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

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Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

PSG INSTITUTE OF MEDICAL SCIENCE & RESEARCH

PEELAMEDU, COIMBATORE – 4.

CERTIFICATE

This is to certify that the dissertation titled **'A prospective case control study of the Lower Esophageal Sphincter Pressure in patients with Type II Diabetes Mellitus presenting with heartburn'** is an original work done by Dr. R. Pavitra Vyshnavi Yogisparan, Post graduate student, during the period of her post graduation in Physiology in our institution. This work is done under the guidance of Dr.G.V. Lathadevi, Professor, Department of Physiology, PSG Institute of Medical sciences and Research, Coimbatore.

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DECLARATION

I hereby declare that this dissertation entitled "A prospective case control study of the Lower Esophageal Sphincter Pressure in patients with Type II Diabetes Mellitus presenting with heartburn" was prepared by me under the guidance and supervision of Dr.G.V. Lathadevi, Professor, Department of Physiology, PSG IMS&R.

This dissertation is submitted to The Tamilnadu Dr. MGR Medical University in fulfillment of the university regulations for the award of MD Degree in Physiology.

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To
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Postgraduate
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Guides: Dr T Uma Maheswari / Dr L Venkatakrishnan / Dr K Deepalakshmi
PSG IMS & R
Coimbatore

Ref: Project No.15/370

Date: December 30, 2015

Dear Dr Pavitra,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 11.12.2015 to conduct the research study entitled *"A prospective case control study of the lower esophageal sphincter pressure in patients with type II diabetes mellitus presenting with heartburn"* during the IHEC meeting held on 24.12.2015.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 11.12.2015)
3. Informed consent forms (Version 1 dated 11.12.2015)
4. Data collection tool (Version 1 dated 11.12.2015)
5. Permission letter from concerned Head of the Department
6. Current CVs of Principal investigator, Co-investigators
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 24.12.2015 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr. R. Nandakumar	BA., BL	Legal Expert, Chairperson	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr D Vijaya	M.Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr Sudha Ramalingam
Alternate Member - Secretary
Institutional Human Ethics Committee

PSG Institute of Medical Sciences & Research
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November 14, 2016

To
Dr R Pavithra Vaishnavi Yogisparan
Postgraduate
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Guide/s: Dr T Uma Maheshwari / Dr L Venkatakrishnan / Dr K Deepalakshmi
PSG IMS & R
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The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore - 4, has reviewed your proposal on 11th November 2016 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to renew the approval and to include two co-investigators for the study entitled:

"A prospective case control study of the lower esophageal sphincter pressure in patients with type II diabetes mellitus presenting with heartburn"

The following documents were received for review:

1. Request for renewal dated 09.11.2016
2. Status report

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The approval is valid for one year (30.12.2016 to 29.12.2017).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

Proposal No. 15/370

URKUND

Urkund Analysis Result

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Submitted: 10/9/2017 12:12:00 PM
Submitted By: pavitra87@gmail.com
Significance: 2 %

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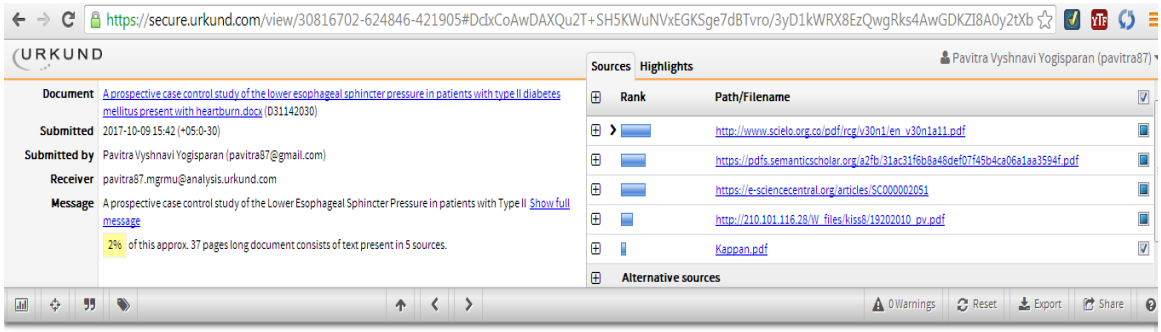

INTRODUCTION Evolution has made man to be one of the most complex beings in the world. May it be from the beginning of time in accordance with the religious scriptures or scientific theories starting with "The Big Bang" what we have learned is that all but one essential concept, all living things need 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. Diabetes Mellitus Diabetes Mellitus has been a fast growing concern among humankind for the past few decades. However, the existence of this disease dates as far back as 3,500 years, as recorded in the papyrus by the ancient Egyptians. They wrote about a polyuric syndrome which we presume to be diabetes. Simultaneously, the verdic medical treaties of India describe this condition a step further going into classifying it as either congenital or late onset. It was Sushrant (an Indian Physcian) in the 5th century AD who reported this polyuria to be a sweet tasting substance. In the late 90 AD Areatus of Cappodocia stated, "Diabetes is a wonderful affection being a melting down of flesh and limbs into urine." This disease gained its significance only after experimental backup in the 2nd half of the 18th century.(1) When attempted to define Type II DM we come across a textbook definition of, it is a heterogeneous group of disorders characterized by variable degrees of

a) Insulin resistance, b) Impaired insulin secretion and

c) Increased glucose production.(2)

There are certain criteria for diagnosing Diabetes Mellitus:

Fasting Plasma Glucose <126mg/dL Random Blood Glucose <200mg/dL Post Prandial Blood Glucose < 200mg/dL

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First of all, I express my deepest gratitude to Dr.S.Ramalingam, Dean, PSG Institute of Medical Sciences and Research, for allowing me to do my dissertation in PSG IMS&R.

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Introduction

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.

Diabetes Mellitus

Diabetes Mellitus has been a fast growing concern among humankind for the past few decades. However, the existence of this disease dates as far back as 3,500 years, as recorded in the papyrus by the ancient Egyptians. They wrote about a polyuric syndrome, which we presume to be diabetes. Simultaneously, the verdic medical treaties of India describe this condition a step further going into classifying it as either congenital or late onset. It was Sushrant (an Indian Physician) in the 5^{th} century AD who reported this polyuria to be a sweet tasting substance. In the late 90 AD Areatus of Cappodocia stated, "Diabetes is a wonderful affection being a melting down of flesh and limbs into urine." This disease gained its significance only after experimental backup in the 2^{nd} half of the 18^{th} century. (1)

When attempted to define Type II DM we come across a textbook definition of, it is a heterogeneous group of disorders characterized by variable degrees of

a) Insulin resistance,
b) Impaired insulin secretion and
c) Increased glucose production. [2]

There are certain criteria for diagnosing Diabetes Mellitus:

Fasting Plasma Glucose > 126mg/dL

Random Blood Glucose > 200mg/dL

Post Prandial Blood Glucose > 200mg/dL during oral glucose tolerance test

HbAlc ≥ 6.5% [2]

Up to 75% of patients with diabetes have been known to experience GI symptoms as observed in clinical practice [3]. A recent study showed that 25% of patients with Type II Diabetes had heartburn and acid regurgitation. [3]

Diabetes and Gastrointestinal Tract

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. [4] 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. [4] 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. [5]

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. [3]

Gastroesophageal Reflux Disease (GERD)

The high-pressure zone created by the lower esophageal sphincter protects the esophagus against reflux from caustic gastric contents. [5] When this mechanism is breeched it gives rise to a group of symptoms, which may be classified under Gastro-Esophageal Reflux Disease. In the above said condition there is presence of chronic relapsing reflux of stomach contents into the esophagus provoking symptoms and/ or complications. [6] These will present as symptoms such as heartburn and regurgitation. In a commonly based survey of randomly selected individuals 20-40% has experienced reflux like symptoms during a six to twelve month period with variable

intensity and frequency. However this reflux becomes pathological when symptoms impair quality of life.

GERD is the consequence of an impaired anti reflux barrier of the lower esophago-gastric regions. Due to the copious amount of exposure of the lower esophagus to gastric components like pepsin, acid and bile, reflux symptoms result.

It was believed until 1982, until proven by Dodds et al, that the main mechanism for GERD was not the defective LES pressure. However, it was shown that the majority of GERD patients had reflux during Transient Lower Oesophageal Sphincter Relaxation (TLOSR). TLOSR are prolonged relaxations of the LES despite there being no swallowing.

These TLOSR are from stimulation of gastric vagal afferents, which result from distention of the stomach, more specifically the sub-cardial region. This distention of the stomach may be due to presence of free air, inflation of an intra-gastric balloon or an ingested meal. The presence of stretch receptors in the sub-cardial region may be held accountable to mediate the response to distention. It is hypothesized that there is presence of a vagovagal reflex pathway. These vagal afferent fibers synapse in the nucleus tractus solitaries (NTS), which in turn activate motor neurons in the dorsal motor nucleus of the vagal nerve thereby relaxing the LES. It was also believed that these pattern generators in the brainstem also sent projections to the nucleus of phrenic nerve, present in the spinal cord inhibiting the crural diaphragm. [5]

This normal process of motility of the gastro intestinal tract, and the tonically active lower esophageal sphincter, which physiologically relaxes upon swallowing, gets disturbed resulting in GERD. This GERD as mentioned above is due to failure of the anti-reflux barrier, causing increased exposure of the esophagus to gastric acid, resulting in symptoms. Therefore, it is found that gastro esophageal reflux disease is one of the most common disorders of the upper GI tract. [4]

Knowing that the problem lies in diabetic patients who along with the general population enter the OPD come with symptoms of heartburn, these patients were subjected to high-resolution manometry. It is evident that the lower esophageal sphincter pressure can be determined by means of high-resolution esophageal manometry. Therefore, in order to study the LES pressure in both diabetics and non-diabetics who present with heartburn high-resolution esophageal manometry was used in this study.

This, high-resolution manometry reveals the dynamic action of the upper esophageal sphincter, the segmental character of esophageal peristalsis and the functional anatomy of the esophago-gastric junction. HRM makes it practical to use as it gives good quality pressure measurements from the esophagus. [7] With the assistance of this tool, it becomes easier to know if there is a relationship between the presence of diabetes in patients who present with heartburn.

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 & Objectives

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.

Review of Literature

Review of Literature

Diabetes Mellitus, in today's world is everyone's worst feared disease. It is treatable however not curable, for this one lifelong imposition on one's health one tends to fear this disease. With its fast growing spread across the world, more specifically India, in 2014 a study conducted by Kaveeshwar et al found that more than 62 million suffer from this disease. In the year 2000, India held the largest population with diabetes, at 31.7 million, followed by China and finally the United States of America. [8]In a meta-analysis conducted in 2015 Sun et al and team found that patients with diabetes mellitus are at greater risk of developing gastro esophageal reflux disease than those who don't have diabetes. They also concluded that in their findings they saw that there was a greater association in patients over the age of 50 years and the Asian population being at risk for gastro esophageal reflux disease in those who have diabetes. [9] With these facts in mind it is important to understand the pathogenesis of this disease by studying the basic anatomy and physiology of the upper gastrointestinal system.

Lower Esophageal Sphincter (LES)

The Lower Esophageal Sphincter is a physiological sphincter placed between the lower end of the esophagus and the stomach. This junction consists of three vital elements, initially the esophageal smooth muscles, which are more prominent towards the stomach, are known as intrinsic sphincter. The second element is the fibers of the crural portion of the diaphragm. Finally, fibers from the stomach known as sling

fibers create a flap valve that closes the esophageal gastric junction. [1] There are some specific functions of the lower esophageal sphincter, one of which is to prevent significant acid reflux from the stomach along with its contents. There lies a valve-like mechanism, which extends from the esophagus into the stomach; this specialized mechanism also helps prevent reflux. [10]

Although the integrity of this lower esophageal sphincter is highly maintained in normal beings there arises a possible breech in this perfectly functioning one-way path physiologically. One may wonder how is it physiologically possible for this LES integrity to be compromised and still be considered normal. The mechanism of belching and vomiting are physiological mechanisms that alter the LES integrity to allow air or food to deviate away from this one-way pathway. This is made possible by the high-pressure zone present around the lower esophageal sphincter. The 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.

Innervation of the Esophagus

The esophagus is innervated primarily by the vagus nerve. They are of two types, the somatic motor which arises from the nucleus ambiguous. The second is the visceral motor type starting from the dorsal motor nucleus. Both these nerves are found to synapse at different areas, the somatic motor nerves are found to synapse directly with the striated muscle fibers of the esophagus whereas the visceral motor nerves synapse with nerve cell bodies that lie between the longitudinal and circular muscle layers. [11]

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. [5]

Upper esophageal sphincter is tonically contracted to seal the esophagus during rest. During swallowing these tonic contractions fails to appear for less than one second, this is in order for all the bolus to enter into the esophageal lumen. How does its tonic state of contraction exist during a period of rest? It is the result of the somatic motor nerves that excite contraction of this muscle. Therefore swallowing needs to be during a period of relaxation, where this state of contraction is transiently suppressed. The origin of this nerve is from the motor nuclei in the brainstem, which traverses as the tenth cranial nerve. [12] The tone of the LES is controlled by the neural pathway. The relaxation and contraction (maintenance of the tone) to keep the LES is controlled by the discharge of acetylcholine from vagal nerve endings, causing the latter. The release of nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) from the interneuron cause the LES to relax. The phrenic nerves coordinate respiration along with the contraction of the chest and abdominal muscles. This active complex mechanism contributes to the maintenance and working of the lower esophageal sphincter. [13] 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 gastro esophageal junction. [5]

The esophagus propels the food through the lower esophageal sphincter into the stomach. This lower esophageal sphincter prevents reflux of gastric contents. The esophageal gastric mucosa contains a protective squamous epithelium, which prevents significant diffusion or absorption. This propulsive movement is strictly aboral, relaxing the upper and lower esophageal sphincters during swallowing. **[2]**

Central control of swallowing will send a series of sequential impulses to progressively distal segments within the esophagus. As a result of these peristaltic contractions occur. Even with bilateral vagotomy (cutting of the vagus) peristalsis can occur with the aid of the intrinsic nerve plexus or smooth muscle cells themselves. The intrinsic properties of smooth muscle fibers regulate the LES contraction, along with neural and humoral influences. The smooth muscle in response to passive stretching will contract in order to oppose the stretch.

An example of this is the increased resting tone by cholinergic agonists and by gastrin a gastrointestinal hormone. However, the sphincter tone is decreased by prostaglandin E_1 and isoproterenol. [11] The excitatory myentric neurons, which are present in the LES, are cholinergic and act to stimulate muscarinic receptors present in the smooth muscle. Whereas the inhibitory motor neurons receive cholinergic nicotinic inputs from vagal efferent. [14] While the vagus nerve stimulation usually results in relaxation, the splanchnic nerve stimulation relaxes the LES by activating

adrenergic neurons through nicotinic and non-nicotinic mechanisms of neural transmission. This results in β-adrenergic inhibitory effect on the LES. [15, 16] All these factors are experimentally observed in various mammalian experiments. [17]

Gidda and colleagues in 1984 identified two types of vagal fibers, which were differentiated according to its discharge patterns. The two types of fibers had unusual latency gradients. The speculation was that the short latency fibers projected to the inhibitory myentric neurons whereas; the long latency fibers projected to the myenteric excitatory neurons. [18]

The neurochemical basis for transient lower esophageal sphincter relaxation is hypothesized to be due to vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) as stated before. [11] The relaxation is mediated through nerves, which act by releasing VIP or NO. Along with this, increase in intragastric pressures further constricts the sphincter as mentioned above through vagal reflex. Gastrin released in excessive amounts, more than within physiological limits, also increase the tone of the sphincter. [19]

Physiology of Peristalsis

By peristalsis material is propelled from the pharynx to the stomach by means of a tube like structure, known as the esophagus. [11] The esophagus is divided into two separate parts. The cervical esophagus being the first part, which consists of, striated muscle. The thoracic esophagus is the second part, which is made up of smooth

muscles. [20] The movement of the bolus is carried out by coordinated contractions of muscular layers within the esophagus. [14] In 1883 Kronecker a German scientist and his medical student Meltzer investigated how food is transported through the esophagus. [20] They concluded that the bolus was pumped by the tongue into the esophagus. The esophagus to them was only a passive channel for the transportation of the bolus into the stomach. [20] However, what would happen to food or water if swallowed in a recumbent position? A scientist named Ingelfinger observed this by means of fluoroscopy upon a barium bolus swallow with a head down position. This is when he came up with the concept of a peristaltic wave carrying the bolus into the stomach. [20] Due to a large portion of the esophagus being present in the thorax, where pressure is lower than the pharynx and stomach, the esophagus can withstand the entry of air and gastric contents. The esophagus is protected at both ends by the presence of sphincters on either end. With the help of pressure sensing devices at various levels of the esophagus, monitoring of pressures during swallowing is achieved. This helps to indicate that between swallows, both upper esophageal sphincter and lower esophageal sphincter are closed and the body of the esophagus is flaccid. The contractions begin when a bolus is swallowed, with a contractile wave moving towards the stomach. The velocity at which the contractions move down the esophagus is very slow, around 2-6cm/sec, it can even take up to 10 seconds for it to reach the lower end of the esophagus. [11]

