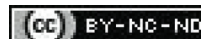


# Oestrogen and Gastroesophageal Reflux Disease Dynamics in Premenopausal and Postmenopausal Women: A Cross-sectional Study

M PRAVEENA<sup>1</sup>, R NAGASHREE<sup>2</sup>

## ABSTRACT

**Introduction:** Gastroesophageal Reflux Disease (GERD) is a common clinical disorder characterised by the reflux of stomach contents into the oesophagus, primarily due to the temporary relaxation of the Lower Oesophageal Sphincter (LES). The aetiology of GERD is multifactorial. The prevalence of GERD in females has been found to sharply increase throughout the postmenopausal period compared to the reproductive phase.

**Aim:** To study the relationship between serum oestrogen levels in premenopausal and postmenopausal women with GERD.

**Materials and Methods:** In this cross-sectional study, 60 patients with GERD were divided into 30 premenopausal and 30 postmenopausal groups. The study subjects underwent high-resolution oesophageal manometry. The Cobas e 411 immunoassay analyser was utilised to measure serum oestrogen levels through electrochemiluminescence. The

independent, unpaired Student's t-test was employed to analyse the collected data.

**Results:** The statistical analysis revealed that the mean reduced LES pressure of  $9.76 \pm 3.80$  mmHg and the mean reduced Oesophagogastric Junction Contractile Integral (EGJ-CI) of  $14.503 \pm 10.64$  mmHg were lower in women with postmenopausal GERD who exhibited lower oestrogen levels compared to those with premenopausal GERD. An increase in LES pressure was also associated with an increase in EGJ-CI, demonstrating a statistically significant positive linear correlation between LES pressure and EGJ-CI. The p-value  $< 0.05$  was deemed highly statistically significant.

**Conclusion:** Parameters such as basal LES pressure and EGJ-CI were observed to be reduced in postmenopausal women with GERD who had low oestrogen levels. This study suggests that oestrogen plays a crucial role in safeguarding the oesophageal epithelium against the reflux of gastric contents.

**Keywords:** Estradiol, Lower esophageal sphincter, Manometry, Regurgitation

## INTRODUCTION

GERD is a multifactorial disease defined by the Montreal Consensus as a long-term condition characterised by the reflux of stomach contents into the oesophagus, causing troublesome symptoms and/or complications [1]. GERD is a motility disorder that occurs due to transient LES relaxation or disorders of peristalsis, leading to the entry of excessive amounts of acid, pepsin, and bile into the lower oesophagus [2,3]. The major symptoms of GERD are heartburn and regurgitation [4]. Heartburn typically occurs after ingesting spicy foods, large fatty meals, caffeine, chocolates, smoking, alcohol, and citrus fruits. It is characterised by a burning sensation in the retrosternal region that can spread to the chest, neck, throat, and back. Regurgitation involves the entry of refluxed gastric contents into the hypopharynx or mouth due to low LES pressure [5].

In India, the prevalence of GERD ranges from 7.6-18.7% [6]. Genetic factors are polygenic, and their association with GERD ranging from 0-22%. Other risk factors include changes in lifestyle, dietary habits, and socio-economic status. The prevalence of GERD during the postmenopausal phase is notably higher than in the reproductive phase [7]. The three main physiological forms of oestrogen found in women are estrone (E1), estradiol (E2) or  $17\beta$  estradiol, and estriol. Oestrogen is a female steroid hormone synthesised by the ovaries that regulates the menstrual cycle. During menopause, the production of oestrogen and progesterone from the ovaries decreases, leading to increased levels of Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH), along with decreased levels of estrone, estradiol, and sex hormone-binding globulin in the circulation, marking a natural endocrine menopausal transition [8].

Serum levels of  $17\beta$  estradiol decrease by 85-90% in menopause [9]. Oestrogen receptor alpha and beta are found in the immune system, muscles, and epithelial cells. Oestrogen helps in preserving the tight junctions present in the epithelial cells and upregulates the tight junction component occluding protein. Consequently, lower E2 levels in postmenopausal women and men impact these junctions, increasing membrane permeability to harmful substances and causing mucosal damage. The gastric mucosal epithelium acts as a barrier that helps maintain its integrity and protects against damage. Due to lower oestrogen levels, the mucosa in postmenopausal women is more susceptible to injury, leading to an increasing spectrum of erosive GERD in postmenopausal females [10].

