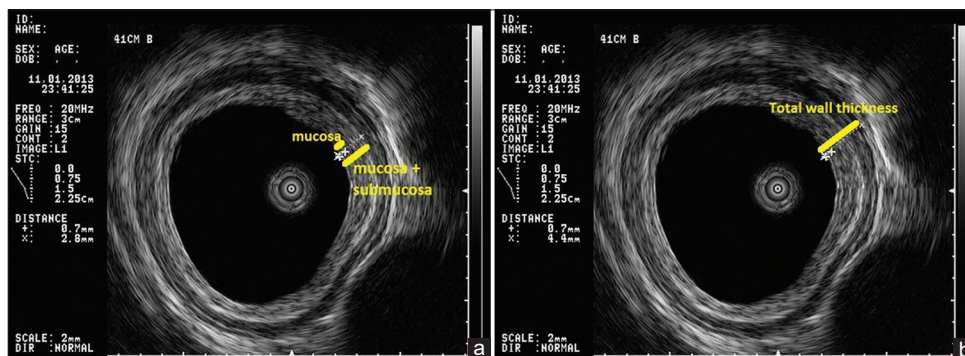
As shown in Figure 4, multiple linear regression of only the 23 controls with full data sets was used to predict the TWT in the distal esophagus. Initial regression models were calculated that included age, height, and weight. This did not yield a model superior to that using age alone, and hence, the final model used age only. Since the sample sizes are small, attention was paid to the coefficient of multiple determination and root mean squared error rather than statistical tests to gauge model suitability. The question of homoscedasticity was crudely assessed from scatterplots. A 95% prediction interval (PI) was generated for each model. The interpretation of the PI is that if the model is valid, then the TWT of 95% of children without EoE will fall within the limits of the PI.

Two-tailed Wilcoxon signed-rank tests were used to compare the controls from treated EoE and in Figure 5 to compare mid-with distal-esophageal measurements of the following parameters: TWT, mucosa, mucosa + submucosa, and muscularis propria.

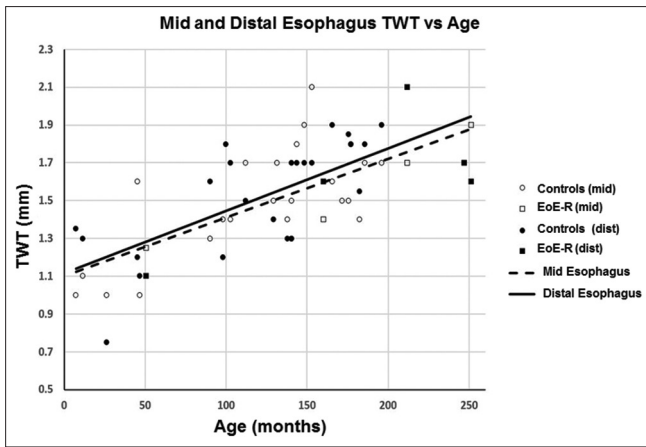
## RESULTS

### Patient characteristics

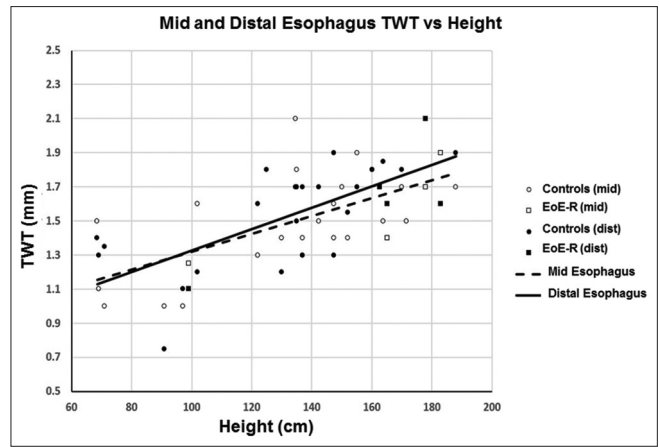
The study cohort included 18 males and 12 females