The esophagus carries out two types of peristaltic movements. This is classified into primary peristalsis and secondary peristalsis. The primary peristalsis is follow-up movement from the pharynx, which takes place at the end of the pharyngeal stage of swallowing. From the pharynx to the stomach this movement takes about 8-10 seconds. When the primary peristalsis is incomplete and leaves food in the esophagus, due to the distention in the esophagus caused by the retained food, secondary peristalsis begins. [10] The initial wave relaxes the esophagus in order to accommodate the bolus; this is followed by a wave of contraction, which propels it. If the individual is upright then gravity will aid in the peristalsis. [21]

The control of sphincters opening and closing is quite a complex, coordinated set of events. The peristalsis which occurs in the striated part of the esophagus is controlled by the swallowing center in the brain stem. Central mechanisms through experimental studies proved to be the only pathway for esophageal peristalsis. In an in vitro mammalian setup electrical stimulus gave rise to a tetanic type of contraction, which was terminated only upon stoppage of stimulus. On the other hand, in an in vivo setup swallowing evoked a peristalsis, but electrical stimulation of the vagal efferent produced non-peristaltic tetanic contractions. [16] This proved that the control was central. [11] Christensen and team et al in the 1970s found that the esophageal smooth muscles were inhibited during the period of stimulation and that contraction took place only after, as a rebound phenomenon. This rebound was after stimulation of the inhibitory nerves. He also made a discovery that the walls of the smooth muscle

part of the esophagus had an inbuilt latency gradient. This showed that the longest latency of contraction was in the proximal part of the esophagus and the shortest latency was towards the distal end of the esophagus. The inhibitory nerves were found to be responsible for the peristalsis in the esophageal smooth muscle portion. [12]

Closure of the upper esophageal sphincter is by the normal elasticity of the sphincteric structures and the active contraction of the cricopharyngeal muscle. As such the relaxation of the upper esophageal sphincter is coordinated with the contractions of the pharyngeal muscles. The relaxation of this muscle is brought about by suppression of nerve impulses from the swallowing center through the activity of the nucleus ambiguous. The cricopharyngeal area is displaced. The displacement will cause the sphincter to open. [11]

Gastroesophageal Reflux Disease (GERD)

When this normal tone is deviated, the patient becomes symptomatic. Alteration above normal will cause a hypertensive sphincter. When a bolus is swallowed there is failure of relaxation, because of a hypertensive sphincter, producing a condition known as achalasia. Here esophageal peristalsis is absent and the resting LES tone is elevated. The above motor abnormalities lead to accumulation and retention of saliva and food within the esophagus. Symptomatically the patient will have dysphagia to both solids and liquids and regurgitation. This may finally lead to malabsorption and weight loss. [5] Histological evidence reveals a decrease in the number of myentric neurons, more specifically inhibitory NO releasing neurons. The

reason for this decreased count remains unknown. While this is one end of the spectrum in the other end lies a hypotensive sphincter. Therefore when the LES is hypotensive or lax it results in a series of symptoms. Pyrosis, heartburn, is the most common feature seen in hypotensive sphincter. This is characterized by a burning sensation or discomfort behind the sternum, this sensation arises from the epigastrium and radiates all the way up to the neck at times. [21] Heartburn is most commonly experienced after eating, while in a recumbent posture or during vigorous exercise. Katzka et al found in a national survey that up to 40 percent of adults suffered from heartburn. [22]

The pathophysiology of heartburn is due to dysfunction within the lower esophageal sphincter. As mentioned previously, the barrier, which prevents reflux acid travelling backwards, is the high-pressure zone. This zone is between the low pressures of proximally the esophagus and distally the stomach. Abnormalities in this baseline tone of the sphincter or prolonged opening of the LES will lead to heartburn. The most common reason for the patient being symptomatic is due to a term, which was introduced before, transient lower esophageal sphincter relaxation (TLOSR). The LES will relax and eliminate the existing pressure gradient between the stomach and esophagus. Prolonged TLOSR is not the only cause, along with these factors which cause predisposition for severe gastro esophageal reflux disease (GERD) is a hypotonic LES, where the tone is persistently low.

The lower esophageal sphincter plays an important role in the pathogenesis of GERD. Motility helps in removing the acidic reflux from the esophagus back to the stomach. Here we find that when the motility is reduced the esophagus remains exposed to acidic reflux for longer duration of time, and is unable to return back to the stomach and progress onwards. This disturbance in motility leads to delayed gastric emptying, which creates a higher opportunity for reflux to take place. The esophageal mucosa is not only exposed to acid from the stomach but also bile and pepsin. The combination of the above mentioned products with acid cause major harm to the esophageal lining epithelium. All these factors lead to discomfort, and a retrosternal burning sensation, most commonly referred to as heartburn. [23]

A less known fact is that the saliva contains many components, one of which is epidermal growth factor that has healing properties. Lack of this in saliva will lead to the esophageal mucosa lacking a major defense mechanism. On the contrary, concomitant to the onset of heartburn the individual will experience excessive salivation as a consequence of a triggered vagal reflex leading to acidification of the esophageal mucosa. The patient describes this event as an unpleasant sensation within the mouth. The mouth rapidly fills with a salty thin fluid. This is known as water brash. [23]

Another common presentation is regurgitation that is specifically due to a lax LES. Regurgitation is defined as the effortless return of food or fluid back into pharynx in the absence of nausea or retching. When the patient bends forward,

belches or maneuvers in ways, which increase the intra-abdominal pressure, this will bring forth a sour burning fluid in the throat or mouth which at times may even contain undigested food particles. [23]

With these symptoms in mind, a classification was made. Here with, arises a term referred to as GERD which encompasses all of the components that are symptoms and or lesions caused by the reflux of gastric contents. [23] While it is known that some degree of gastro esophageal reflux is normal, physiologically intertwined with the mechanism of LES relaxation, but excessive reflux leads to esophagitis accompanied by an impaired clearance of refluxed gastric juice.

Even though many patients experience a variety of symptoms all over the world, for a long period of time there were no clear guidelines or definition for reflux symptoms. Finally to make it easy for primary care physicians all over the world to classify and grade these symptoms they came up with a solution. Through modified Delphi process a consensus definition of GERD was formed. This was not done in an easy way. The principal steps in this process were first the selection of a consensus group and the development of a draft of statements. This was followed by a systemic overview of literature to pinpoint the evidence to support each individual statement and a grading was prepared in accordance with the evidence. Finally a voting discussion repeatedly was done anonymously on the series of iterations of statements until a consensus was achieved. [24]

The exact definition of Gastroesophageal Reflux Disease, which has been universally accepted, is by the Montreal Consensus. “A condition, which develops when reflux of stomach contents causes troublesome symptoms and/ or complications.” One may want further clarification as to what defines the term “troublesome”, which they go about to further state that it is negatively affecting an individual’s sense of wellbeing. [24] It also satisfactorily describes the negative characteristics of the symptoms from a patient’s standpoint, and allows the definition to be translated into various languages. Those who defined this consensus recognized the symptoms of GERD to be retrosternal burning (also known as heartburn) and regurgitation. This classification was made so simple that it allowed patients to be diagnosed not only by typical symptoms alone or on the basis of investigations, which prove reflux of stomach contents. [24] One may wonder how often these “troublesome” symptoms appear, in a population based study, mild symptoms which appear two or more days a week, or moderate to severe symptoms, occurring more than one day a week fall into this definition.

Diagnostics

The symptoms which the patient experiences most commonly heartburn and regurgitation may be further acknowledged by diagnostic testing. Heartburn can be interpreted in many ways; this depends on where they live and how they express that sensation to the physician. Therefore, the consensus defined heartburn as a burning sensation behind the breastbone in the retrosternal area. Regurgitation was

more specified as the perception of flow of refluxed gastric content into the mouth or hypopharynx. [24] The gold standard for monitoring reflux is an ambulatory pH-monitoring device. [25] 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. [26]

The basics of manometry are that, pressure patterns that drive a bolus transport during a particular period is measured and recorded. [27] Intra- esophageal pressure measurements were started in the late 19th century. Initially there were balloon tipped catheters, which were used for animals and humans for the measurement of pressures. The basic balloon kymographic method had a water manometer to record the volume changes, which took place. This was connected to an intra luminal balloon. They found that this method was highly inaccurate as the pressure changes recorded were of the balloon and not the intra luminal pressures. The balloon also caused a hindrance to the water or solid, which was being swallowed by the studied subject. This primitive method was overcome by the use of miniature balloons that were mounted over a micro transducer or was directly placed to the end of an open tipped catheter. Further modifications occurred by making the balloon material polyester, which was non-distensible. This preserved the original shape and diameter of the balloon. With this they were able to execute accurate and pull through measurements in the sphincter. [28] During the first part of the 20th century non-perfused, open-tipped

catheters were placed to measure pressure and propulsive contractions by Brody and coworkers. These catheters slowly started to evolve; introduced next was a pneumo-hydraulic perfusion system with side holes on the catheters. This method showed that the measurements were more accurate. [29]

There are many types of manometry systems present, however the basic concept is that the data is recorded digitally to a computer and analyzed. The pressure recorded is transmitted through a pressure signal to the computer. The pressure recorded is the intra-luminal and wall contact pressure. Factors, which need to be taken into consideration in order to make sure the readings are precise, are the spacing and orientation of the pressure sensors, the rate of increase in pressure which is being recorded, the accuracy of the measurement being taken and finally the rate of digitization of the signal being transmitted. [30]

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. Three characteristics of recording are obtained while performing manometry. Spatial resolution is the distance between the recording points, temporal resolution that is the rate of pressure measurement sampling and finally the accuracy of what is being measured.

Two types of manometric recording systems are available. They are distinguished by the location of sensors within the catheter itself or its placement externally. When the sensors are placed externally, the pressures are transmitted along

a column of water perfused slowly through the catheter. In either case, the signal is digitized and recorded by means of a computer.

Most of the South Asian studies have used external transducers, which are water-perfused. This is due to its low cost and easy maintainability when compared to the intra luminal transducers. Even though this type of transducers is easy to use and the dynamic performance of these systems is excellent, the catheter is expensive and delicate. They are usually stiffer than the water perfused catheters and are sensitive to temperature change. Small temperature changes cause fluctuations in the pressure recorded. This will alter the baseline of the individual's recordings.

The water perfusion system contains transducers placed externally, so when water passes through them by a pneumo-hydraulic pump the rate at which the water flows within each channel is measured. This determination of the water flow is by means of the resistance of a capillary, placed upstream from the catheter. Due to this the flexibility of the thinner catheter patients feels more comfortable during the procedure.

Generally, the pressure measured by means of manometry is not continuous even though this would be ideal for accuracy. However, this is not possible therefore; recordings at a distance of 1 cm are considered adequate across the pharynx and lower esophageal sphincter. The ideal distance for recording within the body of the esophagus has not been determined therefore we go by the commercially available

systems, which record at a distance of 1-3 cm. A pressure recorded at a frequency of 25 Hz or above provides an ideal temporal resolution. [30]

In order to determine the accuracy of the pressure measurement recordings, various factors need to be taken into consideration. The characteristics as mentioned above, the placement of the transducers, pressure artifacts during recording, and mechanical factors. To further explain what those mechanical factors are we can consider the changes in the pressure which drive the pneumo-hydraulic pump and the effect of the perfusion bubbles through the capillary resistors, which are present within the lumen of the catheter. Transducer drift is another factor, which can alter the accuracy. This is the instability in the baseline pressure, which is recorded through the transducer. As mentioned before, this may be caused by minute temperature changes or electrical activity.

In order to calibrate this device a known pressure to the transducers are applied and recorded. Pressures should rise in each transducer equally and should remain constant for a period of 20-30 minutes of recording. This can be accomplished by placing the transducers within a water bath to simulate placement within the gastrointestinal tract.

The artifacts, which may arise in the pressure recordings, may be due to multiple reasons. One of which is the compression of adjacent structures such as blood vessels and liver. Another reason may be due to the catheter bending within the GI tract and its compression on the wall of the tract. Faulty transducers can cause

electrical disturbances to appear as artifacts. According to need the catheter should be repositioned in order to get an ideal reading.

Upon recording and viewing on the computer screen the live feeds, the catheter will show physiological structures such as the lower esophageal sphincter as increased pressured areas. Deep breathing and swallowing during a recording of esophageal manometry can accentuate the physiological features such as the position of the diaphragm or presence of the sphincter. The recording can be viewed as either a spatiotemporal topographic color plot or a line plot. The analysis software will allow the doctor to view pressures at any point and time of recording. These recordings are displayed as spatiotemporal topographic plots. This software will include the ability to measure particular aspects of the gastrointestinal function, which has to do with the region being observed in relation to certain events such as swallowing. [30]

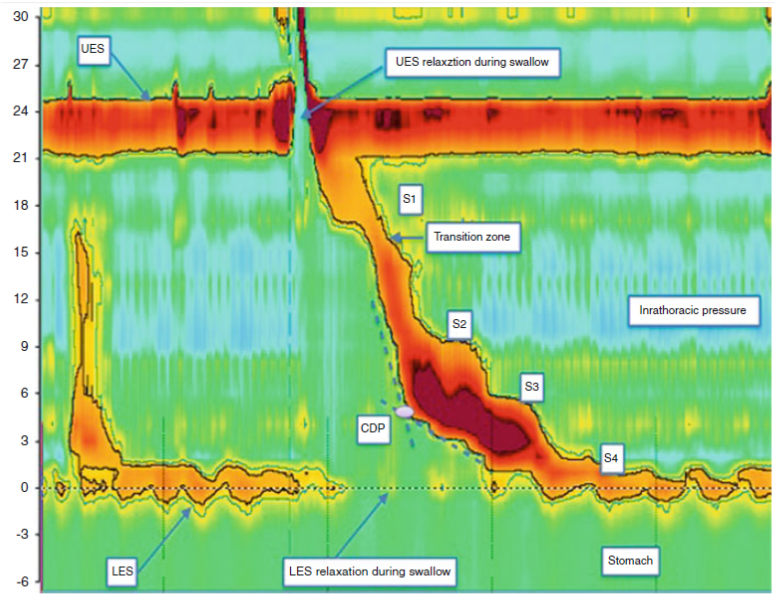
Verma et al states the purpose of esophageal manometry is that it will take a close look into the functional integrity of the portions of the upper gastrointestinal tract, which have to do with entry of bolus. [30] Yadlapati et al in an in a question answer session commented that initially the conventional manometry which was used had five pressure sensors spaced widely apart, compared to which we use now, a 36 pressure sensor catheter spaced 1 cm apart. The only advantage of the older conventional version was it's the cost effectiveness; however this is nothing in comparison to the accuracy achieved by high-resolution manometry. [31] The two-dimensional conventional plots consisted of the y-axis subjected as pressure and x-

axis subjected as time. The difficulty lies in the exact placement of the catheter in the lower esophageal sphincter. [30]

Wyle Jerry Dodds and Ron Arndorfer first devised the first high fidelity manometry system in the 1970s. This method was used for almost 20 years before Ray Clouse modified it in the early 1990s-giving rise to the new high-resolution manometry (HRM). The spacing between each sensor was 1 cm and the numbers of pressure sensors were increased along with an increase in the length of the catheter. With these modifications, it was made possible to visualize both the upper and lower esophageal sphincters with each swallow. This provided a complete spatial and temporal depiction of the motor function of the esophagus. [32] What made a huge difference in the recording and analysis portion of HRM was that they added a third axis to the existing 2-dimentional plot; the z axis stacked the pressure waves giving birth to a topographical graph. The z-axis contained gastric pressures to the front and pharyngeal pressures in the back of the topographic graph. Amplitude was changed to the y-axis and time on the x-axis remained the same. Clouse and team color coordinated the pressures and gave it a 3 dimensional contour. The low pressures were blues and greens and the high pressures were of red and yellow spectrum. [32] The most important and crucial landmark in esophageal HRM is the esophago-gastric junction. This junction consists of the lower esophageal sphincter and the crural diaphragm. The basic terms, which need to be identified when dealing with HRM, are as follows and these terms will be interrelated into the Chicago Classification. [31] The

Chicago Classification sorts esophageal motility disorders according to its high-resolution manometry topographic plots. These are also known as Clouse plots, named after the founder of HRM Ray E Clouse. [33]

Fig 1: High-resolution oesophageal pressure topography (Clouse plot)

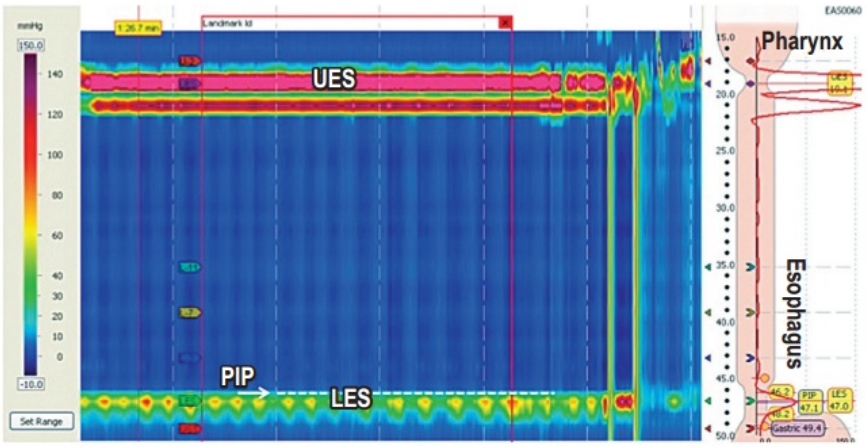


Hani et al and colleagues opinioned that the edge which the HRM had over the conventional type of manometry, was that simultaneous view of the upper esophageal sphincter, the esophageal body and the lower esophageal sphincter was made possible.