A limited number of studies suggest a possible link between increasing GERD and decreased oestrogen levels that accompany menopause [7, 11]. The significance of oestrogen in premenopausal and postmenopausal females is highlighted in present research. This study also illuminates the intricate relationship between oestrogen and acid reflux in premenopausal and postmenopausal women. The study aims to compare the association between premenopausal and postmenopausal women with GERD and oestrogen levels. The research objectives include comparing basal LES pressure in relation to oestrogen levels between premenopausal and postmenopausal women with GERD, as well as comparing EGJ-CI with oestrogen levels between premenopausal and postmenopausal women with GERD.

## MATERIALS AND METHODS

This cross-sectional study was conducted in the Gastroenterology Department at PSG Institute of Medical Sciences and Research,

Coimbatore, Tamil Nadu, India between March 2018 and 2019. 60 patients with GERD were divided into 30 premenopausal and 30 postmenopausal groups. The study was conducted after receiving approval from the Institutional Human Ethics Committee (17/366, dt. 29/12/2017). Informed written consent was obtained from all study participants.

**Inclusion criteria:** Female participants with GERD aged between 35 and 70 years were included in the study.

**Exclusion criteria:** Women younger than 35 years and older than 70 years, those who had undergone hysterectomy, had upper gastrointestinal tract malignancy, history of gallstones or pregnant, were excluded from the study.

**Sample size calculation:** In the study by Kumar S et al., the GERD prevalence was found to be 18.7% [12]. The calculated sample size was 59, rounded up to 60 using the formula  $n = Z^2(1-\alpha/2)p(1-p)/d^2$ , with a precision of 10% and 95% confidence interval. There were a total of 60 study participants, with 30 postmenopausal women with GERD and 30 premenopausal women with GERD.

### Study Procedure

For each study participant, a detailed history was taken, height, weight, and body mass index were measured, and then a high-resolution oesophageal manometric study was performed. Serum oestrogen levels (17 $\beta$  estradiol) were measured by collecting blood samples between the 8<sup>th</sup> and 10<sup>th</sup> day of the menstrual cycle in menstruating females with a regular cycle and analysed using the Cobase 411 immunoassay analyser by electrochemiluminescence. The results were obtained through a reagent barcode created by an instrument-derived specific two-point calibration master curve [13].

The water-based perfusion HRM system used in the study was manufactured by the Royal Melbourne Hospital in Australia. Participants were instructed to fast overnight for the oesophageal manometry procedure and to lie supine on the procedure couch on the day of the procedure.

A 16-channel water-perfused manometry with a catheter coated with lignocaine gel was guided into the nasal cavity, pharynx, upper oesophageal sphincter, body of the oesophagus till the LES, by instructing study participants to swallow the catheter-like saliva. The LES was recognised by colour changes on the colour graph and as a band of high-pressure zone on a computer screen. By fixing the probe in the band of the high-pressure zone, one basal reading for one minute was documented. The study participants were instructed to swallow about 5 mL of water slowly at a time

duration in seconds, and EGJ-CI units in mmHg/cm were obtained [16]. In the water-perfused HRM assembly, the mean basal pressure was found to be 3.0-29.8 mmHg [17].

### STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) software version 24.0 was used to statistically analyse the data from premenopausal and postmenopausal GERD women. The parameters like basal LES pressure and EGJ-CI were compared in relation to oestrogen levels between the premenopausal and postmenopausal GERD women. To compare the normally distributed continuous variable between the two groups, the unpaired Independent Student's t-test was used and presented as mean $\pm$ Standard Deviation (SD). To find the association between LES pressure, EGJ-CI, and oestrogen levels, the Pearson correlation test was used. To find the effect of oestrogen on reduced LES pressure and EGJ-CI, logistic regression analysis was used. The probability value <0.05 was considered statistically significant.

### RESULTS

A total of 60 GERD females were subjected to oesophageal manometry. Out of these 60 patients, 30 were premenopausal and 30 were postmenopausal GERD women with a mean age of 40.4 $\pm$ 4.45 years and 57.7 $\pm$ 7.55 years with a p-value <0.001.