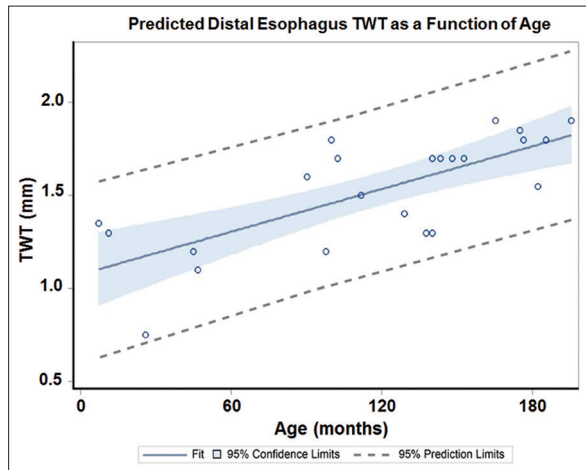
**Figure 1.** EUS images obtained using an Olympus miniprobe from normal appearing esophageal mucosa. The cursors highlight the values that were measured for the figures and tables. (a) demonstrates the hypoechoic bands that define the mucosa and submucosa and (b) illustrates the borders that define the total wall thickness



**Figure 2.** Esophageal total wall thickness correlates with age. In both Figures 2 and 3 mid-esophageal data are drawn as dashed lines and the distal esophageal data as solid lines. Individual EUS data points from the distal esophagus are solid circles or boxes, and open circles or boxes from the mid-esophagus. The 25 controls are plotted as circles and the five EoE-R measurements are represented by the boxes

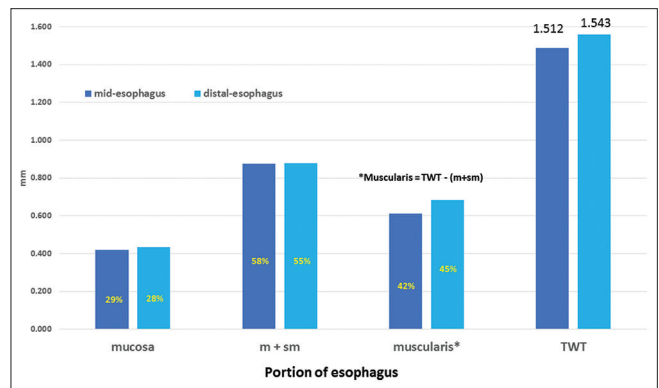


**Figure 3.** Esophageal total wall thickness correlates with height. Legends are as described in Figure 2



**Figure 4.** Multiple regression was performed on the distal esophageal total wall thickness for only the 23 control patients with complete EUS data. There is a statistically significant correlation between total wall thickness and age and a best fit equation was generated. The blue area contains the mean total wall thickness for that age with 95% confidence. The dotted lines correspond to the range that predicts with 95% confidence the esophageal total wall thickness for a child with GERD

(all in the control group). The maximum eos/hpf was 5 distal and 10 mid-esophagus. Twenty-five patients had no eosinophils in the mid-esophagus and 19 had none in the distal esophagus. The patients ranged from infancy (7 months) to young adults (20 years and 10 months) with an average age of  $10.9 \pm 5.4$  years. Accordingly, their anthropometrics represented a good deal of the pediatric spectrum: from 69 to 188 cm (mean  $136 \pm 34$  cm); from 9 to 115 kg (mean  $42 \pm 26$  kg); and BMI from 14 to 43 (mean  $20.2 \pm 6.0$ ). There were 13 (52%) males among the 25 controls. Five patients with EoE



**Figure 5.** Mean values of the EUS measurements are compared between the mid and distal esophagus. Measurements of the mucosa, mucosa + submucosa, and the derived value of the muscularis propria (esophageal total wall thickness – [mucosa + submucosa]) are shown for both the distal- and mid-esophagus. The percentages that the individual layers contribute to the total wall thickness are shown as well as the actual measurements of the total wall thickness. There are no differences in any of the individual layers between the mid- and distal-esophagus

had received effective therapy to reverse clinical, endoscopic, and histologic features. All were followed with serial examinations and after documentation of sustained remission for >12 months were then included. These five were all males, had been followed for a longer period, and were slightly older than the controls ( $15.3 \pm 6.9$  years *vs.*  $10.0 \pm 4.7$  years,  $P = 0.045$ ).