This made HRM have a complete representation in time and space of the motor function of the entire esophagus. Through HRM they go further to support that, occurrence of reflux events can be predicted and the components of the anti-reflux barrier can be made quite evident. [34]

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. The below diagram depicts the presence of the upper and lower esophageal sphincter, as well as a term identified as PIP (pressure inversion point). This PIP is the point at which the negative pressure caused by the intra thoracic pressure changes to positive pressure, which is caused by the intra-gastric pressure. In other words, it is the division caused by the diaphragm separating the chest and the abdomen. [34]

Fig 2: UES& LES depicted by differentiating colors with identification of PIP



Basal lower esophageal sphincter pressure is the high pressure zone in normal individuals which is above the intra-gastric pressure that accounts for about 90

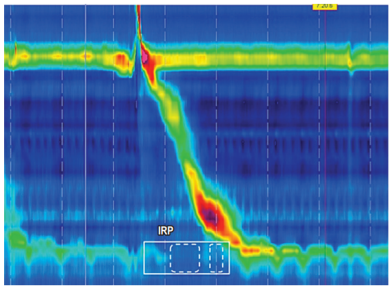
percent of the basal pressure which is evident at the gastro esophageal junction. [5] This was said to be recorded and found to be around 29.35 mmHg and the mean EGJ relaxation pressure was 16.79 mmHg in a study conducted by Bogte et al. [27] Niebisch et al states in an article that the normal values for esophageal high resolution manometry are although essential are limited. The objective of his study was to provide a second set of 'normal values' to support the existing metrics. The assessment of the esophageal gastric junction is a high-pressure zone. This is represented by the LES and crural diaphragm complex, which is recorded for a 30 second landmark frame during which the overall length, resting pressure are determined. From the above study they concluded that the LES pressure (respiratory mean) was to be 27.9 ± 11.5 mmHg. The range of this pressure was noted to be 12.3 mmHg – 52.2 mmHg. [35] 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.

Basal Inspiratory and Basal Expiratory Pressure. The end expiratory sphincter pressure (basal expiratory pressure) is a more accurate reading rather than the Mid-respiratory lower esophageal sphincter pressure because this value includes many respiratory artifacts and does not accurately measure the lower esophageal

sphincter pressure. [36] During manometric profile the LES pressure is represented by an increase in pressure during inhalation. This increase in pressure is due to the contraction of the diaphragm, which surrounds the esophagus. [37] Therefore the normal range of basal expiratory pressure is said to be the basal lower esophageal sphincter pressure of 10-35 mm of Hg.

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. [30] This median IRP is in simpler terms the assessment of the LES relaxation. [34] In order to measure the integrated relaxation pressure the EGJ junction should be pinpointed. In the region of the EGJ from the opening of the upper esophageal sphincter gives a deglutition window of 10 seconds. Inside this window period the computerized software gives the lowest mean pressure for those 4 seconds. The software excludes the pressure created by the crural diaphragm and the bolus itself. [30] A value of the median IRP being greater than 15 mmHg can be considered as an increased resistance to bolus transit at the esophago-gastric junction, and this can be interpreted as being pathologic. [34]

Fig 3: Integrated Relaxation Pressure (IRP)



EGJ –CI

Esophago-gastric 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: esophago-gastric 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. The median IRP assess only the gastroesophageal junction in conditions of post swallow residual pressures, along with the adequacy of transit through the junction, which comes along with the swallow. The median IRP however does not take into account the anti reflux barrier function of the gastroesophageal junction. The EGJ contractile integral is a novel HRM metric that evaluates the EGJ barrier function. [38]

Determination of the peristaltic activity needs to be noted; it will be either normal or failed. This depends on the pressure extending over 2-5 cm, which is labeled as short peristaltic defect, or if it is greater than 5 cm it is labeled as long peristaltic defect. The minimum pressure of 20 mmHg was chosen because it is the lowest pressure at which the esophago-gastric junction works adequately.

Fig 4: Long Peristaltic Defect >5 cm

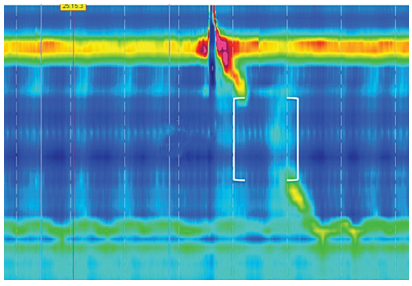
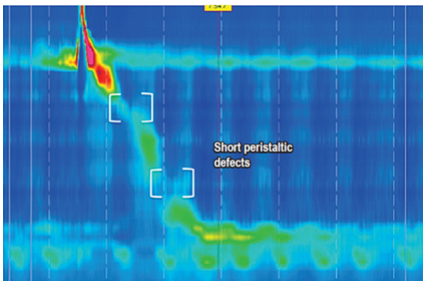


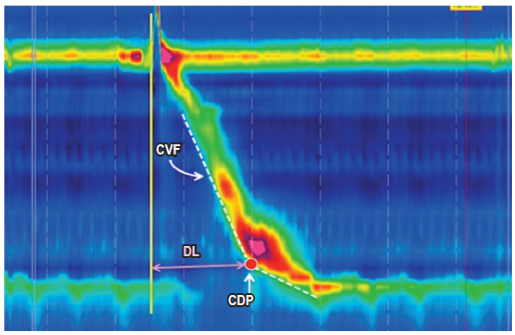
Fig 5 : Short Peristaltic Defect 2-5 cm



Next what is evaluated is the strength of the contraction created within the esophagus. This is labeled as **Distal Contractile Integral (DCI)**. The term distal is used because of the measurement taken from the distal segment of the esophagus. It can also be denoted as the amplitude x duration x length (mmHg-s-cm) of the distal esophageal contraction. A value more than 20 mmHg from the proximal to distal pressure will be shown as troughs in the graph.

Another most commonly used term is the **contractile deceleration point (CDP)**, which is the location in the lower esophagus in which the velocity of peristaltic contraction reduces suddenly. This is due to the fact that the bolus will empty into the stomach at certain points along the entire length of the esophagus. Due to this esophageal emptying the resistance offered by the EGJ will slow down the velocity of peristaltic waves. The speed of the peristaltic wave is determined and labeled as **contractile front velocity (CFV)**. The software calculates the slope of the line between the transition zone and CDP. Its normal value should not exceed 9cm/sec.

Fig 6: High resolution Manometry showing: Contractile deceleration Point (CDP) Contractile Front Velocity (CFV)



The final term is the **distal latency (DL)**, this is identified as the time taken from the beginning of the upper esophageal sphincter relaxation to the CDP. This helps identify the peristaltic timing and period of deglutition inhibition. Another concept, which needs to be noted, is something referred to as a peristaltic break. It is a measure of the peristaltic integrity of the esophagus itself. In order to identify this, an isobaric contour line of 20 mmHg needs to be drawn. 20mmHg as the contour line was decided upon by simultaneous fluoroscopic imaging, which correlated with the minimum pressure, required for successful transfer of bolus. [30] Breaks along this line shows that a hypotensive peristalsis leads to failed bolus transit. These breaks can be classified as small (2-5 cm) or large (>5cm).

When a deeper look is taken into the analysis portion of esophageal manometry according to the Chicago classification the upper limit for IRP is 15 mmHg. Any pathological condition that hinders flow across the EGJ can increase the IRP. Such examples are achalasia, neoplasm or strictures at the EGJ. The evaluation of the propagation of the pressure values can be either with the contraction front velocity (CFV) or the distal latency. The CFV is a measure of the velocity in the smooth muscles of the esophagus to the point of CDP as mentioned before. This CFV can appear rapid in a case in which the bolus is pressurized in-between the EGJ that doesn't give way and a peristaltic contraction. The normal CFV should not go beyond 9 cm/sec. According to the Chicago classification a short DL, which indicates an early arrival of the esophageal contraction to the distal esophagus, is considered more

reliable in diagnosing distal esophageal spasm rather than the CFV. The recorded lower limit for the DL is 4.5 seconds.

DCI measures the robustness of the peristaltic contraction within the smooth muscle of the esophagus. In case of HRM the DCI integrates pressures, distance and time taken along the course of the esophagus. It is essentially takes into account the mean contraction amplitude of the smooth muscle of the esophagus, the length over which the contraction propagates and the duration of this contraction.

Absent peristalsis is portrayed by a normal IRP and no peristalsis in the smooth muscle within the esophagus. This pattern may be indicative of many conditions including diabetes mellitus, especially if the patient complains of being symptomatic from gastro esophageal reflux disease accompanied by absent peristalsis. [32]

To take a deeper look into the EGJ tone in a HRM recording, there is a robust phasic section during normal respiration, which is connected with the crural diaphragm contraction, which takes place during inspiration. Due to this large measure the effect of respiration needs to be accounted for. In order to eliminate this concern both the inspiratory and expiratory EGJ pressure averaged over 3-5 respiratory cycles are taken within reference to the intra-gastric pressure. The LES pressure integral was found to be lower in patients with pathological esophageal acid exposure when compared with normal esophageal acid exposure. The current statement stands that the best method to assess the EGJ pressures is an average of inspiratory and expiratory values for three normal respiratory cycles. [33]

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. The measured amplitude of the contraction is determined between the balance of intrinsic excitatory cholinergic and inhibitory nitrergic to the musculature. The vagal afferent neurons are influenced by the bolus, which transits in the esophagus sending signals to the solitary nucleus where the vagal motor efferent will initiate the smooth muscle action. Ineffective esophageal motility is characterized in HRM by a DCI value of <450 mmHg/s/cm (weak contraction) or value < 100 mmHg/s/cm (failed contraction). Chen et al states that ineffective esophageal motility is very common in patients with GERD who come with dysphagia and heartburn. [39]

There are other means of validating acid reflux. The 24-hour pH monitoring as mentioned before is the standardized testing for acid reflux. This device allows direct measurement of esophageal acid exposure, reflux episode frequency and the association between the episodes with the patient's symptoms. There are two ways of monitoring acid reflux, one is through a wireless capsule and another is by means of a trans-nasal catheter. This procedure is usually done with the patient off acid suppression medication. For either technique utilized there should not be any change in the patient's diet or routine, in order to capture an accurate day-to-day esophageal acid exposure. [25,40] Some of the advantages of wireless capsule are that the patient

experiences minimum amount of discomfort. The placement of the capsule is by means of endoscopy in the mucosa of the distal esophagus, to be precise it is placed 6 cm above the squamo-columnar junction. The device is a radio telemetry pH-sensing capsule, which measures pH and transmits the data via a radiofrequency signal to a small receiver which is attached to the patient's belt. [41] The fixed position of the capsule is at times an advantage and a disadvantage. The advantage is that it doesn't move out of position, as does the trans nasal catheter while swallowing and talking. Disadvantage of this capsule is the cost of the device as well as the placement and removal of it requires endoscopy both times. [40] Agrawal et al states that over diagnosis of GERD sometimes occurs with intake of acidic food items. [42] Chawla et al found that when administered propofol prior to placement of the pH capsule, which is mostly done in children, there was increased number of episodes of reflux for the first 6 hours from placement of device. [43] Another major advantage is the capsule allows for longer periods of recording ranging from 2-4 days. Here arises a need for these sophisticated testing methods. The reason behind this is due to the substantial disease burden of GERD and understanding by the physicians that the patient has become unresponsive to proton pump inhibitors (PPI). Therefore, need is to improve the monitoring methods for diagnosis and to oversee the outcome after therapy. [44]

Miguel et al concluded that esophageal manometry and 24 hour pH monitoring are effective methods for proving the functional modification, which is achieved by anti-reflux surgery. He did this by performing these tests both pre-operatively and

post-operatively. Out of 41 patients who had a hypotonic sphincter on average their preoperative pressure reading was 9.2 mm of Hg and postoperatively came up to about 15.2 mm of Hg. The pH monitoring showed that a high DeMeester score of 31.4 was brought down to 3.2 after surgery. [45]

The other type of monitoring is trans nasal catheter pH testing, here the major advantage is that the patient has an added testing known as impedance. There can be differentiation between acid and non-acidic reflux. This is done by detecting changes in the resistance to electrical current across adjacent electrodes, allowing it to differentiate the ante grade and retrograde bolus transit of both liquid and gas. The disadvantage of this method is that the patient experiences discomfort due to the catheter placement trans nasally. The patient can also only tolerate the test for 24 hours. Finally an analysis of the symptom-reflux correlation is made. The association between the reflux events and the symptoms are calculated. A positive association along with abnormal esophageal acid exposure gives evidence that lead to the diagnosis of GERD. [24]

In a study conducted by Häkanson BS and team compared wireless to catheter-based pH monitoring in 55 patients with GERD and 53 healthy individuals. The catheter recorded for 24 hours while the capsule recorded for 48 hours. However, the catheter system recorded almost double the acid exposure time in both groups on study subjects. There was correlation between pH values and a concurrence of

diagnostic yield of 82.1%. Even with such positive results scientists feel that the two methods cannot be interchanged. [45]

Upper gastrointestinal endoscopy doesn't hold much use in the diagnosis of GERD; however it helps with diagnosing the complications, which arise with GERD, such as esophagitis and Barrett's esophagus. The upper endoscopy is usually utilized to place the wireless catheter in case of pH monitoring. Biopsies can be done with the help of upper GI endoscopy in order to confirm any adenocarcinoma caused by prolonged exposure to acidic reflux. [26]

Johnston et al conducted a study comparing barium esophagram to esophageal pH monitoring and assessed the accuracy of the barium screening as a predictor of the acid exposure. The sensitivity and specificity of barium radiography for acid reflux and its degrees were insufficient and the test is no longer recommended for the diagnosis of GERD. [47] However, this method of diagnosis is used for evaluation of complications related to GERD as well as evaluation of dysphagia in the post anti-reflux surgery patients. [26]

Diabetes Mellitus

Diabetes mellitus has become a world renowned and dreaded disease. However, throughout the world its origin varies but from South East Asia and more specifically India diabetes mellitus has had its roots dating to the ages of the Gods. It has been told through many historical stories that lord Ganesha had "prameha", Pra denoting excess

and meha referring to urine. This was the ancient terminology used for diabetes mellitus. To this why we would philosophically connect diabetes with lord Ganesh is for a very obvious reason, his love for sweets and his sedentary life style.

Indian medicine was so advanced in the 10^{th} century BC that it distinguished two types of diabetes mellitus. Later diabetes was termed "madhumeha" madhu meaning honey and meha again meaning urine. The two variants were krisha (lean) denoting type 1 diabetes mellitus and sthula (obese) denoting type II diabetes. This is the remarkable origin of diabetes from India.

Diabetes Mellitus on Gastrointestinal Tract

When we look more specifically at how diabetes affects the gastrointestinal tract we can come to understand the side effects of gastro esophageal reflux disease in relation to diabetes. Hopefully, getting ample insight into how much involvement the gastrointestinal system has with hyperglycemia. It is a known concept that after the intake of food the postprandial blood glucose rises. Therefore it is by means of the gastrointestinal tract that the absorption of nutrients influences the blood glucose.

Acharya et al confidently states that the prevalence of various upper gastrointestinal symptoms occur more frequently in diabetic patients with relation to their hyperglycemic control. When we want to scrutinize more into the various effects of diabetes mellitus on the gastrointestinal tract we can start with its effects on the esophagus, stomach, small intestine, large intestine, liver, gall bladder, and pancreas.

In the esophagus, esophageal motility disorders and esophageal reflux disease are well known conditions. When we enter the stomach there lays impaired gastric emptying, gastro paresis and diabetic dyspepsia. Small and large intestine effects vary from diarrhea to constipation and fecal incontinence in the anorectal region. Since the liver, gallbladder and pancreas are part of the gastrointestinal system, we can briefly look into the effects caused to those organs. Non-alcoholic fatty liver disease, hepatocellular carcinoma, gallstone formation, cholecystoparesis and finally emphysematous gallbladder may be the effects of diabetes mellitus.

It has been documented that gastrointestinal symptoms such as nausea, heartburn, vomiting, are more common in those with diabetes. The upper gastrointestinal symptoms are believed to be caused by autonomic neuropathy and or hyperglycemia. The neuroendocrine system of the gut gives out peptides and various amines, which show its effect on gastrointestinal motility. These are the frontrunners for gastrointestinal complications and the appearance of symptoms. Due to all these effects and complications being so common, a term such as diabetic enteropathy was coined to cover all effects on the gastrointestinal system.