Postmenopausal women had a lower mean LES pressure compared to premenopausal women, and this difference in mean LES pressure was statistically significant (p-value=0.001) [Table/Fig-1]. Although a higher proportion of postmenopausal women had a lower mean LES pressure (60% vs. 40%) compared to premenopausal women, the difference between the two groups was not statistically significant (p-value=0.121) [Table/Fig-2]. Postmenopausal women had a lower mean EGJ-CI compared to premenopausal women, and this difference in mean EGJ-CI was statistically significant (p-value=0.002) [Table/Fig-1]. Although a higher proportion of postmenopausal women had a lower mean EGJ-CI (56.2% vs. 43.8%) compared to premenopausal women, the difference between the two groups was not statistically significant (p-value=0.301) [Table/Fig-3]. Postmenopausal women had lower mean oestrogen levels compared to premenopausal women, and this difference in mean oestrogen levels was statistically significant (p-value<0.001) [Table/Fig-1]. There was a statistically significant positive linear correlation between LES pressure and EGJ-CI, indicating that a rise in LES pressure will also result in a rise in EGJ-CI and vice versa, with a significant p-value [Table/Fig-4]. The odds

Groups	No. of patients	LES Pressure Mean $\pm$ SD (mmHg)	p-value	EGJ-CI Mean $\pm$ SD (mmHg)	p-value	Oestrogen level Mean $\pm$ SD (pg/mL)	p-value
Premenopausal	30	14.89 $\pm$ 7.14	0.001*	29.183 $\pm$ 21.34	0.002*	121.12 $\pm$ 49.01	<0.001*
Postmenopausal	30	9.76 $\pm$ 3.80		14.503 $\pm$ 10.64		9.93 $\pm$ 6.51	

**[Table/Fig-1]:** Comparison of mean LES pressure, Oesophagogastric Junction Contractile Integral (EGJ-CI) and oestrogen levels between premenopausal and postmenopausal GERD women (n=60).

\* p-value <0.05 was considered to be statistically significant

and not to swallow saliva in between swallowing water. Ten wet swallows were given at intervals of 30 seconds, and parameters like LES pressure and EGJ-CI were recorded between two wet swallows. After 10 wet swallows, the nasal catheter was safely removed. Using the Trace 1.2.3 Chicago categorisation (Geoffrey S. Hebbard, RMH, and Australia), metrics like LES pressure and EGJ-CI were documented [14]. The tracing proceeds for three inspiration and expiration cycles, during which no swallows occur. The band of the high-pressure zone denotes the LES sphincter, and the basal LES pressure was recorded. The normal basal LES pressure is 10-35 mm Hg [14,15]. The Chicago group suggested EGJ-CI units to measure EGJ contractility in HRM analysis. The Distal Contractile Integral (DCI) technique was also utilised to determine the EGJ-CI. Next, the DCI value was divided by the three respiratory cycle

Groups	Normal LES Pressure N (%)	Reduced LES Pressure N (%)	Total	p-value
Premenopausal	18 (60)	12 (40)	30 (50)	0.121
Postmenopausal	12 (40)	18 (60)	30 (50)	

**[Table/Fig-2]:** Comparison of subjects with reduced LES pressure between premenopausal and postmenopausal GERD women (n=60).

Groups	Normal EGJ-CI N (%)	Reduced EGJ-CI N (%)	Total	p-value
Premenopausal	16 (57.1)	14 (43.8)	30 (50)	0.301
Postmenopausal	12 (42.9)	18 (56.2)	30 (50)	

**[Table/Fig-3]:** Comparison of subjects with reduced EGJ-CI between premenopausal and postmenopausal GERD women (n=60).

ratio for oestrogen levels to predict the development of reduced LES pressure and EGJ-CI was statistically significant at 0.982 and 0.989, indicating that oestrogen levels have a protective effect (OR<1) in the prevention of reduced LES pressure and EGJ-CI. This odds ratio remained statistically significant even after adjusting for the age factor [Table/Fig-5].