None of the patients in the study cohort had either endoscopic or histologic quantitative scores associated with EoE, as described in the methods. The cohort's maximum EREFS score was 1. The mean ( $0.1 \pm 0.3$ ) was similar to the values previously published for control children (0.2) and was significantly different than the published values in children with



untreated EoE (2.4).<sup>[14]</sup> The mean EoEHSS grade scores (distal 0.09, mid 0.08) were slightly less than the published cohort of children with EoE who had responded to treatment (distal 0.29, mid 0.14) and were substantially different from their untreated cohort (distal 0.47 and mid 0.44).<sup>[15]</sup> The mean stage scores of our cohort (distal 0.07, mid 0.06) were also less than those noted in the published cohort of treated patients (distal 0.21, mid 0.13), which were themselves statistically different from their untreated counterparts (distal 0.5, mid 0.46).<sup>[15]</sup> Individual scores, EREF scores, Eos/hpf, and individual EUS measurements for the entire cohort are available in Supplementary Table 1.

### Total wall thickness in normal children

Figure 2 plots the EUS-derived TWT as the independent variable at both the mid- and distal esophagus as a function of age in months. Data from both sites show a statistically significant increase in TWT with older children ( $P < 0.001$ ). While it appears that the thickness of the distal esophagus is slightly greater than the mid-esophagus, Figure 5 compares the mean values and indicates that they are not significantly different. The scatter of the measurements obtained, represented as the inverse of the coefficients of determination ( $R^2$ ), was determined. In this small cohort, the degrees of scatter were very similar between the mid- and distal esophageal TWT measurements, as shown in Table 1.

Figure 3 similarly plots the EUS-derived TWT as the independent variable *versus* the patients' height and again demonstrates a statistically significant increase in TWT with increasing size at both sites ( $P < 0.001$ ). Table 1 shows that the scatter of the measurements obtained was slightly greater in the distal compared to the mid-esophageal TWT as a function of height. Only the distal esophageal measurements correlated with the BMI, but the scatter of the data was so poor that it is not recommended to base TWT on a pediatric patient's BMI [Table 1].

Figure 4 provides a more rigorous statistical analysis of the distal esophageal data that permits formal calculations of 95% PIs. This linear regression model is based only on measurements obtained from the cohort of 23 controls with a complete set of data [Supplementary Table 1]. The blue section indicates the 95% confidence level of the mean TWT UES measurement for children at different ages. The regression plot predicts the distal esophageal TWT in mm to be equal to  $1.076 + (0.0038 \times \text{age in months})$ .

**Table 1. Total esophageal wall thickness, mucosa, mucosa + submucosa, and muscularis thickness correlate with height and age in both the mid- and distal-esophagus**

Dependent variable	M or D	Layer	SD	R <sup>2</sup>	P
Height	M	TWT	0.2815	0.4059	**
Height	D	TWT	0.3048	0.4933	**
Age	M	TWT	0.2815	0.5134	**
Age	D	TWT	0.3048	0.5109	**
BMI	M	TWT	-	0.0533	NS
BMI	D	TWT	-	0.1442	*
Height	M	M	-	0.2729	**
Height	D	M	-	0.2945	**
Height	M	M + SM	-	0.1611	*
Height	D	M + SM	-	0.3691	**
Height	M	Muscularis	-	0.5030	**
Height	D	Muscularis	-	0.3162	**

TWT, mucosa, mucosa + submucosa, and muscularis thickness correlate with height and age in both the mid and distal esophagus. The coefficients of determination ( $R^2$ ) were calculated for the data points providing the lines shown in figures 2 and 3. The values for height and age are similar and provide a more accurate assessment than employing BMI to predict EUS TWT.  $P$  values correlating the thickness of the individual layers to age were similar to correlations with the height and are not shown. In general, the scatter of the measurements ( $R^2$ ) was greatest in the mucosa and least in the muscularis.  $P$  values were defined as: \* =  $< .05$ , \*\* =  $< .005$ . SM: Submucosa, SD: Standard deviation

Based on this pilot study, 95% of children having an endoscopy to evaluate esophageal symptoms but not having EoE, would be anticipated to be within 0.43 mm of this predicted value. A parallel analysis of the mid-esophageal data (data not shown) generated a linear regression line which predicted mid-esophageal TWT in mm by the sum of  $1.070 + (0.0035 \times \text{age in months})$ . The mid-esophageal TWT 95% predicted index would be within 0.47 mm of this value.