In 1937, Ferroir et al reported that in those diagnosed with diabetes mellitus the contractions within the stomach were slow and the contractions were due to lack of vigor which would die out quickly. The culprit being hyperglycemia was proved by all symptoms being alleviated by administration of insulin. Insulin was found to resolve the secretory and motor abnormalities. There was no correlation between the

duration of the disease and the onset of symptoms, and that it showed its effect on both type I and type II diabetes patients. [4]

Now there comes shift of focus from the effect of diabetes in general to specifically the esophagus and the structures within it. The basics lie in esophageal motility and sphincter control by the nervous system. At first the gastrointestinal symptoms were accredited to irreversible autonomic neuropathy however now there lies a change in concept and the thinking is that they are acute changes in blood glucose concentration, which affect the gastrointestinal motor function, which lead to these symptoms. It is believed those autonomic neuropathy and glycemic controls, which are closely related to the pathogenic effect of symptoms.

Animal studies showed morphological changes in the autonomic nerves, which supplied the gut, which included decrease in the number of myelinated axons, reduction in neurotransmitters, and deficiency in the interstitial cells of Cajal. In rodent studies, which were conducted, rodents with diabetes had a reduced amount of nitric oxide (NO) synthase expression within the myentric neurons. This was associated with slower gastric emptying. However this doesn't hold true for humans as nitric oxide accelerate gastric emptying. Therefore we cannot hold true the entire animal model in relation to humans. Stunkard et al proved that with IV infusion of glucose, solid and liquid gastric emptying rates are slower in elevated blood glucose levels compared to a euglycaemic state. This proves that hyperglycemia has effects throughout the entire gut and not only on particular portions. In a population based

study asking about gastrointestinal symptoms in diabetes vs controls with 423 diabetic patients and 8185 controls the diabetic patients showed more symptoms of gastrointestinal tract. The reason for these symptoms in diabetics are due to many reasons, ranging from, disordered motility, autonomic neuropathy, visceral hypersensitivity, changes in gastrointestinal myoelectrical activity, use of medications and psychological distress. Visceral hypersensitivity plays a role in which, patients with symptoms show acute changes in blood glucose thereby affecting the perception of sensations arising from the gut. However due to this untouched aspect, the mechanism behind why blood glucose concentration affects gut function remains unknown. In many studies the evaluation of contractile activity of the esophageal body and lower esophageal sphincter is by means of manometry, esophageal pH recording and endoscopy. Manometric studies in these conditions ideally show increased number of abnormal pressure waves and a reduced lower esophageal sphincter pressure. [48] A study conducted by de Boer et al found that in induced hyperglycemia decrease in lower esophageal sphincter pressure and decrease in velocity of the esophageal peristaltic wave was found to be associated. [49] However there are no studies to evaluate the effect of altering blood glucose levels on the esophageal motility in diabetics. [48] It is stated in textbooks that the presence of gastro-esophageal disease is increased in those with diabetes as a result of delayed emptying from the proximal stomach. It is also stated that the prevalence of esophagitis has not been formally evaluated. [48]

Delayed gastric emptying leads to esophagitis as mentioned before and this may be due to lax lower esophageal sphincter leading to the exposure of the epithelium to acidic content. The earliest documented study was done in 1945 by Rundles et al who found that out of 35 diabetics 5 of them had delayed gastric emptying with clinical evidence of peripheral neuropathy. [50] Along with all these data there lays a controversy that could the development of diabetes be due to the delayed gastric emptying, which causes higher postprandial blood glucose concentrations. [48] There are many controversies discussed in this area with regard to diminished gastric acid secretion as an outcome of autoimmune gastritis and atrophy. Along with the above mentioned, there may be associated pernicious anemia where due to vitamin B 12 deficiency peripheral neuropathy may arise. In such situations how can one differentiate this peripheral neuropathy from that of diabetic neuropathy. This is supported by the fact that presence of peptic ulcers and gastric acid secretory disease appear to be less in diabetics. [48] Horowitz and Dent et al conducted a manometric study with recordings of pressures in the antrum, pylorus and duodenum were taken after the intake of a solid meal, in a normal volunteer the number of antral contractions were normal however in the diabetic there was hypo motility in 87 with blood glucose concentration of 14mmol/L. [48] Through this manometric study it becomes evident that the antral waves are reduced in number which in turn is temporarily associated with duodenal waves. All these factors contribute to the delayed gastric emptying.

Along with the membranes of the smooth muscle fiber present within the wall of the gut there is a continual slow intrinsic electrical activity. There are two types of electrical waves, slow waves and spikes. The resting membrane potential of the gastrointestinal tract is not constant even under normal conditions. One may quote according to the textbook value that the resting membrane potential of the gastrointestinal tract is about an average of -56 mV; however multiple minute changes can disrupt this value.

These electrical changes are what control the motor activity of the gastrointestinal tract. The above-mentioned slow waves show rhythmic changes and not proper action potentials. The slow waves are graphical representations of undulated changes, which occur, in the resting membrane potential. As mentioned previously there is no such constant resting membrane potential in the smooth muscles of the gastrointestinal tract. The intensity varies from 5 to 15 mV and the frequency changes in accord to the location of the concerned part of the gastrointestinal tract. It is believed that in the smooth muscle the slow waves are caused by the interaction between the smooth muscle cells and a specialized cell known as the interstitial cells of Cajal, which was mentioned previously. These cells are also known more commonly as electrical pacemaker cells of smooth muscles. These specialized cells form a network with one another and are placed between smooth muscle layers, with synaptic like contacts to the smooth muscle cells.

These cells undergo cyclic changes in membrane potential due to ion channels which open passing pacemaker currents, which lead to slow wave activity, this occurs periodically. The second type of wave pattern is a spike potential. These spike potentials are proper action potentials which make the resting membrane potential more positive. The higher the slow wave potential increases the more spike potentials are likely to get generated. The frequency varies from 1-10 spikes in one second. These spike potentials, which are generated, are due to large amounts of calcium entering with small amounts of sodium ions entering. The depolarization of the membrane causes the stretching of the muscle and this stimulation is caused by acetylcholine, which is released from the parasympathetic nerves. Stimulation of sympathetic nerves on the other hand causes hyper polarization.

Along with all these events taking place the gastrointestinal tract has a mini brain or the enteric nervous system. This enteric nervous system contains somewhere around 100 million neurons. This system is essential in controlling gastrointestinal movements and to a lesser extent secretions. There lies presence of two plexus of nerves, the outer plexus, myenteric plexus or commonly known as Auerbach's plexus and the inner plexus, or sub mucosal/ Meissner's plexus. The myenteric plexus gives rise to gastrointestinal movements where as the Meissner's plexus controls the gastrointestinal secretions. The sympathetic and parasympathetic fibers connect to both myenteric and submucosal plexuses. With the addition of the sympathetic and

parasympathetic systems the gastrointestinal functions are greatly influenced, compared to when they are innervated alone by the enteric nervous system. [10]

The cranial parasympathetic fibers are most commonly recognized as the vagus nerve, which innervates a majority of the gastrointestinal tract. These fibers extensively innervate the esophagus, stomach and pancreas. [10] Heatley et al comments that several of the physiological abnormalities that are associated with gastro esophageal reflux are similar to those which are found after surgical truncal vagotomy. Some of these features are due to the rise in lower esophageal sphincter pressure and increased abdominal pressure, which is decreased in patients with gastro esophageal reflux disease, similar to that of what, appears after surgical vagotomy.

Another feature is due to delayed gastric emptying as gastric stasis occurs after a truncal vagotomy. Heatley et al goes further in stating that vagal impairment caused by diabetic autonomic neuropathy is seen as a decrease in lower esophageal sphincter pressure and could give rise to gastro esophageal reflux. In a study conducted with 34 patients the vagal function was tested in patients suffering from gastro esophageal reflux by measuring the gastric secretory response to insulin induced hypoglycemia. Manometry showed that the LES pressure ranged from 0-26 mmHg. One finding in this study was that the loss of vagal function favors gastric stasis, and the presence of large amounts of irritant substances in the stomach leads to gastro esophageal reflux and esophagitis. [50]

In another study conducted in Konkuk South Korea, 190 diabetics and 190 controls were enrolled. 137 out of the 190 diabetics and 116 of the 190 controls had gastrointestinal symptoms. Kim et al expresses with concern about the prevalence of diabetes worldwide and more specifically in South Korea, moving into becoming an epidemic. The effects of diabetes are numerous, like obesity and the sedentary lifestyle take quite a toll on the human body. The need for this study having to be conducted in various regions giving rise to their own values and standards and its importance is discussed. Due to variation in ethnicity and race all over the world diabetes affects each ethnic group in different ways; therefore a generalization cannot be made. Therefore the need for such population studies holds considerable value. It has been proved that diabetes mellitus affects various regions of the gastrointestinal tract, depending upon the region and the presence of various symptoms. Many pathogenic mechanisms may be suggested in its etiology however controversy always revolves around those mechanisms. To name a few mechanisms some like autonomic neuropathy, diabetic peripheral neuropathy, glucose imbalance, diabetic duration and psychiatric disorders exist. The above study was conducted in an attempt to identify the frequency of gastrointestinal symptoms in the subjects and to unravel its etiology.

This study was in so much detail that the diabetic complications, which the patients were having, were specifically and individually investigated. Those who had diabetic nephropathy were classified into this complication after defining it as prominent proteinuria upon urine analysis or serum creatinine, which exceeded

133μmol/L. With the assistance of nerve conduction studies peripheral neuropathy was assessed. Diabetic retinopathy was diagnosed based on fundoscopic examination by trained ophthalmologists. The patient's HbA1c was also measured by means of high performance liquid chromatography. The patients' administration of oral hypoglycemic drugs and insulin was also documented.

After statistical analysis was performed the results indicated the following findings. The frequency of the gastrointestinal symptoms in diabetic patients was 72% where as in the controls was only 62%. After multiple logistic regression analysis being done the results showed that the diabetics presented with a much higher frequency of upper gastrointestinal symptoms rather than the controls. To one's surprise there was no difference in the lower gastrointestinal symptoms between the two studied groups. Among the various upper gastrointestinal symptoms offered to the individuals in the questionnaire the results showed that globus, heartburn and dysmotility like dyspepsia were more frequent among the diabetics in comparison to the controls. Another astounding finding was that among those diabetics with upper gastrointestinal symptoms, there was presence of more complications with elevated HbA1c, with those who had symptoms for a longer duration. There showed prevalence in upper gastrointestinal symptoms in subjects with an HbA1c between 8%-9%.

With all these statistical factors being so evident the presence of chronic gastrointestinal symptoms represents a clinically important problem in a large group

of diabetics around the world. The risk of only upper gastrointestinal symptoms in the diabetic group showed statistically significant increase. Very commonly gastrointestinal symptoms in diabetics have been recognized to be motor dysfunction which may be due to irreversible autonomic neuropathy accordingly to the above study.

Kim et al observed that acute changes in blood glucose concentration to alter or reduce the autonomic nerve function. Since this study gave much importance and insight into the various levels of HbA1c in relation to upper gastrointestinal symptoms it is well recommended that in order to avoid serious complications it remains safe to maintain the HbA1c of the diabetic patient below 8%. They finally go forward to state that chronic upper gastrointestinal symptoms can be reversible with a cautious control of blood glucose level. [51]

In most of the above-mentioned studies conducted a term referred to as autonomic neuropathy keeps coming up repetitively. In order to completely understand the entire effect of autonomic neuropathy one needs to completely look into its theory. Autonomic neuropathy is a generally coined term, which can virtually affect any type of autonomic function in a diabetic. Due to its cunning nature of being insidious in onset and involving multiple organs diabetic autonomic neuropathy becomes at times even unrecognizable to the physician. In contrast, when it affects one particular organ alone the patient is subjected to a battery of tests only to misdiagnose the underlying medical condition. They go further to state and claim that

like other various forms of diabetic neuropathy, diabetic autonomic neuropathy is diagnosed by means of exclusion.

The autonomic control for each organ is divided into opposing sympathetic and parasympathetic divisions. These nerve fibers that belong to the autonomic nervous system are anatomically dispersed in a web like pattern making it not easily accessible for study. Even with this natural difficulty, scientists over the past few decades devised many ways to study the autonomic nervous system especially in diabetics. These studies were conducted organ wise making diagnosis and confirmation definitive and easy.

As mentioned previously the gastrointestinal autonomic neuropathy can occur almost anywhere along its entire 15-foot course. However, what remains somewhat a mystery is that asymptomatic esophageal motility disorders are common in long standing diabetes rather than in heartburn and retrosternal discomfort.

As stated by Clarke et al in 1979 diabetic autonomic neuropathy may cause acid secretory and motility disorders. This type of gastropathy has also shown a reduction in frequency of duodenal ulceration in diabetics. [52]

The frequency of gastrointestinal symptoms as mentioned has been proven to be higher in those with diabetes mellitus. However, these symptoms have shown that they can influence the health quality of life, thereby influencing productivity and employment status.

Wang et al remarks that up to 75% of diabetic outpatients referred to tertiary care centers came with gastrointestinal complaints.

Bytzer et al suggest that the rise of gastrointestinal symptoms may be due to neuropathies and majority of these gastrointestinal symptoms are poorly related to neuropathy caused by diabetes but due to psychiatric illness. However, studies remain consistent in the duration of diabetes and its association with those symptoms. This study took into account the relationship between duration of diabetes, HbA1c, BMI, diabetic neuropathy and its existence with GERD symptoms most frequently heartburn and regurgitation. They focused on the role of diabetic neuropathy in the development of symptoms of GERD in type II diabetes mellitus.

This study consisted of 150 diabetic patients. To ensure maximum specificity for analysis of GERD symptoms they took into account only the participants with frequent symptoms and excluded patients with less frequent symptoms than weekly once. The patients were separated into two groups based on the presence or absence of peripheral neuropathy. In a total of the 150 diabetic patients 46 had neuropathy and 104 didn't. Peripheral neuropathy was confirmed by past changes in neuropathy, positive sensory symptoms which varied from limb numbness, pricking and aching pain. They were also subjected to clinical neurological examination where at least one sign had to be positive. Either positive monofilament test where there was decreased pressure or pain sensation, positive cotton wool test which indicated diminished light touch and finally decreased tendon reflexes. In the group studied the duration of

diabetes were 12 ± 9.2 years and the average HbA1c level was 7.7% ±2.0%. All the patients included in the study were actively being treated for type II diabetes mellitus with 56.6% taking metformin for their control. [38] It was stated in a study that intake of metformin gives rise to only lower gastrointestinal symptoms and not upper gastrointestinal symptoms. 30 percent of the patients in this study reported the presence of heartburn at least once a week and 40 % having symptoms of GERD. There seemed to be no difference in age, body weight, BMI or duration between patients with neuropathy and those without neuropathy. However the study concluded that the prevalence of heartburn, chest pain and chronic cough were found to be higher in patients with neuropathy when compared to those without neuropathy. [53]

Zhang et al conducted a study to observe the effect of hyperglycemia on triggering transient lower esophageal sphincter relaxation. As we had seen previously about the functional status of what transient lower esophageal sphincter relaxation was we learned that it contributes an enormous amount to the prevention of reflux. This study was conducted to observe the acute changes in blood glucose levels and its effect on the gastrointestinal motor function in normal patients as well as diabetes. Marked hyperglycemia affects the motility in all structures of the gastrointestinal tract from the esophagus to the anus. In healthy volunteers this acute hyperglycemia decreases the basal lower esophageal sphincter pressure. There has been noted an increase in the duration of passage and decrease in the velocity of the peristaltic pressure wave within the esophagus. This increase in blood glucose concentration

even within normal postprandial range has shown to slow down gastric emptying irrespective of it being solids or liquids. In this article the esophageal function is abnormal as a result of irreversible vagal damage. The most important stimulus for initiating TLESR is the vagal pathways integrated in the brainstem causing gastric distention. By noting the alterations in cardiovascular reflexes and reduction in the secretion of pancreatic polypeptide it is noted that hyperglycemia suppresses vagal activity. Finally this study was conducted in healthy individuals in order to observe the effect of both physiological and marked increase in blood glucose values on triggering TLESR. 15 healthy individuals were subjected to pressure controlled gastric distention during marked hyperglycemia or volume-controlled distention during physiologic hyperglycemia. The controls were euglycemic. Zhang et al found that in healthy volunteers marked hyperglycemia doubles the rate of TLESR triggered due to gastric distention. This is irrespective of if the stimulus is pressure or volume controlled distention. The rate of TLESRs is determined by numerous factors such as, food intake, cholecystokinin, sleep and posture. Marked hyperglycemia reduces gastric antral motility and amplifies pyloric motility. At the same time there is reduction in proximal gastric tone and slowing down of the gastric emptying. Due to the presence of CCK there is presence of gallbladder contraction. Hyperglycemia was also reported to reduce the basal LES pressure, and due to this the possibility of increased reflux episodes occurs. In this study, this theory was disapproved. What this study concluded was that in healthy individuals, marked hyperglycemia and not

physiological hyperglycemia increased the rate of TLESRs. This is however not related to the proximal gastric wall tension. [54]

Promberger et al states the incidence of type II diabetes worldwide in 2010 was 284.8 million people and a projection of 438.7 million diabetics in the year 2030. She also goes to say that 40 percent of the adult population suffers from GERD. Therefore, there lies a need to correlate the two medical conditions. Since diabetes mellitus has been suggested to be a metabolic syndrome varied with visceral fat accumulation, dyslipidemia, hypertension and hyperglycemia correlation with the pressures of GERD can be done. Hyperglycemia shows that there will be an increase in gastric H^+ secretion and as mentioned in previous studies due to increased gall bladder contraction there will be higher levels of bile acids, and decreased bicarbonate levels. This study also confirms that delayed gastric and esophageal emptying exists along with increased rates of TLESRs and reduced LES pressure. This study confirms that most studies prove the presence of GERD on the basis of questionnaires, instead of using GERD standard testing such as pH monitoring, manometry, upper gastrointestinal scopy, and barium studies. This study was particularly carried out to investigate GERD specific symptoms in patients with type II diabetes mellitus, using standard diagnostic instruments. These results were compared to non-diabetic GERD patients to identify the diabetes related differences. All patients were scrutinized by, upper gastrointestinal scopy, manometry, barium esophagram and 24 hour pH monitoring. During the two-year period 130 non-diabetic GERD patients were

enrolled as the control group. 65 diabetics were enrolled. In relation to GERD symptoms, when comparing the two groups no essential differences was noted. Diabetics with neuropathia and those without also didn't differ in the GERD symptoms. The duration of diabetics also had no impact on the GERD symptoms. H-pylori infections upon endoscopy showed a higher prevalence in patients with type II diabetes. Manometry revealed a significantly higher median pressure of LES for diabetics. In this study the HbA1c levels in diabetics didn't correlate with LES pressures, relaxation time or peristalsis.

