

**A PROSPECTIVE CASE CONTROL STUDY OF THE LOWER ESOPHAGEAL
SPHINCTER PRESSURE IN PATIENTS WITH TYPE II DIABETES MELLITUS
PRESENTING WITH HEARTBURN**

Dissertation submitted in

Partial fulfillment of the regulations required for the award of

M. D DEGREE

In

PHYSIOLOGY – BRANCH V



THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

May – 2018

Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

A prospective case control study of the Lower Esophageal Sphincter Pressure in patients with Type II Diabetes Mellitus presenting with heartburn

Principal Investigator: Dr. R. Pavitra Vyshnavi Yogisparan

Guide: Dr. G. V Lathadevi

INTRODUCTION

Evolution has made man to be one of the most complex beings in the world. May it be from the beginning of time in accordance with the religious scriptures or scientific theories starting with “The Big Bang” what we have learned is that all but one essential concept, all living things need food and water to survive. How does this food travel down the path from being ingested to broken down and absorbed to get utilized is a complex process. In this entire complex of mechanical systems the Lower Esophageal Sphincter is one of the major gateways into the world within our bodies.

Diabetic enteropathy refers to all gastro-intestinal complications of diabetes, which may include intestinal complications such as dysphagia, heartburn, nausea, vomiting, abdominal pain, constipation, diarrhea and even fecal incontinence. When studied deeper, in order to find out the underlying cause, epidemiological studies identified the risk factors for developing GI symptoms among diabetic subjects was associated with their poor glycemic control.

A high-pressure zone keeps the gastro esophageal junction closed, but a brief relaxation due to inhibitory neurons permit passage of material through this physiological sphincter. The esophagus is innervated primarily by the vagus nerve. These motor innervations has neurons which may either decrease or increase the tone of the LES by stimulation of inhibitory or excitatory motor neurons in the myentric plexus located in the LES. Theoretically the vagal nerve has innervations to both excitatory and inhibitory myentric motor neurons, however experimental protocols generally show LES relaxation.

This active complex mechanism contributes to the maintenance and working of the lower esophageal sphincter. The LES has an approximate length of four centimeters. This high-pressure zone in healthy individuals generates a tonic pressure of about 15-30 mm of Hg above the intragastric pressure, this account for ninety percent of the basal pressure at the gastroesophageal junction.

When a type II DM patient comes with upper GI symptoms, it should lead the physician to consider all possible causes most importantly autonomic dysfunction. The major cause for diabetic gastroparesis according to textbooks is autonomic neuropathy, intrinsic neuropathy, damage to the excitatory and inhibitory neurons, elevation of blood glucose, and finally psychomotor factors. The so-called Asian Indian phenotype refers to a unique clinical and biochemical abnormality in Indians, which include increased insulin resistance, higher waist circumference despite lower adiponectin, higher levels of C - reactive protein levels. This phenotype makes Asians more prone to diabetes mellitus.

The symptoms which the patient experiences most commonly heartburn and regurgitation may be further acknowledged by diagnostic testing. Esophageal manometry is mostly used for the diagnosis of dysmotility but has some use in the diagnosis of GERD. It is known that in GERD that there is disruption of the anti-reflux barrier and esophageal peristalsis. The only drawback is that there is no pathognomonic manometric pattern for reflux. The basics of manometry are that, pressure patterns that drive a bolus transport during a particular period is measured and recorded.

Manometric studies are carried out for two reasons, one may be to aid in clinical diagnosis and the other is to provide data for research purposes regarding the functioning of the gastrointestinal system.

Interpretations of the high-resolution manometry (HRM) will initially begin with the evaluation of the resting pressures of the upper and lower esophageal sphincters. These are easily identifiable because of their drastic color change from the normal color contour on the screen. As mentioned previously the high-pressure areas of the upper and lower esophageal sphincter take up pink and red shades. Basal lower esophageal sphincter pressure is the high pressure zone in normal individuals which is above the intragastric pressure that accounts for about 90 percent of the basal pressure which is evident at the gastroesophageal junction. Due to this wide variety of normal ranges provided it is suggested by many specialist that each center create its own standardization and range of normal values. In our institute we have taken to the normal values to be from 10 – 35 mmHg for the Basal LES pressure. When the value is below 10 mmHg it is considered as reduced and above 35 mm of Hg it is classified as elevated. Any values between these are considered as being normal.