### Individual esophageal layers in normal children

The mean values derived from the entire cohort are shown in Figure 5. Three measurements were directly obtained by EUS: Mucosa, submucosa + mucosa and TWT. The muscularis propria was a derived value from the other three, ( $\text{TWT} - [\text{mucosa plus submucosa}]$ ). Figure 5 provides insights into the organization of the normal pediatric esophageal wall. There are no significant differences in either the TWT or the diameters of the individual layers between the mid and distal esophagus (all four  $P > 0.05$ ). The diameters of the mucosa and the submucosa are comparable and together they are thicker than the muscularis propria, thus contributing more than half of the TWT. Similar to the TWT, the diameters of each of the individual layers in both the mid and distal esophagus all correlate significantly with height and age [Table 1]. The scatter of the measurements ( $R^2$ )

appears to be greatest in the mucosa and least in the muscularis propria [Table 1]. There are at least two potential explanations for this observation. One is that the mucosa is the thinnest layer, so a small inaccuracy will have a greater proportional impact. A second factor is that in some of the younger children, the hypoechoic band from mucosa to submucosa was not as sharply defined as previously noted,<sup>[3]</sup> while images from the older adolescents were similar to images published in adults.<sup>[4]</sup>

## DISCUSSION

EUS measurements from both the mid- and distal esophagus in a cohort of control children without any evidence of EoE, are presented for the first time that the authors are aware of. The esophageal TWT and the diameters<sup>2</sup> of the individual layers all correlate with age and height at both sites, but not with BMI. There were no significant differences between the scatter of the data obtained in the mid and distal sites. Although the overall means of the distal *versus* the mid-esophagus TWT were not statistically different [Figure 5], the distal diameter appears to be greater than the mid-esophageal wall thickness, especially in the taller children. The probable explanation is that in some children, the upper portion of the lower esophageal sphincter may have been included. Figure 4 provides a more rigorous statistical analysis that is limited to only the 23 controls that have a full set of esophageal TWT measurements. An equation to estimate the distal esophageal TWT based on a child's age in months, and a factor to predict the 95% range of children without EoE is presented. The mid-esophageal equation is nearly identical and is provided as an additional reference.

The combined esophageal mucosa and submucosa were the widest portion of the distal esophagus, as was noted in a small group of children<sup>[3]</sup> and adults<sup>[4]</sup> In addition, this is the first presentation of data establishing that each layer contributes similarly to the TWT in both the distal- and mid-esophagus. Table 1 provides the coefficients of determination,  $R^2$ , which reflects the scatter in the data set. Potential explanations for the scatter noted in this preliminary data set include an inherent feature of the EUS technique, a specific application of EUS in the esophagus such as neighboring structures, esophageal contractions, and the lower esophageal sphincter, or it may represent a true physiologic range in childhood.

The utility of EUS in pediatric EoE was first suggested in a seminal paper by Fox and colleagues in 2003, who demonstrated increased TWT in 11 children with EoE compared to 8 controls who had no gross or histologic evidence of esophagitis.<sup>[3]</sup> Like the present report, their EoE patients had statistically significant thickening of the entire esophageal wall, of the combined mucosa and submucosa, and of the muscularis propria compared to a similar aged cohort of children having endoscopy for another indication.<sup>[3]</sup> The techniques employed were similar, including identical recruiting strategies yielding a similar small number of patients, with a similar mean age. Both studies employed a similar endoscope, an Olympus miniprobe, and an Olympus processor and proprietary software to measure distances.