Symptoms, endoscopy, 24-hour pH and manometry parameters in type II diabetics were analyzed in accordance with the specific treatment they were receiving for type II diabetes mellitus. No difference was found in all parameters between those with dietary restrictions alone, with diet and oral hypoglycemic drugs or those who were insulin dependent. [55]

Esophageal manometric and radiographic abnormalities are common in patients with diabetes mellitus. Most of these patients may go asymptomatic. The pathophysiology of these irregularities are thought to be degenerative effects of diabetes due to its effect on the autonomic nervous system, and not the smooth muscle dysfunction, this is supported by histological evidence and pharmacological data. In initial manometric studies conducted in the late 1960s authors found that there was a decrease in amplitude of peristalsis, and decrease in LES pressure in diabetics who suffered from autonomic neuropathy. Other later studies helped prove the same

findings in those who had and didn't have neuropathy. They go further to state that in a study of 50 diabetics with and without peripheral neuropathy there was a decrease in primary peristalsis which means that there was greater than 10% absence of peristaltic response to a swallow taken, an increase in two or more contractions in more than 25% of the swallows and finally an increase greater than 10 spontaneous contractions during a 35 minute study. All these above findings were in the diabetic population suffering from neuropathy. There was also a noteworthy decrease in the velocity of peristalsis in those with neuropathy. They feel that these variations in the study findings may be due to the development of improved manometric equipment over the course of 40 years.

This particular study contained 25 diabetics who were non-insulin dependent and 25 healthy control volunteers. The individuals were subjected to an eight lumen water perfused catheter with transducers to measure the pressures. The diabetic patients were studied four hours after breakfast was taken. The results after analysis showed that end inspiratory pressure, mid expiratory pressure and end expiratory pressure was similar amongst diabetics and controls. The percentage of relaxations was low in diabetics compared to the controls, this helps prove that the lower esophageal sphincter pressure is significantly lower thereby leading to poor relaxation of the LES in diabetics. The peristaltic velocity was lower in diabetics at both the proximal and distal ends with both wet and dry swallows; therefore it was statistically

significant at the proximal esophagus with dry swallows and distal esophagus with wet swallows. [56]

Abid et al conducted a study with an objective to compare the gastrointestinal symptoms in diabetic patients with controls and its relationship with complications of the disease, duration and glycemic control. There remains much controversy in this as through questionnaires and conducted studies it is proven that the GI symptoms in diabetics are significantly increased when compared to non-diabetics. They have quoted in this article that a study conducted in a Chinese population showed significant correlation between the period of diabetes and the occurrence of symptoms. However, the duration of diabetes and the type of treatment was not found to be related with the increase in regularity of gastrointestinal symptoms. All these studies go back to the basics that the abnormality of the GI motility is a manifestation of irreversible autonomic neuropathy. They go further to explain that other vital factors such as acute changes in blood glucose, oscillation in insulin levels, poor glycemic control and presence of infection of Helicobacter pylori in diabetics should be taken into consideration. A total of 514 patients were enrolled in this study, of this 250 were diabetics and 264 were non-diabetics. They were all subjected to a detailed questionnaire with regard to the gastrointestinal symptoms, which they felt over the past 12 months. The diabetic complications were also included in the questionnaire to determine their presence. The questions for the complications were, “did your doctor tell you about kidney damage?” for nephropathy, “Do you suffer from pins and

needles in your hands and feet?" for peripheral neuropathy, and "are you aware of the eye damage as a result of your diabetes?" for retinopathy. Their HbA1c levels were also recorded.

It was observed in this study that there lies an increase in the number of symptoms in relation to the severity of poor glycemic control in type II diabetics. Based on HbA1c values they have observed that acute or sub-acute changes in the glucose concentration are a key factor for increased frequency in symptoms. Their findings include that an HbA1c of more than 7 showed a significant rise in upper GI symptoms. They go further to hypothesize that this maybe due to the direct effect of hyperglycemia on the vagus nerve, which leads to delayed gastric emptying and increased relaxation of proximal stomach or the central effect of hyperglycemia on the central vagal nuclei. Diabetic autonomic neuropathy is said to be among the slightest documented and understood complications of diabetes. There lie multiple reasons for diabetic neuropathy, which include metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage and neuro-hormonal growth factor deficiency. In diabetics esophageal dysfunction is due to at least in part from vagal neuropathy and delayed gastric emptying largely depend on the function of the vagus nerve. However it cannot be concluded that neuropathy alone is responsible for the gastrointestinal symptoms perceived by patients. In this study no association was found between the duration of diabetes and the gastrointestinal symptoms. Nevertheless, poor glycemic control showed significant generation of upper GI symptoms in diabetics. They

conclude by saying that secondary diabetes prevention methods should be sought out after to better management of diabetes and bring down the caseload related to gastrointestinal symptoms. [57]

In a community based study conducted in the United States among residents of Olmstead county Minnesota, through a questionnaire there was found to be no difference in the prevalence of symptoms such as nausea and vomiting, dyspepsia or constipation among both type I and II diabetics and controls. [58] In another study conducted in the United States, Feldman and Schiller et al found that 76% of patients referred to diabetic clinic had at least one gastrointestinal symptom and 60% reported constipation. [59] In a study conducted by Clouse and Lustman et al found 20% of patients with diabetes mellitus complaining of nausea, abdominal pain and diarrhea, with only 12% had constipation. [60] Looking at a study conducted in Germany constipation and nausea were the more frequent symptoms in type II diabetic individuals presented with. [61] There are many studies conducted in various parts of the world contradicting one another's findings. In a study conducted in Great Britain Maxton and Whorewell et al observed the increased presence of constipation however only in patients with diabetes mellitus complicated with autonomic neuropathy. [62] Although in the previously mentioned above study conducted by Clouse and Lustman et al found that the presence of autonomic neuropathy in patients with diabetes mellitus was unassociated with the gastrointestinal symptoms. With all these controversies in mind, one can wonder if individual's ethnicity, race, socio-economic

status, lifestyle and region of residence play a role in these symptoms. All the previous studies mentioned before conducted within Asia showed much varied results, in comparison with the European and American data. [60]

In order to have a complete understanding we have seen the physiology and functional status of the lower esophageal sphincter. However there lays a physiological process known as aging, which we need to understand if it affects the sphincter control in any way thereby giving hindrance to our study. Aging has been defined as a universal and irreversible degeneration of the human body. [63] Due to this process there is a general decline in physiologic function. Special complains with regard to the foregut is, regurgitation, heartburn and dysphagia. In this study Gutschow et al says that the degenerating effect of aging on motor function and its relation to the esophageal function is not clearly understood. In 1964 a study conducted showed age related changes in the contractile amplitude, incomplete sphincter relaxation and esophageal dilation. However this study was challenged and proven that only minor changes of esophageal motility was present in healthy elderly individuals. The ill esophageal motility, which was present, was because of underlying causes such as GERD rather than the cause of purely aging. In the study conducted by Gutschow a total of 127 women and 199 men were taken into the study and subjected to esophageal manometry. In 96% of the subjects upper GI- endoscopy was done and in 92% of the subjects 24-hour pH monitoring was performed. For the purpose of analysis, patients were divided into 5 groups according their age. 17-39

group 1, 40-49 group 2, 50-59 group 3, 60-69 group 4 and above 70 for group 5. They found that there was no significant difference between the 5 different groups for males and females. GERD was equally found to be distributed among all age groups. There was no difference between any of the groups for both resting pressure and length of LES. No correlation with age for both parameters among GERD and non GERD patients. In GERD patients, there was a significantly lower resting LES pressure than non – GERD patients, this didn't hold true for the length of the LES. [64]

There are studies conducted to see the influence of sex and gender on gastroesophageal reflux disease. GERD has been classified as either being Non-erosive reflux disease or reflux esophagitis. It was found that Non-erosive reflux disease (NERD) affects women more than men. GERD symptoms were found more frequently in patients who suffered from the Non-erosive reflux type rather than the erosive type, making women more symptomatic. However it was found that men were affected more by carcinomatous lesions such as Barrett's esophagus and esophageal adenocarcinoma. With an increasing age above 50, women started to show more incidences in the complications of reflux esophagitis. What protected women till the age of 50, was it due to the anti-inflammatory action of estrogen, a hormone which is prevalent in women. This hormone could protect the esophageal epithelium against refluxate due to its anti inflammatory action. [64] Hence, many factors like sex, age, diabetes play a role in the pathogenesis of GERD.

Materials & Methodology

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

    a. β agaonists
    b. α adrenergic agonists
    c. Nitrates
    d. Ca^{2+} channel blockers
    e. Anticholinergics
    f. Theophylline
    g. Morphine
    h. Meperidine
    i. Diazepam
    j. Barbituates

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.

A thorough history was taken from the patient by the investigator and cross referenced with the existing history present in the patient's file. In case of type II diabetic patients with upper gastrointestinal symptoms, HbA1c was noted in order to find out their glycemic control. The patient was explained about the procedure in detail, its advantages, and explained about the discomfort they may feel. After noting down their name, age, sex and relevant history in the record, they were shown the equipment that was going to be used and explained about the procedure. The catheter, which is to be inserted, was shown to the patient and explained about its flexibility and due to its flexibility their cooperation is essential during its insertion.

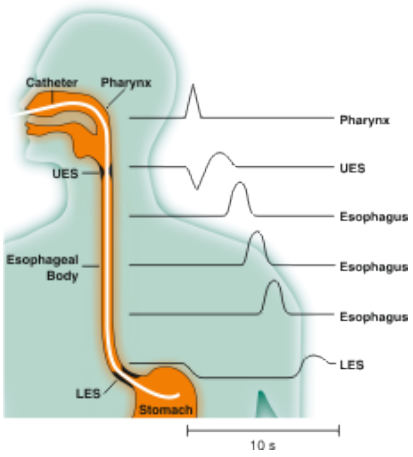
ESOPHAGEAL MANOMETRY:

The patient was asked to come for the testing with overnight fasting and nothing taken orally till the procedure was complete. They were also instructed to stop taking proton pump inhibitors, if they were taking it, 7 days prior to the procedure.

The patient was asked to lie flat in supine position and after application of lignocaine gel on the probe for anesthetic and lubricative purpose the probe was inserted into the esophagus by way of the nasal cavity. Before the insertion was done, the patient's nasal cavity was examined with the help of sufficient light to rule out any nasal deviation or polyp, which could obstruct the entry of the catheter. Once all these factors were ruled out the patient was asked to swallow the tube, like swallowing saliva. The tube was easily passed into the esophagus, due to its small size and flexibility. The disadvantage was the size and flexibility of the tube, which cannot be forced in to the cavity, and therefore complete cooperation from the patient and patience from the person doing the procedure was essential.

Fig 7, the below picture depicts insertion of the catheter through the nasal cavity, pharynx via the esophagus to the stomach.

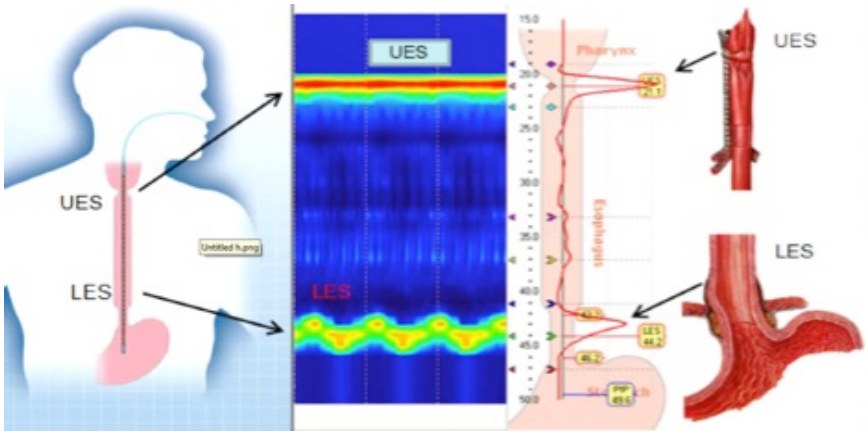
Fig 7



The physiologist monitored the probes entry into the lower esophageal sphincter by observing the pressure changes; which was plotted initially on a line plot and then converted to a color graph on the screen. Once the lower esophageal sphincter was identified the probes were fixed. The lower esophageal sphincter was identified by an increase in pressure in that area, which is depicted by a change in color on the color plot.

Fig 8, below picture depicts how the UES and the LES will appear on a color plot in the screen during manometry.

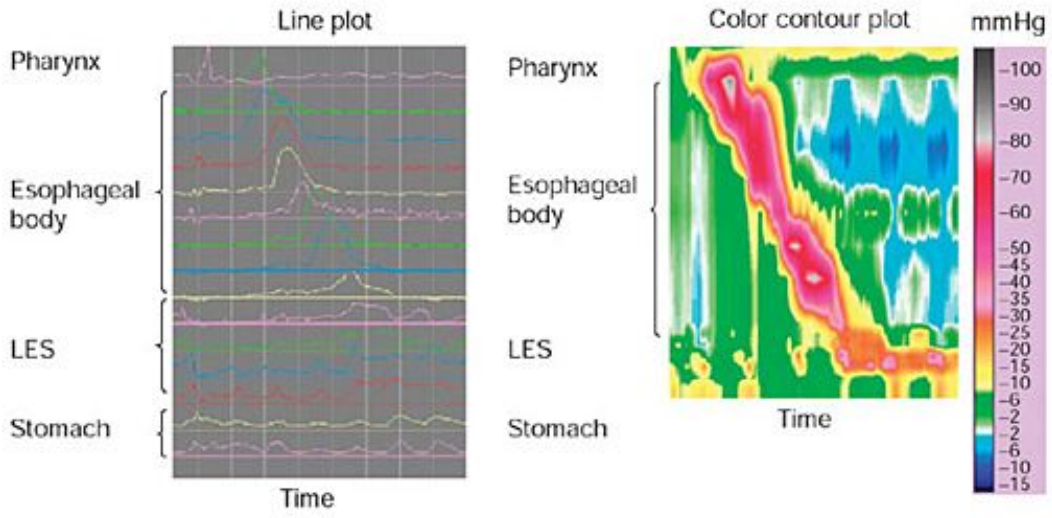
Fig 8



A basal reading was taken for about one minute. Then the patient was given about 5-7 ml of water, which they were asked to swallow slowly. In-between the swallow of water saliva was not to be swallowed and this was clearly instructed to the patient. Between each swallow 30 seconds of recording was done. The patient was made to swallow 10 times and the recording was made between two swallows. After this, the probe was removed from the esophagus. After a small break, the patient was asked to come back for the insertion of pH monitor if needed or prescribed by the consultant.

Fig 9, the picture below shows a normal manometry recording

Fig 9



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 ± 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. The parameters of mean basal expiratory pressure, EGJ-CI

and median IRP in comparison to males and females in both groups, HbA1c in diabetics whose values fell above and below 6.5 were compared each of the above parameters. The same parameters were checked for the duration of diabetes in two groups divided below duration of 5 years and above 5 years.

For all the statistical tests, p values:

$p > 0.05$ was considered statistically insignificant.

$p < 0.05$ was considered statistically significant.

Results

OBSERVATIONS AND RESULTS:

COMPARISON BETWEEN NON-DIABETICS AND DIABETICS WHO PRESENTED WITH HEARTBURN.