Median Integrated Relaxation Pressure (IRP) signifies the mean EGJ pressure during a 4 second continuous or non-continuous window after deglutition relaxation of the upper

esophageal sphincter. This median IRP is in simpler terms the assessment of the LES relaxation. Esophagogastric junction contractile integral (EGJ –CI) is an assessment of the EGJ barrier function on esophageal high-resolution manometry (HRM). The value is measured by the following means: esophagogastric junction contractile integral (mmHg.cm) is calculated by using the distal contractile integral measurement across the EGJ, measured above the gastric baseline and corrected for respiration. Body Motility refers to the esophageal body peristalsis. It can be classified to be either as propagative which is normal or ineffective. This is determined by the powerful peristaltic contraction, which will tell us about the integrity of the neural innervations of the smooth muscle.

While initially framing my research question, I found many discrepancies between various studies that were conducted among diabetics and non-diabetics with acid reflux. I was curious as to why such controversies existed. In the back of my mind I wondered if race and ethnicity of the study population that I was going to study made a difference. There were studies which were done in Asia, however not many pertaining to South Asia and more specifically the South Indian population. If data was collected and analyzed in the South Indian population it will help in devising treatment options and early detection methods to those in the general population, as diabetes mellitus and GERD is one among the most prevalent diseases in today's communities. Due to the paucity of studies conducted in this topic and multiple controversies it is better to have more data collected so that a definitive conclusion can be arrived at.

AIM:

To evaluate the Lower Esophageal Sphincter Pressure in patients with Type II Diabetes Mellitus, presenting with heartburn, by esophageal manometry studies.

OBJECTIVES:

1. To find the correlation between the severity of the GI symptoms and severity of type II diabetes mellitus by use of glycemic index.
2. To determine whether these tests can be used as early indicators of GERD (Gastro-esophageal Reflux Disease) in patients with Type II Diabetes Mellitus.
3. To study the pathophysiology of gastro esophageal reflux symptoms in patients with type II diabetes.

MATERIALS AND METHODOLOGY:

The study was conducted in the Gastrointestinal Motility Laboratory in the Department of Gastroenterology, PSG IMS&R, after getting clearance from the Institutional Human Ethics Committee (IHEC). Informed and written consent was obtained from all those who participated before initiation of the study.

Thirty-five type II diabetes mellitus patients and thirty-five non-diabetic patients presenting with upper GI symptoms were included in this study. Patients with type II diabetes presenting with upper GI symptoms constituted the study group. Non-diabetes patients presenting with upper GI symptoms were labeled to be in the control group. Both these groups were subjected to High Resolution Esophageal Manometry.

A case group of 35 diabetics who presented with heartburn and were referred for high-resolution manometry were included in the study. During the duration of one-year study period all diabetics who presented with heartburn and were asked to undergo high-resolution manometry and fell into the inclusion criteria were included in this study.

The control group was age matched with non-diabetic patients who presented with heartburn and were referred to undergo high-resolution manometry.

INCLUSION CRITERIA:

STUDY GROUP: 35 Type II Diabetes Mellitus patients presenting with heart burn.

EXCLUSION CRITERIA

1. Pregnancy
2. Alcoholics
3. Type I Diabetes
4. Gestational Diabetes
5. Carcinoma of Upper GI tract
6. Upper GI motility disorders
7. On drugs which alter the sphincter tone by acting on the smooth circular muscles of the LES

The following parameters were noted for both the groups during high resolution manometry:

1. Basal Lower esophageal sphincter pressure
2. The Basal expiratory pressure
3. EGJ- CI
4. Median Integrated Relaxation Pressure
5. Body Motility

The results of both the groups were subjected to statistical analysis and significance determined.

Statistical Analysis:

In a study group of 35 diabetics and 35 non – diabetics over a duration of one year study period data was collected and analyzed. SPSS software version 19, Chicago. Illinois was used for statistical analysis of the values obtained.

Continuous variables were presented as Mean \pm Standard Deviation (SD) and categorical variables were presented as absolute numbers or percentages. The comparison of normally distributed variables between the control non diabetic group and the diabetic case group was performed using Unpaired Student's 't' Test. Nominal categorical data was compared using Pearson Chi- Square Test. For the following values Mann Whitney test, a non-parametric test was applied to gain more significance.

All those who were referred for esophageal manometry testing by the gastrointestinal consultant or surgical consultant and who were sent to the GI motility lab and fit the criteria were subjected to this study. Those who had type II diabetes and non-diabetics with upper gastrointestinal symptoms who presented with heartburn were separated into the study and control groups by the principal investigator respectively. Both the control and study group were subjected to high-resolution manometry after explanation of the procedure.