There are several minor differences. The present study measured the mid and distalesophagus, while the former study only reported values from the distal esophagus. As biopsies to identify EoE are routinely taken from the distal mid-esophagus as well, this information was felt to be potentially valuable. The previous study characterized their controls as having no gross or histologic evidence of esophagitis while our cohort was screened with EoE scoring tools that were not available at the time of the earlier study. The earlier study measured the distal esophagus 3-5 cm above the lower esophageal sphincter, whereas our data were obtained 2-3 cm above the same landmark and may have included part of the lower esophageal sphincter. Finally, Fox *et al.* calculated their diameters based on an image when the esophagus was “passively dilated with water” and sought out the “thickest representative portion avoiding thickened folds.” The data reported in this study were obtained from images of a maximally dilated esophagus. Our images obtained at maximal dilation yielded more reproducible measurements. However, the variance in technique is a potential contributor as to why the distal esophageal values in the present cohort are slightly less than the earlier measurements. Comparing similarly aged children, Fox reported greater values for mean TWT (2.1 *vs.* 1.5 mm); mucosa + submucosa (1.1 *vs.* 0.84 mm) and muscularis propria (1.0 *vs.* 0.67 mm). In both cohorts, there were some difficulties distinguishing some of the layers.

Straumann *et al.* were the first to incorporate serial EUS measurements of baseline increased TWT as a secondary outcome in clinical EoE investigations. A cohort of 28 Swiss adults and adolescents (>14 years) with active EoE had EUS performed before and after 50 weeks of either

maintenance topical steroid or placebo.<sup>[4]</sup> The authors interpreted the increase in TWT noted in active EoE, which was associated with increases in histomorphometric markers of fibrosis and elevations of TGF-1 and tenascin C, as representing tissue remodeling. The treated EoE patients had a significant decrease in their TWT, limited to only the mucosal layer, which remained elevated compared to a cohort of 31 older ( $63.3 \pm 13.2$ y) “esophagus healthy” controls. The Swiss control adults had TWT thickness of  $2.18 \pm 0.35$  mm, similar to the Fox pediatric values. However, the actual reported sum of the individual layers (mucosa + submucosa + muscularis) equaled 1.4 mm, virtually identical to the TWT in our cohort. The Swiss paper recognizes this disparity and states that “TWT thickness included entry and exit signals and therefore exceeded the sum of the three single layer signals.”<sup>[4]</sup>

Two smaller published series have yielded EUS TWT results in patients with EoE that emphasize the need for a single, universal methodology to obtain these measurements. Among ten Japanese adults with clinical, histologic, and multiple endoscopic features that included a cobblestone-like appearance in five patients, only a single patient had increased TWT.<sup>[16]</sup> In a small study of 29 Danish children, the mean TWT (3.4 mm distally and 3.2 mm proximally,<sup>[17]</sup> were considerably greater than the corresponding values reported in the Swiss adults above.<sup>[4]</sup> Finally, a case report<sup>[18]</sup> and an abstract presentation<sup>[19]</sup> are preliminary suggestions of the clinical value for EUS. Both anecdotally employed normalization of increased TWT instead of resolution of esophageal eosinophilia to guide pharmacologic management. Both patients required prolonged therapy to reach this endpoint, and both remained in clinical remission after cessation of medical therapy.

As with all anatomic structures, esophageal anatomy would be expected to change as a child grows. If TWT is established as a reliable early marker of esophageal remodeling in EoE, then it may be an even more important disease characteristic than mucosal eosinophilia, as was suggested.<sup>[18]</sup> To interpret EUS measurements in children, where remodeling may be more subtle, normal values for children of similar age and/or heights are required. The two preliminary equations derived from the data points in Figure 4 allow the interpretation of EUS measurements obtained during endosonography on a child with suspected or treated EoE.

There are several limitations of the data presented. First is that the control group is small in number and may not be truly representative of “normal” children. As it is unethical to perform endoscopy under anesthesia with the 5-6 biopsies required to rule out EoE and to then add EUS on completely asymptomatic children, the cohort was rigorously screened with validated scoring systems to rule out any potential patients with EoE. Since diagnostic esophageal EUS will only be applied to children who are having clinically indicated upper endoscopy for esophageal symptoms, the values presented should have utility for this purpose. For the same reason, the sample size is small, composed mainly of children with clinical features suggesting EoE, who had a study performed and then were found to not have any evidence of the disease. By virtue of the small number of data points, the regression model that yielded the 95% prediction values is a preliminary estimation. In addition, since all of the measurements were obtained by a single endoscopist from a single cohort of children, it will need to be validated by other sonographers in different populations.