In this study 70 subjects were included out of which 35 were non-diabetics who presented with heartburn to the gastroenterology outpatient department and 35 diabetics with the same complaints. The study was conducted for a period of one year from September 2016.

Members of both groups were subjected to esophageal high-resolution manometry from which results were obtained. These parameters, which were measured, were compared between the control and study groups.

Table 1(Chart 1): Mean age of Non diabetics and Diabetics

35 controls and 35 diabetics were part of this study. 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.

Table 2 (Chart 2): 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.

Table 3: Basal Lower esophageal Sphincter Pressure

The Basal Lower Esophageal Sphincter Pressure is categorized into normal which falls in a range of 10-35 mm of Hg, elevated when the value goes above 35 mm of Hg and reduced when the value falls below 10 mm of Hg. 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.

Table 4 (Chart 3): Body Motility

The esophageal body motility is classified as being either propagative or ineffective. The two study groups were categorized into either of the following according to their motility manometry reports. 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).

Table 5: 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. This shows that in the diabetic group the value was decreased when compared to the control group. These values had a p value of 0.026, which was found to be statistically significant.

Table 6 and 7 (Chart 4): 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. There shows an increase in the mean basal expiratory pressure in the diabetic group when compared to the control group. When application of Mann Whitney test was performed a p value of 0.005 was obtained showing statistical significance.

Table 8 and 9 (Chart 5): 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. There was an increase in the EGJ-CI value in the study group when compared to the control group. Upon performing

independent t test for both these groups the p value was found to be .657, which shows there was no statistical significance. Upon performing Mann Whitney test for the above parameter a p value of 0.229 was it was not statistically significant.

Table 10 and 11(Chart 6): 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. There was a slight decrease in the median IRP value in the diabetic group. Upon performing independent t test it found that the p value for this was 0.248, which showed no statistical significance. Upon performing Mann Whitney test for the above parameter a significance of 0.288 was found proving no statistical significance.

Table 12 and 13 (Chart 7, 8, 9): 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. There was an increase in this value for the females when compared to the males. 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.

Finally for 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. There was an increase in the median IRP value for males when compared to 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. For the same parameters comparison was done using Mann Whitney test to find significance. The mean rank for males and females for all three parameters were analyzed and found to be as follows. Mean rank for males was 16.54 and 21.18 in females for the parameter of mean expiratory pressure. The p value was found to be 0.224, which was statistically not significant. Mean rank for EGJ-CI for males was 18.13 in males and 17.73 in females with a p value of 0.930, this also not being statistically significant. Finally the mean rank for the parameter IRP was done and found to be 20.52 in males and 12.50 in females with a p value of 0.030 showing statistical significance.

Table 14 and 15 (Chart 10, 11, 12): 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. This value was slightly increased in males. 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. For the same parameters comparison was done using Mann Whitney test to find significance. The mean rank for males and females for all three parameters were analyzed and found to be as follows. Mean rank for males was 19.33 and 16.00 in females for the parameter of mean expiratory pressure. The p value was found to be 0.359, which was statistically not significant. Mean rank for EGJ-Cl for males was 16.69 in males and 19.96 in females with a p value of 0.359, this also not being statistically significant. Finally the mean rank for the parameter for IRP was done and found to be 19.50 in males and 15.75 in females with a p value of 0.293 showing no statistical significance.

Table 16 and 17 (Chart 13, 14, 15): Comparison of Manometric Parameters between those with HbA1c Values <6.5 (Group A)and≥6.5

The two groups, which were compared in this table, were those within the case (diabetic) group whose HbA1c values were < 6.5 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 0.514which is not statistically significant, the individuals who were under control had a high sphincter pressure when compared to the uncontrolled group. For the same 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 ± 2.480for 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. For all the above data the p values showed no statistical significance. For the same parameters comparison was done using Mann Whitney test to find significance. The mean rank for the first group and second group for all three parameters were analyzed and found to be as follows. Mean rank for group A was 20.50 and 17.48 in the uncontrolled group for the parameter of mean expiratory pressure. The p value was found to be 0.535, which was statistically not significant. Mean rank for EGJ-CI for group A was 10.50 and 19.55 in the uncontrolled group with a p value of 0.050, giving a statistically significant value. Finally the mean rank for the parameter for median IRP was done and found to be 12.33 in group A and 19.17 in the uncontrolled group with a p value of 0.146 showing no statistical significance.

Table 18 and 19 (Chart 16, 17, 18): Comparison of Manometric Parameters between Diabetics whose duration of the disease is <5 years (Group A) and ≥ 5 years (Group B)

The two groups which were compared in this table were those within the case (diabetic) group whose duration of diabetes was categorized into being < 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. Those who had diabetes for a longer duration had a increased pressure value when compared to the ones who had diabetes for less than 5 years. Upon performing independent t test in the above data the p value was found to be 0.041, which was statistically significant. For the same 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). Finally for 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. For the above data the p values showed no statistical significance. For the same parameters comparison was done using Mann Whitney test to find significance. The mean rank for the first group and second group for all three parameters were analyzed and found to be as follows. Mean rank for Group A was 11.67 and 20.19 for Group B for the

parameter of mean expiratory pressure. The p value was found to be 0.031, which was statistically significant. Mean rank for EGJ-CI for group A was 20.33 and 17.19 in Group B with a p value of 0.446, giving a statistically non-significant value. Finally the mean rank for the parameter median IRP was done and found to be 17.61 in-group A and 18.13 in the group B with a p value of 0.897 showing no statistical significance.

Tables

TABLE 1

Comparison of mean age of Non-diabetic and Diabetic group

Non-diabetic group (n = 35)		**Diabetic group (n = 35)**		
Age (in years)		**Age (in years)**		
Mean ± SD	**Range**	**Mean ± SD**	**Range**	**P value**
51.23 ± 10.393	37-76	54.23 ± 11.330	33 - 74	0.252

*P-value < 0.05 - statistically significant

TABLE 2

Comparison of distribution of sex between Non-diabetic and Diabetic group

			Group		
			Non-diabetic (control)	**Diabetics (case)**	**P value**
Sex	**Male**	Count	24	21	
		% within Group	68.6%	60.0%	.454
	Female	Count	11	14	
		% within Group	31.4%	40.0%	

* P-value < 0.05 - statistically significant

TABLE 3

Distribution of Basal Lower Esophageal Sphincter Pressures between Non-diabetic and Diabetic group

			Group		
			Non-diabetic (control)	Diabetics (case)	P value
Basal LOS Pressure	**Normal**	Count	25	26	.777
		% within Group	71.4%	74.3%	
	Elevated	Count	2	3	
		% within Group	5.7%	8.6%	
	Reduced	Count	8	6	
		% within Group	22.9%	17.1%	

* P-value < 0.05 - statistically significant

TABLE 4

Distribution of Esophageal Body Motility between Non-diabetic and Diabetic group

			Group		P value
			Non-diabetic (control)	**Diabetics (case)**	
Body Motility	**Propagative**	Count	31	31	1.000
		% within Group	88.6%	88.6%	
	Ineffective	Count	4	4	
		% within Group	11.4%	11.4%	

* P-value < 0.05 - statistically significant

TABLE 5

Comparison of Mean Basal Inspiratory Pressure between Non-diabetic group and Diabetic group

Non-diabetic Group (n = 35)	Diabetic group (n = 35)	
Mean ± SD	**Mean ± SD**	**P value**
28.246 ±11.362	22.627 ±9.125	0.026*

* P-value < 0.05 - statistically significant

TABLE 6

Comparison of Mean Basal Expiratory Pressure between Non-diabetic group and Diabetic group

Non-diabetic Group (n = 35)	**Diabetic group (n = 35)**	
Mean ± SD	**Mean ± SD**	**P value**
17.617 ± 9.17	23.514 ± 9.66	0.011*

* P-value < 0.05 - statistically significant

TABLE 7

Mann Whitney test to compare Mean Basal Expiratory Pressure levels in the Non-diabetics and Diabetics

Parameter	Non-diabetic group	Diabetic group	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Mean Expiratory Pressure (mm of Hg)	28.71	42.29	.005	**0.005***

* P-value < 0.05 - statistically significant

TABLE 8

Comparison of EGJ – CI between Non-diabetic group and Diabetic group

Non-diabetic Group (n = 35)	**Diabetic group (n = 35)**	
Mean ± SD	**Mean ± SD**	**P value**
29.920 ± 19.001	31.68 ± 13.635	0.657

* P-value < 0.05 - statistically significant

TABLE 9

Mann Whitney test to compare EGJ –CI levels in the Non-diabetics and Diabetics

Parameter	Non-diabetic group	Diabetic group	Mann Whitney (U)	P value
	Mean rank	Mean rank		
EGJ-CI	32.57	38.43	.229	**0.229**

* P-value < 0.05 - statistically significant

TABLE 10

Comparison of Median Integrated Pressure between Non-diabetic group and Diabetic group

Non-diabetic Group (n = 35)	**Diabetic group (n = 35)**	
Mean ± SD	**Mean ± SD**	**P value**
7.877 ± 5.886	6.337 ± 5.147	0.248

* P-value < 0.05 - statistically significant

TABLE11

Mann Whitney test to compare Median Integrated Pressure levels in the Non-diabetics and Diabetics

Parameter	Non-diabetic group	Diabetic group	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Median IRP	38.09	32.91	.288	**0.288**

* P-value < 0.05 - statistically significant

TABLE 12

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

Parameters	Males N = 24	Females N = 11	P value
	Mean ± SD	Mean ± SD	
Mean Expiratory Pressure	15.658 ± 6.372	21.891 ±12.766	0.061
EGJ- CI	27.597 ± 14.361	35.027 ± 26.672	0.288
Median IRP	8.883 ± 5.440	5.682 ± 6.275	0.137

* P-value < 0.05 - statistically significant

TABLE 13

Mann Whitney test to compare manometric parameters between Males and Females in the Non-diabetic (Control) Group

Parameter	Male	Female	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Mean Expiratory Pressure	16.54	21.18	.224	**.224**
EGJ- CI	18.13	17.73	.930	**.930**
Median IRP	20.52	12.50	.030	**.030***

* P-value < 0.05 - statistically significant

TABLE 14

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

Parameters	Males N = 21	Females N = 14	P value
	Mean ± SD	Mean ± SD	
Mean Expiratory Pressure	24.995 ± 11.022	21.293 ± 6.293	0.273
EGJ- CI	29.833 ± 13.910	34.464 ± 13.218	0.332
Median IRP	6.648 ± 4.960	5.871 ± 5.572	0.669

* P-value < 0.05 - statistically significant

TABLE 15

Mann Whitney test to compare manometric parameters between Males and Females in the Diabetic (Case) Group

Parameter	Male	Female	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Mean Expiratory Pressure	19.33	16.00	0.359	**0.359**
EGJ- CI	16.69	19.96	0.359	**.0.359**
Median IRP	19.50	15.75	0.293	**0.293**

* P-value < 0.05 - statistically significant

TABLE 16

Comparison of Manometric Parameters between those with HbA1c Values < 6.5 and≥ 6.5

Parameters	HbA1c < 6.5 N = 6	HbA1c ≥ 6.5 N = 29	P value
	Mean ± SD	Mean ± SD	
Mean Expiratory Pressure	25.900 ± 12.403	23.021± 9.181	**0.514**
EGJ- CI	22.300 ± 11.530	33.628 ± 13.388	**0.063**
Median IRP	3.700 ± 2.480	6.883 ± 5.410	**.171**

* P-value < 0.05 - statistically significant

TABLE 17

Mann Whitney test to compare manometric parameters between those with HbA1c Values < 6.5 or ≥ 6.5

Parameter	HbA1c < 6.5	HbA1c ≥ 6.5	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Mean Expiratory Pressure	20.50	17.48	0.535	**0.535**
EGJ- CI	10.50	19.55	0.050	**0.050***
Median IRP	12.33	19.17	0.146	**0.146**

* P-value < 0.05 - statistically significant

TABLE 18

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

Parameters	Group A < 5 years N = 9	Group B ≥ 5 years N = 26	P value
	Mean ± SD	Mean ± SD	
Mean Expiratory Pressure	17.889 ± 5.372	25.462 ± 10.112	**0.041***
EGJ- CI	34.733 ± 12.025	30.631 ± 14.215	**0.445**
Median IRP	6.589 ± 6.827	6.250 ± 4.592	**0.868**

* P-value < 0.05 - statistically significant

TABLE 19

Mann Whitney test to compare manometric parameters between Diabetics whose duration of the disease is < 5 years (Group A) and ≥ 5 years (Group B)

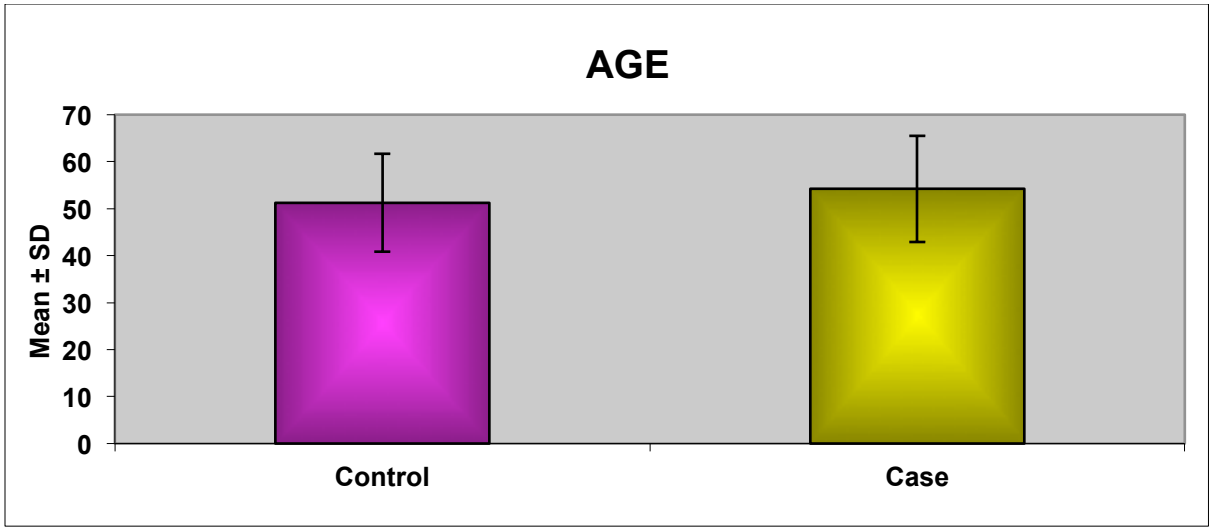
Parameter	Group A < 5 years	Group B ≥ 5 years	Mann Whitney (U)	P value
	Mean rank	Mean rank		
Mean Expiratory Pressure	11.67	20.19	0.031	**0.031***
EGJ- CI	20.33	17.19	0.446	**0.446**
Median IRP	17.61	18.13	0.897	**0.897**

* P-value < 0.05 - statistically significant

Charts

CHART 1

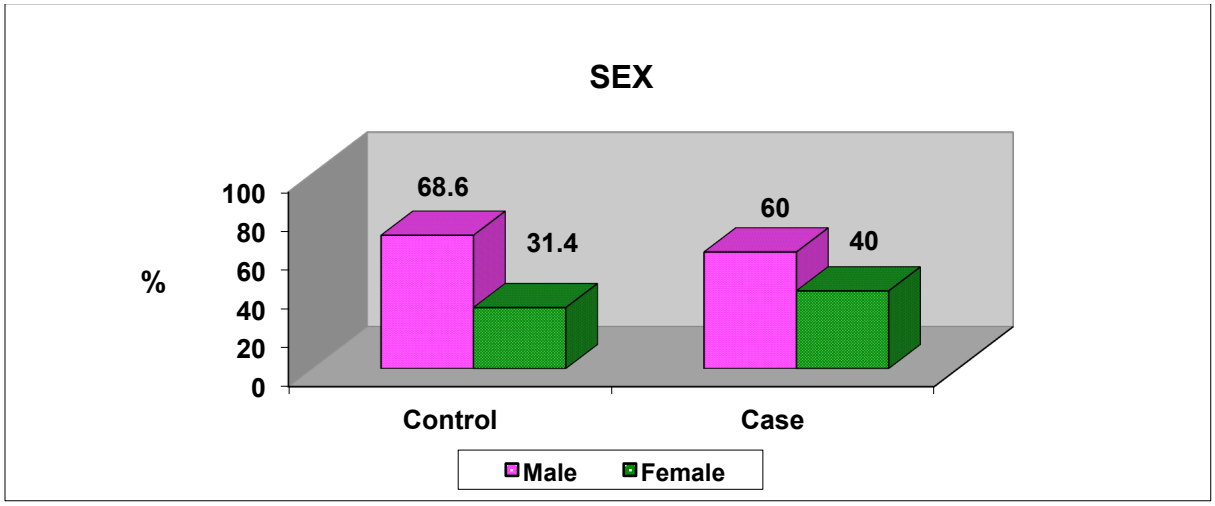
Age Distribution between Non-diabetics and Diabetics