Variables	Pearson correlation (r-value)	p-value
LES pressure and EGJ-CI	0.539	<0.001*
LES pressure and oestrogen level	0.583	<0.001*
EGJ-CI and oestrogen level	0.504	<0.001*

**[Table/Fig-4]:** Correlation between LES pressure, EGJ-CI and oestrogen levels (n=60).

\*p-value <0.05 was considered to be statistically significant

Independent variable	Reduced LES pressure		EGJ Contractile Integral (EGJ-CI)	
	Unadjusted Odds ratio (OR)	Age adjusted Odds ratio (AOR)	Unadjusted Odds ratio (OR)	Age adjusted Odds ratio (AOR)
Oestrogen levels	0.982	0.971	0.989	0.985
95% confidence interval	0.971 to 0.992	0.953 to 0.989	0.980 to 0.998	0.972 to 0.998
p-value	0.001*	0.001*	0.013*	0.023*

**[Table/Fig-5]:** Logistic regression analysis for effect of oestrogen on reduced LES pressure and EGJ- CI (n=60).

\*A p-value <0.05 was considered to be statistically significant

## DISCUSSION

This study was conducted to assess LES pressure and EGJ-CI with oestrogen levels between premenopausal and postmenopausal GERD women. Postmenopausal GERD women were found to have lower basal LES pressure and EGJ-CI. GERD is one of the most prevalent disorders of the upper gastrointestinal tract characterised by symptoms like heartburn and regurgitations [18].

In this present study, basal LES pressure was found to be lower in postmenopausal than premenopausal GERD women. These findings were consistent with a study conducted by Kim SY et al., which revealed that the onset and duration of menopause are connected to the rise in the prevalence of GERD. The protective benefits of oestrogen on the oesophageal mucosa are significantly reduced at menopause [19]. A study conducted by Infantino M suggested that low oestrogen and progesterone levels in menopause cause modulation in the contractile function of the gastrointestinal tract and lead to GERD symptoms [20].

The study conducted by Kim K et al., in his animal model conveyed that low oestrogen levels lead to impaired protective barrier function of the lower oesophagus by modifying the expression of calcium-related genes [21]. Serum E2 levels raise intracellular calcium by controlling the expression of genes linked to calcium, which causes reduced muscle contraction and increased secretion of mucus in the oesophagus. Reduced oestrogen levels cause changes in mucin composition leading to impaired lower oesophagus protective barrier function. Thus, oestrogen modulates mucus secretion and oesophagus muscle contraction.

Postmenopausal women had lower mean EGJ-CI compared to premenopausal women in present study. The findings of present study, which concurred with those of Kim SY et al., revealed that the alpha and beta receptors for oestrogen are found in epithelial cells [19]. The tight junctions present in the epithelial cells are preserved by oestrogen (E2). The tight junction component occludin protein is upregulated by oestrogen. Therefore, these junctions are weakened by the lower oestrogen levels in postmenopausal women, increasing permeability of the membrane to harmful substances and causing mucosal damage. Honda J et al., using a rat model in their study supported the above findings by explaining that oestrogen increases

the expression of occludin, which amplifies the tight junction and strengthens the adhesion between the neighbouring epithelial cells of the oesophagus [11]. The tight junction is destroyed by the reflux of gastric acid, thereby increasing permeability of the paracellular space, dilatation of intercellular space, and decreases transmembrane resistance. The lower oesophagus epithelium is damaged by the conversion of nitrate in the meal into reactive nitrogen oxide species [7]. Thus, the female sex hormone oestrogen plays a vital role in maintaining the oesophageal gastric junction contractile integrity in preventing gastric acid reflux.

## Limitation(s)

This cross-sectional study evaluates GERD symptoms and oestrogen levels at a given point in time with a small sample size. In future research, evidence for a causal inference might be obtained from longitudinal studies over time. Oestrogen interacts with other potential confounders like lifestyle risk factors and other hormones that could influence GERD symptoms. In future research, investigating these interactions would yield a comprehensive understanding of the underlying mechanisms.

## CONCLUSION(S)

The study suggests that the female steroid hormone oestrogen preserves the oesophageal epithelium against acid reflux. The high-resolution oesophageal manometry metrics, such as basal LES and EGJ-CI findings, highlighted that oestrogen prevents gastrointestinal epithelial damage in premenopausal and postmenopausal GERD patients. Enhancing research on disease risk will necessitate greater awareness that describes the protective effect of oestrogen in premenopausal and postmenopausal GERD women.

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**PARTICULARS OF CONTRIBUTORS:**

1. Assistant Professor, Department of Physiology, Trichy SRM Medical College, Hospital and Research Centre, Irungalur, Trichy, Tamil Nadu, India.
2. Professor, Department of Physiology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. M Praveena,  
NO G-C, C Block, Sowkiya Residency, Old Palpannai Road,  
Trichy-621105, Tamil Nadu, India.  
E-mail: drpraveena2000@gmail.com

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