At present, there are no universally accepted guidelines regarding the application of EUS to measure any portion of the GI tract in children. The small published investigations referenced above highlight the technical challenges of utilizing esophageal EUS measurements in clinical decision-making or research investigations. Questions that will need to be addressed include if data from the mid- or distal-esophagus or both should be routinely obtained, how many cm above the LES should the distal esophagus be measured, and where to measure the mid-esophagus. Most critically, whether a technique that includes maximal or passive esophageal distension should be employed will need to be agreed on. Utilizing maximum distension provides a more recognizable and reproducible image. However, compared to passive distension, it may underestimate the true dimensions of the inflamed (remodeled) esophagus. Finally, the two pediatric studies utilized a 20 MHz mini-probe to create an interface for EUS, while the Swiss adult study employed a scope with a “built-in” ultrasound probe, Olympus GFUM 160 instrument (5–20 MHz; outer diameter, 12.7; Olympus, Optical Co Ltd, Tokyo, Japan). Whether measurements obtained from these two approaches and those obtained with the recently introduced EUS mini-probe balloon by Olympus will all yield interchangeable results still needs to be determined.

## CONCLUSIONS

The present investigation attempts to provide insights regarding anatomic relationships that have eluded previous characterization. Identifying submucosal changes in the esophageal wall will be valuable if observations that EoE yields esophageal remodeling are confirmed. As ultrasound is an operator-dependent technique, a detailed description of the methodology employed is provided to allow other endosonographers to utilize the presented TWT prediction curves. If it is established that diagnostic EUS is a valuable addition to clinical care and research, then a panel of experienced ultrasonographers should critically evaluate and modify the present approach. The revised technique could then be disseminated, as Hirano *et al.* did for EREFS.<sup>[11]</sup> While the above algorithm appears quite arduous, the intriguing potential for diagnostic EUS to emerge as the most accurate, cost-effective, method to rapidly identify and study submucosal GI pathology without exposing the patient to radiation, appears to merit further investigation.

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### Supplementary materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1. Demographics for patients included in the study**