P value 0.252

CHART 2

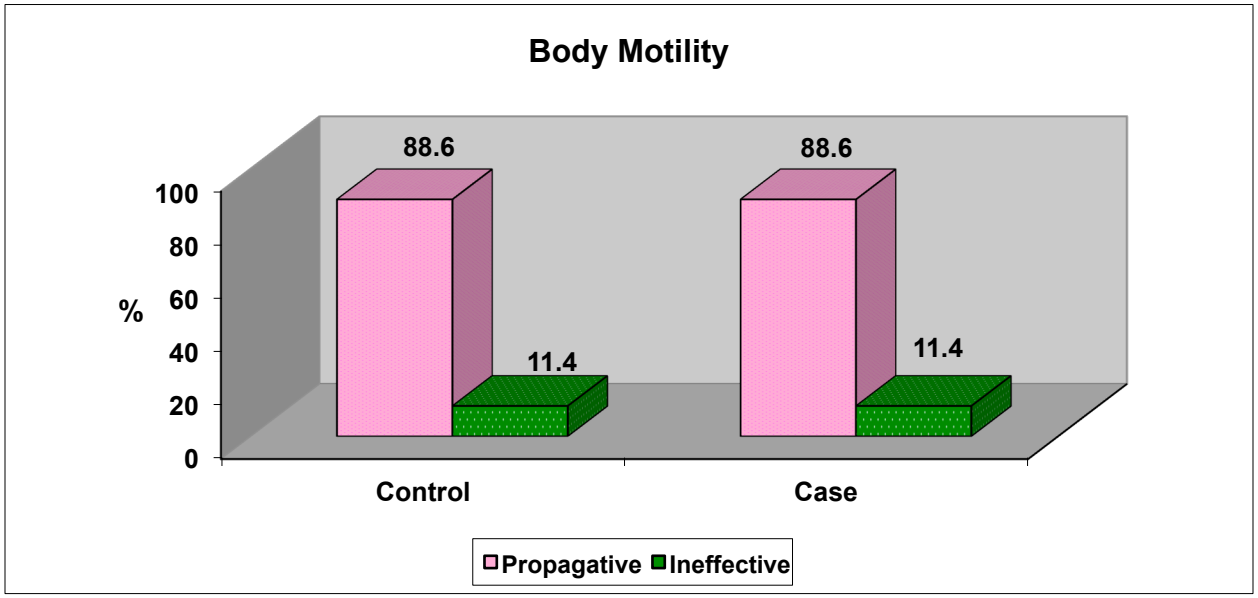
Sex Distribution between Males and Females in Control and Case Groups



P value 0.454

CHART 3

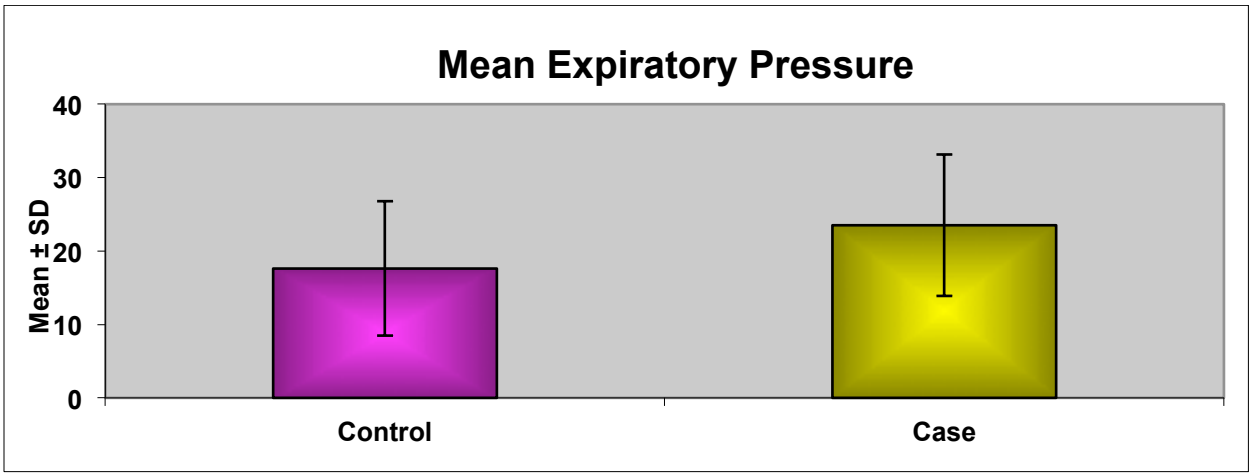
Distribution of Body Motility between Control and Case Groups



P value 1.000

CHART 4

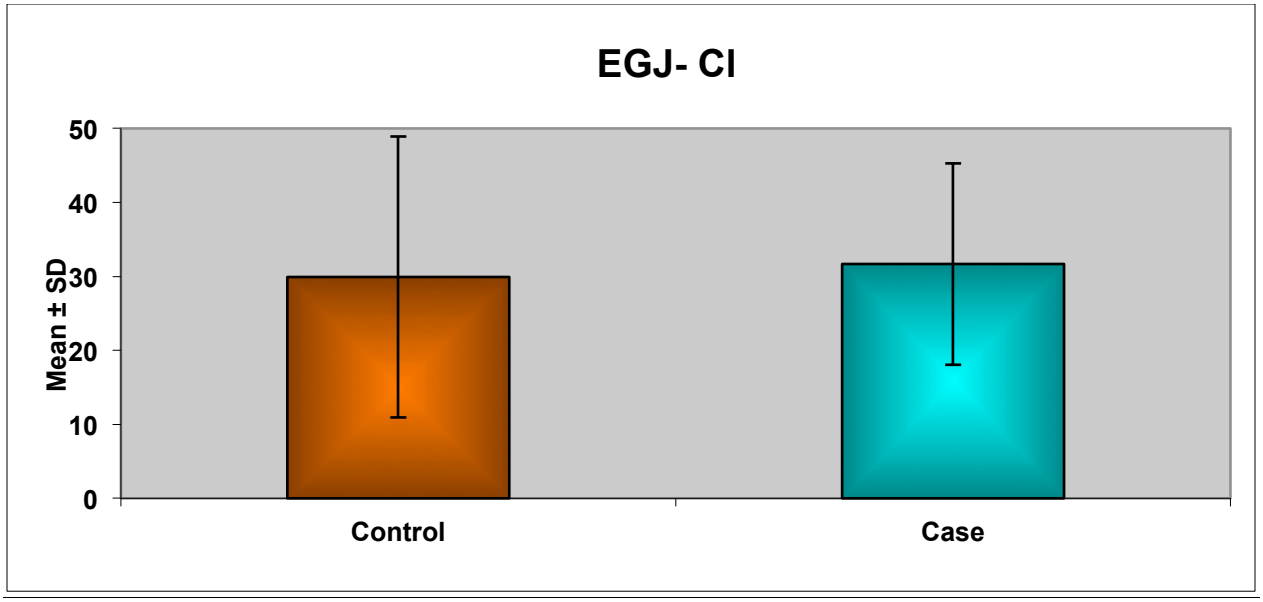
Mean Basal Expiratory Pressure between Non-diabetics and Diabetics



P value 0.011*

CHART 5

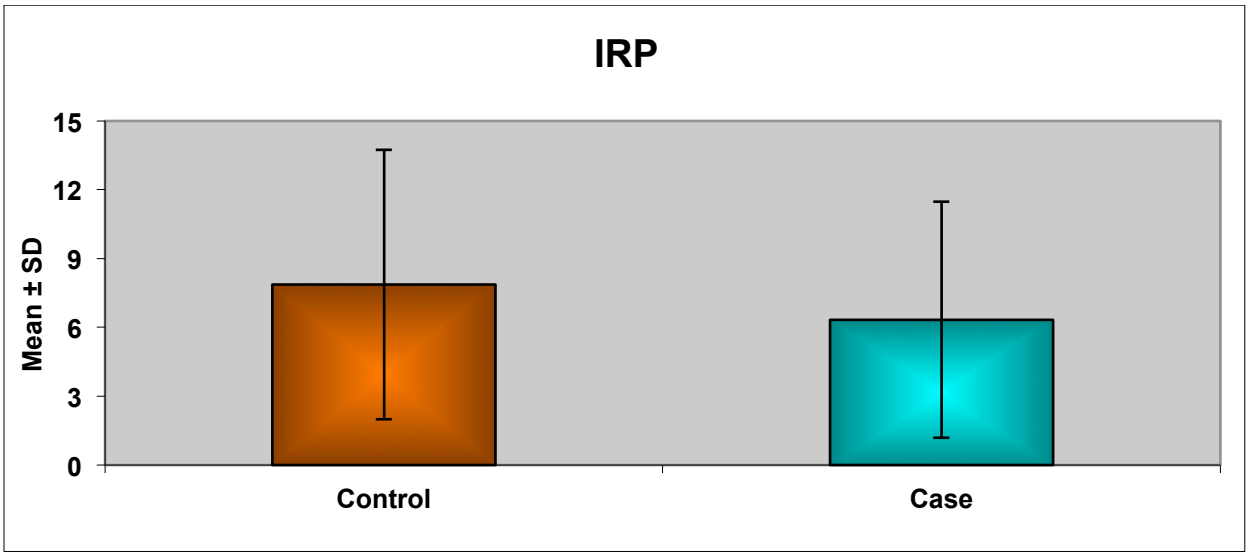
EGJ - CI between Non-diabetics and Diabetics



P value 0.657

CHART 6

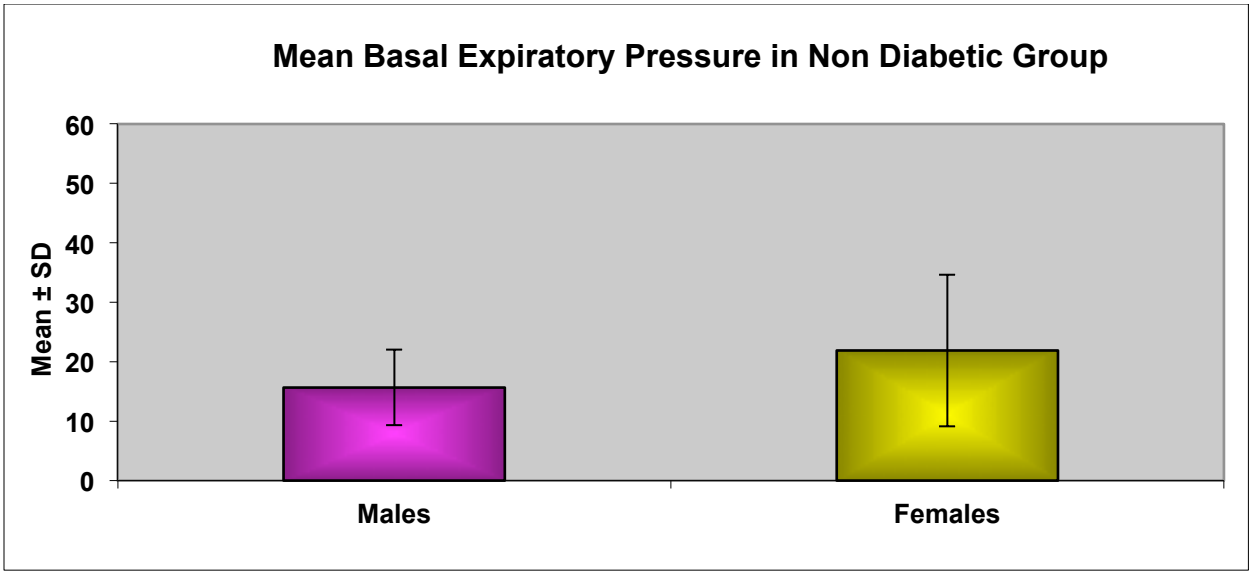
Median IRP between Non-diabetics and Diabetics



P value 0.248

CHART 7

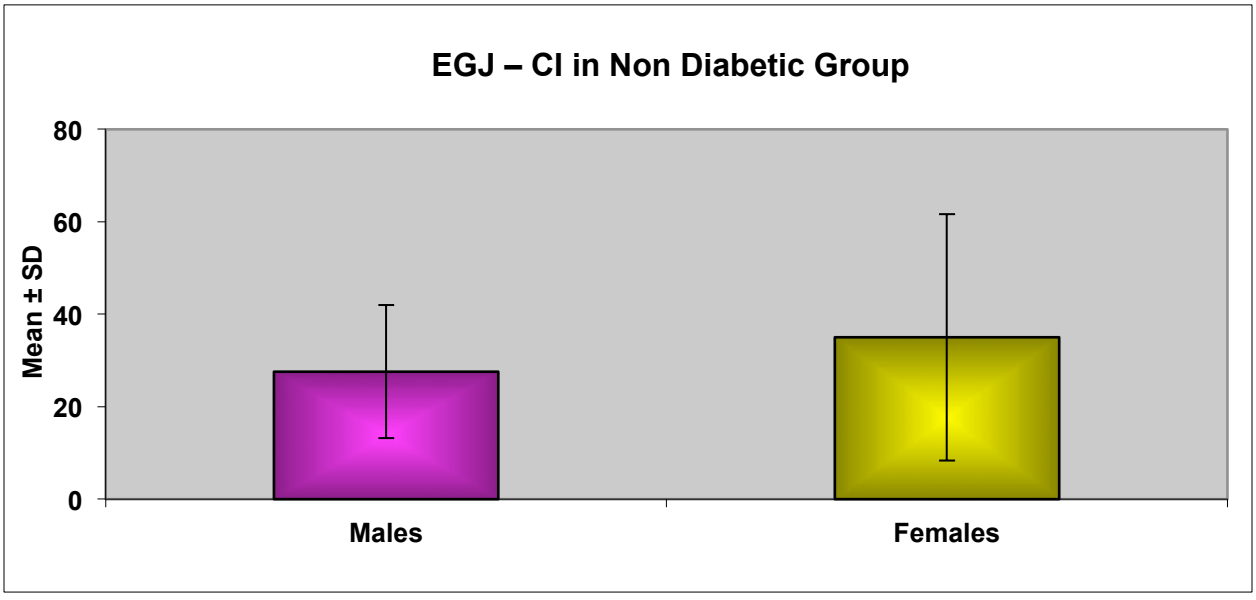
Mean Basal Expiratory Pressure in Non-diabetic Male & Female