RESULTS:

Mean age of Non diabetics and Diabetics

The age of the 35 controls had a mean and SD of 51.23 ± 10.393 years. The diabetics in the study group had a mean and SD of 54.23 ± 11.330 years and the difference was found to have a p value of 0.252, which is statistically not significant. This shows that the age of both the groups is matched in our study.

Comparison of sex in the Non-diabetic and Diabetic groups

The distribution of sex in the control group was as follows, there were 11 females (31.4%) and 24 males (68.6%) in the non diabetic group and 14 females (40.0%) and 21 males (60.0%) in the diabetic study group. After analysis through Pearson Chi-Square test significance was found to be .454, which is statistically not significant.

Basal Lower esophageal Sphincter Pressure

The numbers for this is as follows: Normal count in control group was 25 (71.4%) and case group was 26 (74.3%) having a total number of 51 members. In the elevated category in the control group was 2 (5.7%) and case group was 3 (8.6%) bringing the total to a number of 5 members. Finally in the reduced category a count of 8 (22.9%) in the control group and 6 (17.1%) in the case group bringing the total to a value of 14 members. Upon performing Pearson Chi-Square test significance value of .777 (not significant) was obtained.

Body Motility

A total of 62 of the 70 individuals had propagative type of motility of this 31 were in the control group and 31 were in the case group. 8 out of the 70 had ineffective motility and this was also evenly distributed as 4 in each group. There was no significance found in this comparison (p value 1.000).

Mean Basal Inspiratory Pressure

The Mean Basal Inspiratory Pressures which were measured for the control group had a mean and SD of 28.246 ± 11.362 and diabetic group a mean and SD of 22.627 ± 9.125 . These values had a p value of 0.026 which was found to be statistically significant.

Mean Basal Expiratory Pressure

The Mean Basal Expiratory Pressure recorded during manometry for the control group of 35 members in number, had a mean and SD of 17.617 ± 9.17 . In the diabetic group consisting of 35 members the mean basal expiratory pressure was found to have a mean and SD of 23.514 ± 9.66 . P value was found to be statistically significant with a value of 0.011.

EGJ-CI

The Esophageal-Gastric Junction Clearance recorded for the control group of 35 members was a mean and SD of 29.920 ± 19.001 . In the diabetic group the EGJ-CI was found to be a mean and SD of 31.68 ± 13.635 . Upon performing independent t test for both these groups the p value was found to be .657, which shows there was no statistical significance.

Median Integrated Relaxation Pressure

The Median Integrated Relaxation Pressure for the control group's mean and SD was found to be 7.877 ± 5.886 . The study group of 35 diabetic patients had a mean and SD of 6.337 ± 5.147 . Upon performing independent t test it found that the p value for this was 0.248, which showed no statistical significance

Comparison of Manometric Parameters between Males and Females in the Non Diabetic (Control) Group

The mean basal expiratory pressure in the 24 males present in the control group had a mean and SD of 15.658 ± 6.372 . The Females 11 in number had a mean and SD of 21.891 ± 12.766 . Upon performing independent t test for the above data the p value was found to be 0.061, which is not statistically significant. For the same group the EGJ-CI showed a mean and SD values of 27.597 ± 14.361 for males and for females mean and SD values of 35.027 ± 26.672 showing an increased value for females. Upon performing independent t test for the above values the p value was found to be 0.288. The same group of males and females the mean and SD of median IRP was found to be 8.883 ± 5.440 for males and 5.682 ± 6.275 in females. Upon performing independent t test for the above values the p value was found to be 0.137. For all the above data the p values showed no statistical significance.

Comparison of Manometric Parameters between Males and Females in the Diabetic (Case) Group

The mean basal expiratory pressure in the 21 males present in the case group had a mean and SD of 24.995 ± 11.022 . The females 14 in number had a mean and SD of 21.293 ± 6.293 . Upon performing independent t test for the above data the p value was found to be 0.273, which is not statistically significant. For the same group the EGJ-CI was seen holding mean and SD values of 29.833 ± 13.910 for males and for females mean and SD values of 34.464 ± 13.218 , being increased in the female group. Upon performing independent t test for the above values the p value was found to be 0.332. Finally for the same group of males and females the mean and SD of Median IRP was found to be 6.648 ± 4.960 for males and 5.871 ± 5.572 in females. Upon performing independent t test for the above values the p value was found to be 0.669. For all the above data the p values showed no statistical significance.