Sex	Age (years)	D esophagus thickness (mm)				M esophagus thickness (mm)				Eos/hpf		EREF	Weight (kg)	Height (cm)	BMI	Histology scores			
		M	M + SM	TW	LP	M	M + SM	TW	LP	D	M					Grade		Stage	
																D	M	D	M
Male	20.9	0.3	1.0	1.6	0.6	0.4	1.0	1.9	0.9	0	0	0	79.8	182.9	23.9	0.10	0.05	0.01	0.05
Male	20.6	0.5	0.7	1.7	1.0	0.5	1.0	1.7	0.7	3	0	1	65.8	162.6	24.9	0.13	0.05	0.08	0.05
Male	17.6	0.6	1.0	2.1	1.1	0.5	1.0	1.7	0.7	2	0	0	73.9	177.8	23.4	0.19	0.17	0.14	0.21
Male	13.3	0.5	0.9	1.6	0.7	0.5	0.8	1.4	0.6	0	0	0	65.8	165.1	24.1	0.05	0.05	0.05	0.05
Male	4.2	0.5	0.8	1.1	0.3	0.4	0.9	1.3	0.4	0	0	0	14.2	99.1	14.4	0.05	0.05	0.05	0.05
Female	15.2	0.4	0.8	1.6	0.8	0.4	0.8	1.4	0.6	2	2	0	61.7	152.0	26.6	0.05	0.05	0.05	0.05
Female	11.5	0.4	0.8	1.3	0.5	0.5	0.9	1.4	0.5	0	0	0	57.6	147.3	26.5	0.05	0.05	0.05	0.05
Female	15.5	0.5	1.0	1.8	0.8	0.5	0.9	1.7	0.8	0	0	0	50.8	170.0	17.5	0.10	0.10	0.10	0.10
Female	14.6	0.4	1.0	1.9	0.9	0.4	0.8	1.5	0.7	0	0	0	115.0	163.8	42.8	0.05	0.05	0.05	0.05
Male	16.3	0.6	0.9	1.9	1.0	0.5	0.8	1.7	0.9	0	0	0	64.9	188.0	18.4	0.05	0.05	0.05	0.05
Female	13.8	0.6	1.0	1.9	0.9	0.5	0.9	1.6	0.7	1	0	0	42.4	147.3	19.5	0.05	0.10	0.05	0.05
Male	12.7	0.4	0.9	1.7	0.8	0.4	1.2	2.1	0.9	0	0	0	33.1	134.6	18.3	0.13	0.21	0.04	0.04
Male	14.7	0.5	1.0	1.8	0.8	0.5	1.0	1.8	0.8	0	0	0	42.2	160.0	16.5	0.10	0.13	0.10	0.13
Male	10.8	0.3	0.9	1.4	0.6	0.3	1.0	1.5	0.5	2	0	0	8.8	68.6	18.7	0.17	0.05	0.17	0.05
Male	12.3	0.5	1.1	1.7	0.6	0.4	1.1	1.9	0.8	0	0	0	48.1	155.0	20.0	0.05	0.05	0.05	0.05
Male	11.7	0.5	0.9	1.7	0.8	0.5	0.9	1.5	0.6	0	10	0	43.1	142.2	21.3	0.10	0.10	0.05	0.05
Female	12.0	0.5	1.0	1.7	0.7	0.5	1.1	1.8	0.7	0	0	1	34.9	135.0	19.3	0.05	0.04	0.05	0.04
Female	11.7	0.4	0.7	1.3	0.6	0.5	0.7	1.3	0.6	2	2	0	26.8	137.0	14.2	0.08	0.18	0.08	0.13
Male	8.1	0.3	0.8	1.2	0.4	0.3	0.7	1.4	0.7	3	0	0	34.2	130.0	20.4	0.14	0.14	0.14	0.14
Male	3.9	0.5	0.7	1.1	0.4	0.3	0.5	1.0	0.5	0	0	0	13.6	97.0	14.6	0.08	0.04	0.04	0.04
Female	9.3	0.4	0.8	1.5	0.7	0.5	1.0	1.7	0.7	1	1	0	35.2	135.0	19.4	0.17	0.05	0.17	0.05
Male	8.5	0.5	0.8	1.7	0.9	0.4	0.8	1.4	0.6	0	0	0	28.1	137.0	14.9	0.04	0.04	0.04	0.04
Female	7.5	0.4	1.0	1.6	0.6	0.4	0.9	1.3	0.4	0	0	1	23.1	122.0	15.6	0.10	0.10	0.05	0.05
Male	3.7	0.5	0.7	1.2	0.5	0.6	0.9	1.6	0.7	2	0	0	15.9	102.0	15.4	0.08	0.04	0.04	0.04
Male	2.2	0.2	0.4	0.8	0.4	0.2	0.6	1.0	0.4	0	0	0	12.7	91.0	15.2	0.10	0.14	0.05	0.10
Female	0.9	0.3	0.6	1.3	0.7	0.3	0.6	1.1	0.5	0	0	0	7.3	69.0	15.4	0.04	0.05	0.04	0.05
Female	0.6	0.3	0.6	1.4	0.8	0.4	0.7	1.0	0.3	0	0	0	7.6	71.0	15.1	0.05	0.05	0.05	0.05
Female	8.3	0.5	1.1	1.8	0.7	NA	NA	NA	NA	1	2	0	28.1	125.0	18.2	0.10	0.08	0.05	0.04
Male	14.3	NA	NA	NA	NA	0.4	0.9	1.5	0.6	5	0	1	87.6	171.5	29.8	0.14	0.05	0.10	0.05
Male	10.9	NA	NA	NA	NA	0.5	0.9	1.7	0.8	0	0	0	45.8	150.0	20.4	0.05	0.10	0.05	0.05

To confirm that none of the patients had any evidence of esophageal thickening related to EoE, quantitative, validated, endoscopic (EREF) and histologic (EoEHSS) scoring systems for EoE were applied, as described in the methods. The shaded area corresponds to the five patients with EoE-R that are plotted in Figures 2 and 3 and the remainder are the 25 controls. Figure 4 consists of the first 23 of the control patients, omitting the last two rows who do not have distal TWT measurements