Comparison of Manometric Parameters between those with HbA1c Values <6.5 (Group A) and ≥6.5

The mean basal expiratory pressure in the 6 individuals with HbA1c value <6 had a mean and SD of 25.900 ± 12.403 . The remaining 29 individuals who belonged to the group of uncontrolled diabetes with HbA1c values ≥ 6.5 had a mean and SD of 23.021 ± 9.181 . Upon performing independent t test in the above data the p value was found to be 0.514 which is not statistically significant, the individuals who were under control had a high sphincter pressure when compared to the uncontrolled group. The EGJ-CI was seen holding mean and SD values of 22.300 ± 11.530 and for the second uncontrolled group mean and SD values of 33.628 ± 13.388 . Upon performing independent t test for the above values the p value was found to be 0.063 (statistically not significant). Finally for the same group of controlled and uncontrolled HbA1c levels the mean and SD of Median IRP was found to be 3.700 ± 2.480 for the first group and 6.883 ± 5.410 in the second group. Upon performing independent t test for the above values the p value was found to be 0.171.

Comparison of Manometric Parameters between Diabetics whose duration of the disease is <5 years (Group A) and ≥ 5 years (Group B)

The mean basal expiratory pressure in the 9 individuals who belonged to Group A had a mean and SD of 17.889 ± 5.372 . The remaining 26 individuals who belonged to the group B had a mean and SD of 25.462 ± 10.112 . Upon performing independent t test in the above data the p value was found to be 0.041 which was statistically significant. Group A the EGJ-CI had a mean and SD values of 34.733 ± 12.025 and for Group B the mean and SD values were 30.631 ± 14.215 . Upon performing independent t test for the above values the p value was found to be 0.445 (statistically not significant). Group A mean and SD of Median IRP was found to be 6.589 ± 6.827 and for group B 6.250 ± 4.592 . Upon performing independent t test for the above values the p value was found to be 0.868.

CONCLUSION:

As mentioned previously controversy can lead to the discovery of new information and theories, which sets forth a path towards the betterment of treatment. With the high prevalence of diabetes and gastro esophageal reflux disease it lies crucial to find a reason and create a solution for these issues.

The age in our study was matched therefore showing in comparison with other studies that with increasing age there lay an increase in the incidence of GERD as age progresses regardless of the presence of diabetes mellitus. Gender in relation to the control group and diabetic group was also found to be matched. This gave proper comparison when esophageal parameters were checked between males of the two groups and females of the two groups. The comparison of these parameters is discussed below.

More than 80% of both study and control groups had propagative motility unlike various other studies, which showed, decreased motility. Above 70% of the control and study group showed normal basal lower esophageal sphincter pressures and the rest had either hypertensive sphincter pressures or hypotensive sphincter pressures.

Mean basal inspiratory pressure was increased in the study group when compared to that of the control group but was within the normal range.

On comparison of mean expiratory pressure between males and females in the non diabetic group the females had high values when compared to the males, this may be due to the benefits of estrogen as mentioned above, and that all the women in the control group were within the reproductive age group.

The EGJ-CI, denotes the esophagogastric junction barrier function. On comparison between those who were under the HbA1c value of less than 6.5 gms/dL and above 6.5 gm/dL the uncontrolled diabetic patients showed a high mean rank when compared to those who had glycemic control. These results may help to prove that uncontrolled diabetes may lead to complication of diabetes, one of which is autonomic gastro neuropathy due to the damage of the vagus nerve. It is within the normal range of median integrated relaxation pressure in both groups.

Regarding the duration of diabetes, mean expiratory pressures was lower when compared with those who were diabetic for more than 5 years. This may be attributed to the fact that those who have had diabetes for a shorter duration still had not established proper glycemic control when compared to those who have had diabetes for longer duration. However this is not a definitive result, as comparison should be done between the short duration and glycemic control for conclusive statements to be made.

It was found in our study, even though certain manometric parameters had statistical significance they all fell within the normal range. This shows that the presence of diabetes

has less impact on these manometric parameters. Even though the data found in this study can be helpful in adding to the controversies which lie between GERD and its association with diabetes mellitus, it can be helpful in coming to a conclusion about the duration and control of diabetes and its effect on upper gastrointestinal symptoms. To further validate this study, it can be continued over a longer duration of time with more number of patients and also with the addition of healthy volunteers to under high-resolution esophageal manometry in order to come to a definite conclusion.

KEYWORDS:

GERD, Type II Diabetes Mellitus, High Resolution Esophageal Manometry, Heartburn.