P value 0.061

CHART 8

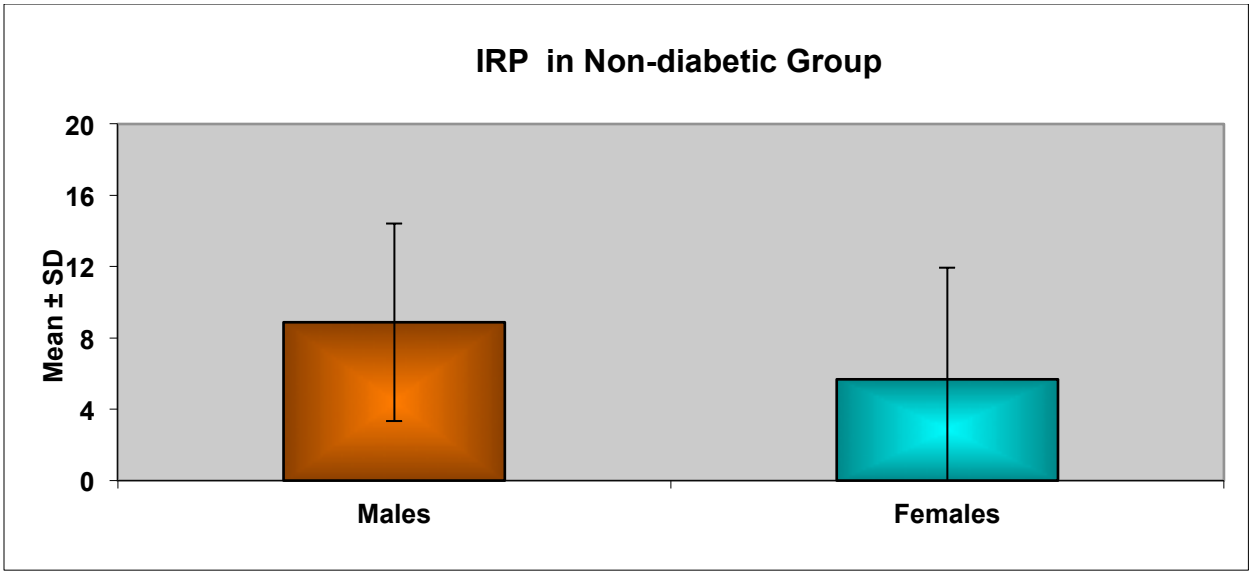
EGJ- CI in Non-diabetic Male & Female



P value 0.288

CHART 9

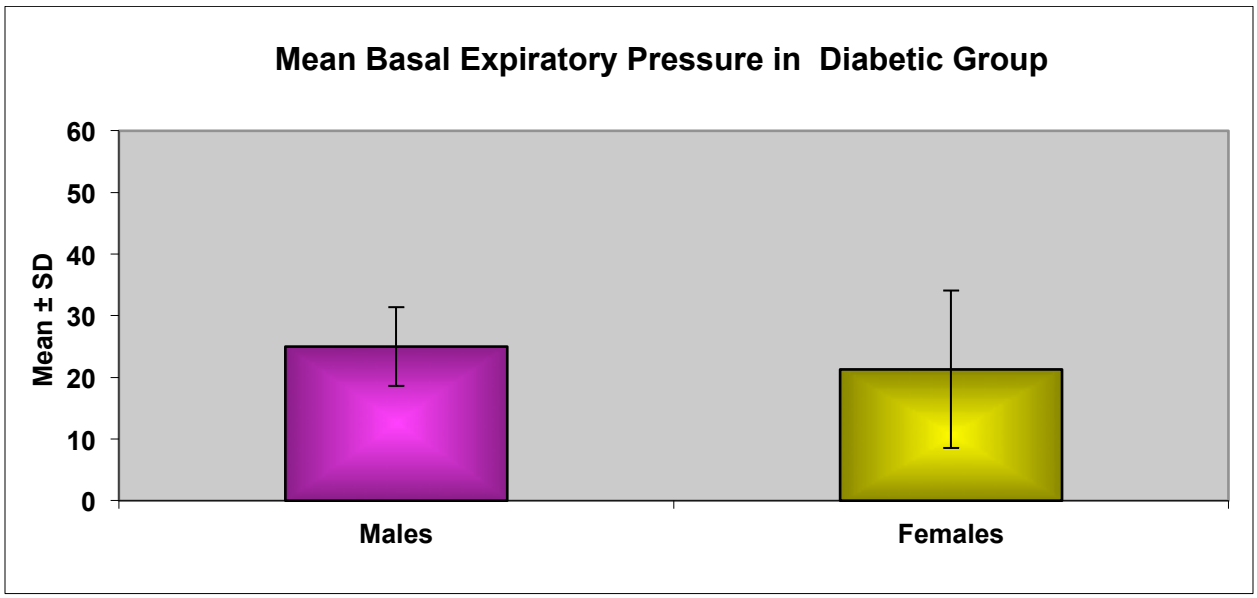
IRP in Non-diabetic Male & Female



P value 0.137

CHART 10

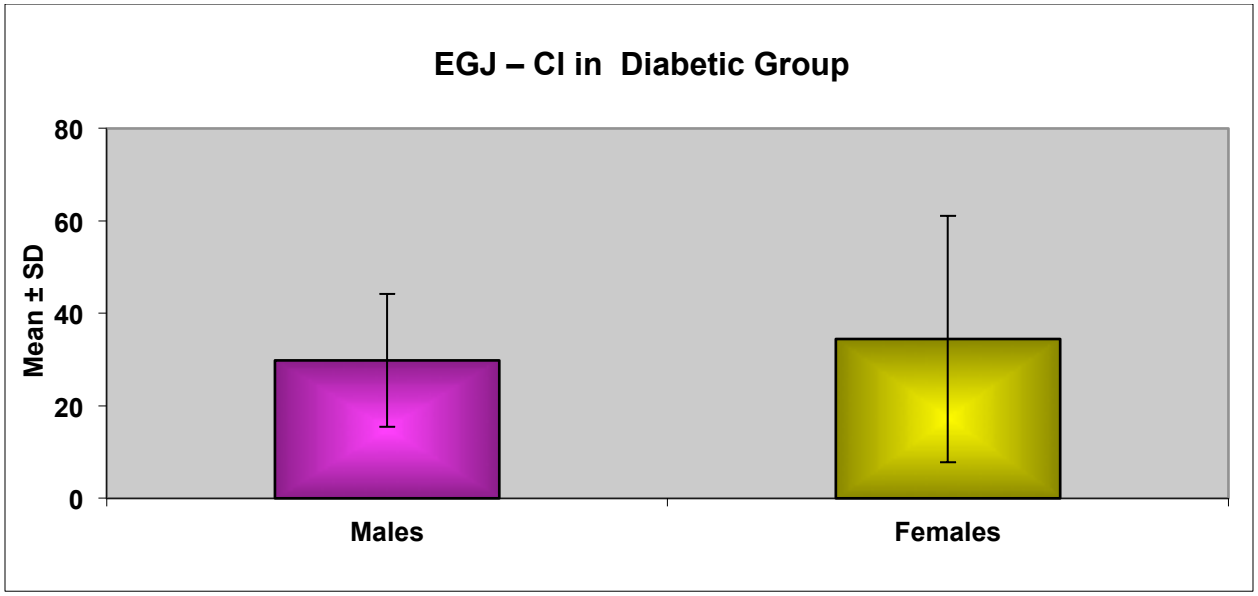
Mean Basal Expiratory Pressure in Diabetic Male & Female



P value 0.273

CHART 11

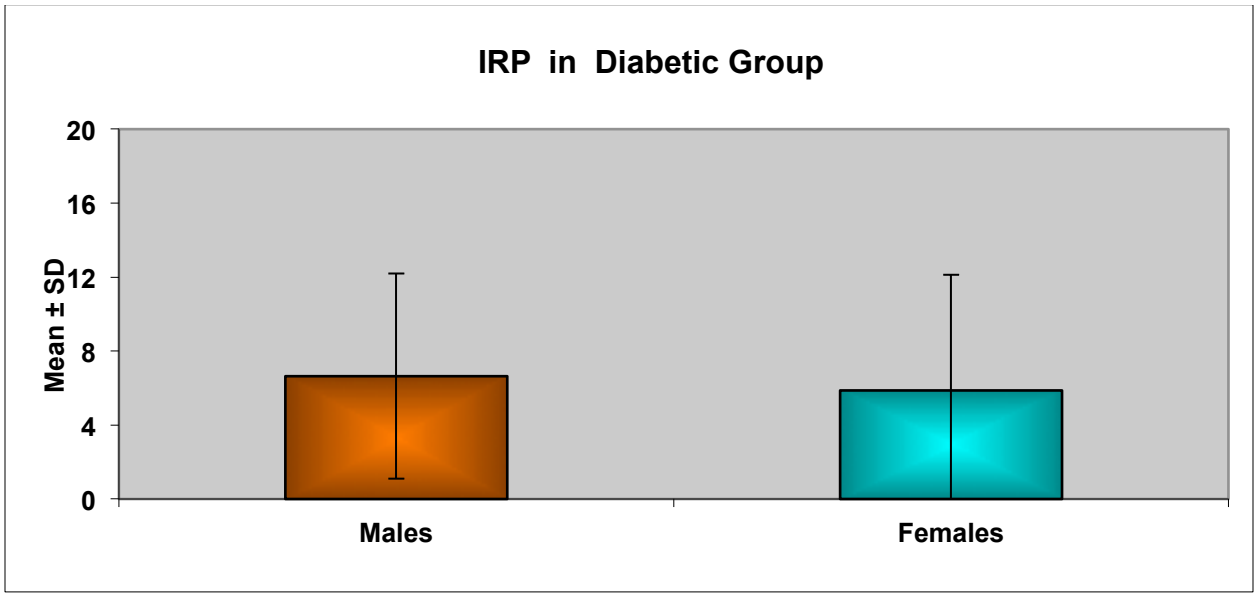
EGJ-CI in Diabetic Male & Female



P value 0.332

CHART 12

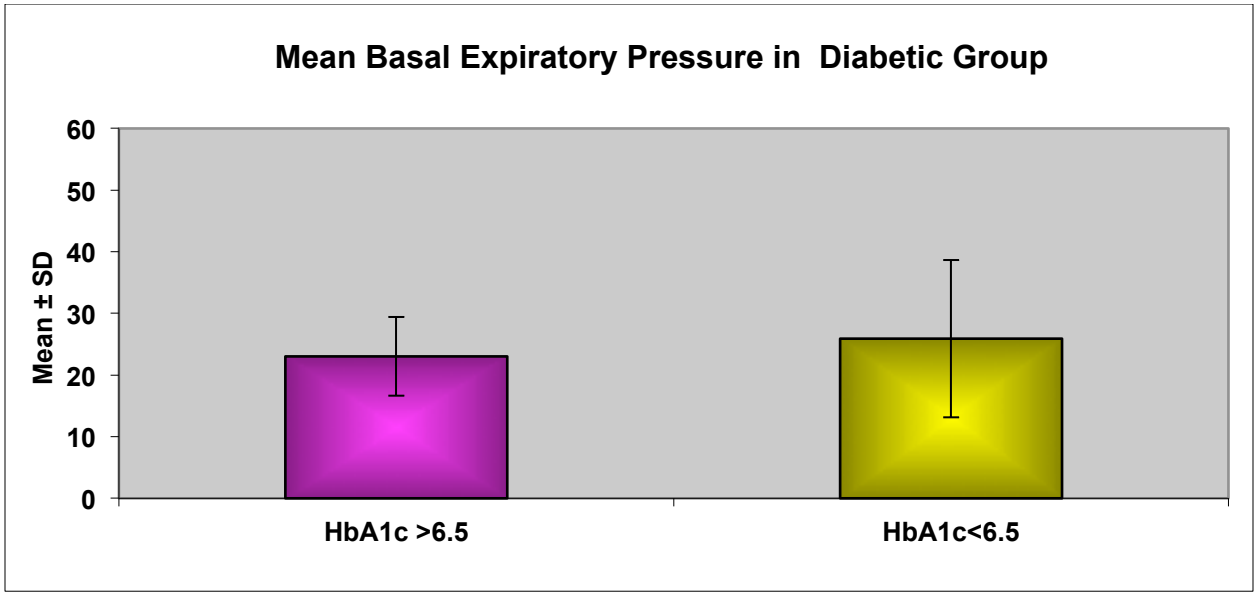
IRP in Diabetic Male & Female



P value 0.669

CHART 13

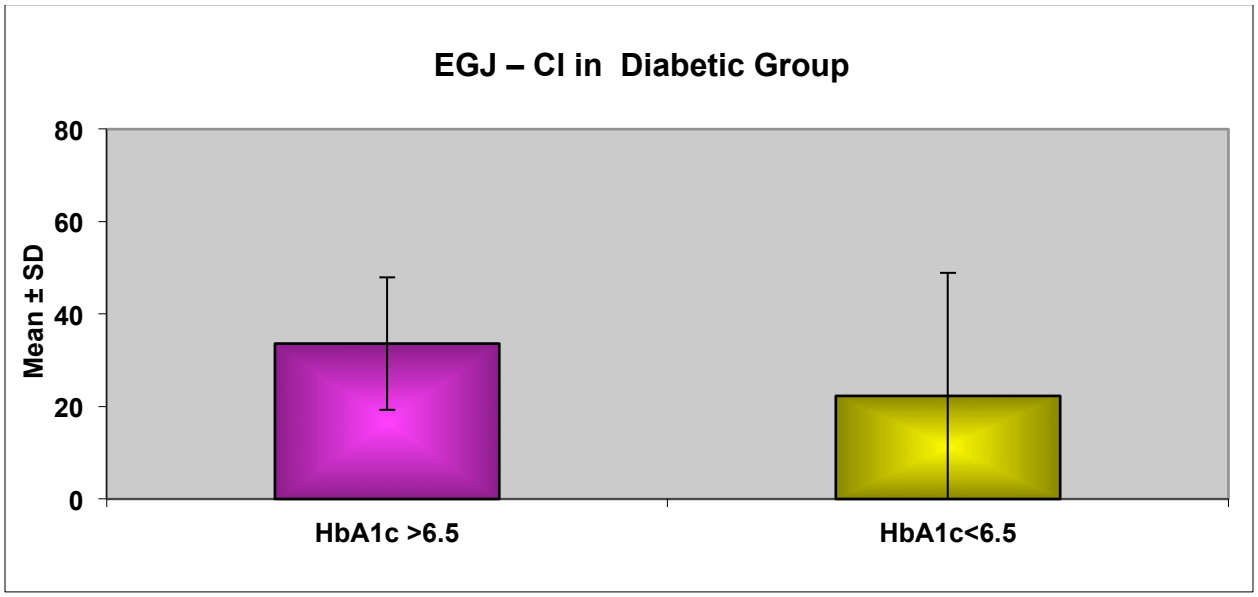
Mean Basal Expiratory Pressure in uncontrolled and controlled Diabetics



P value 0.514

CHART 14

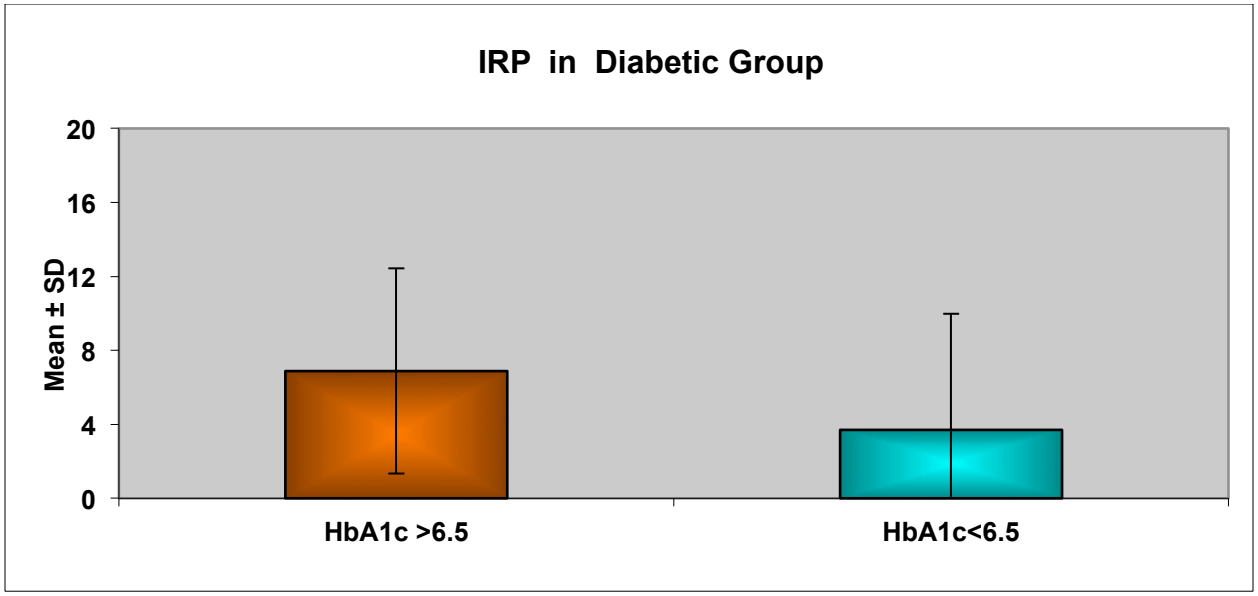
EGJ- CI in uncontrolled and controlled Diabetics



P value 0.063

CHART 15

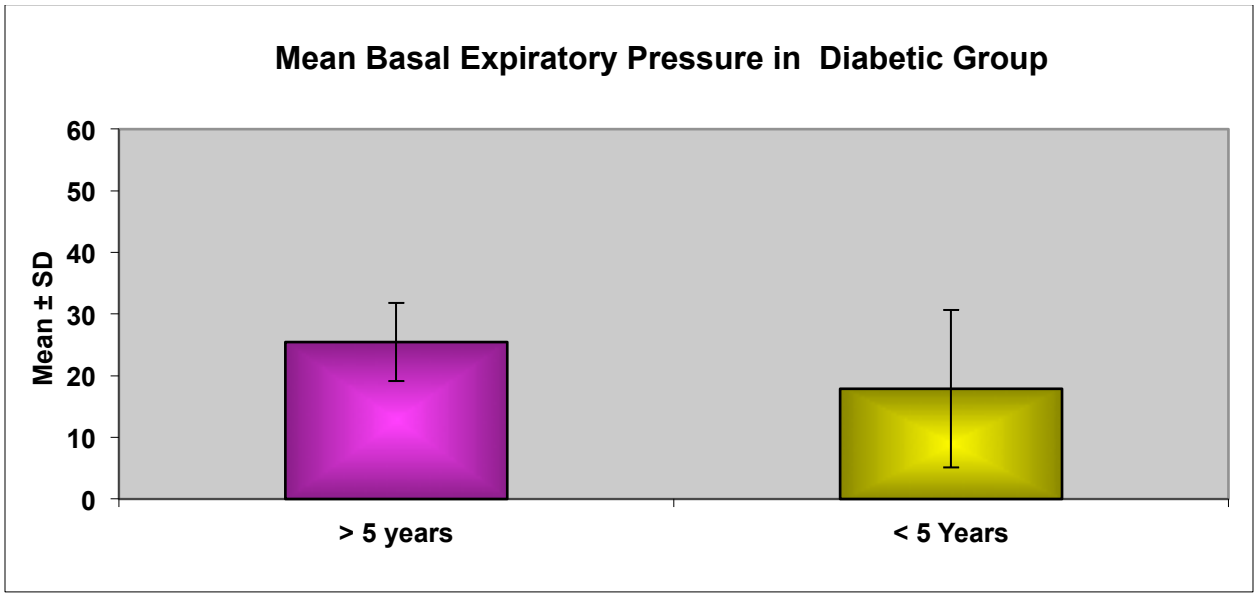
IRP in uncontrolled and controlled Diabetics



P value .171

CHART 16

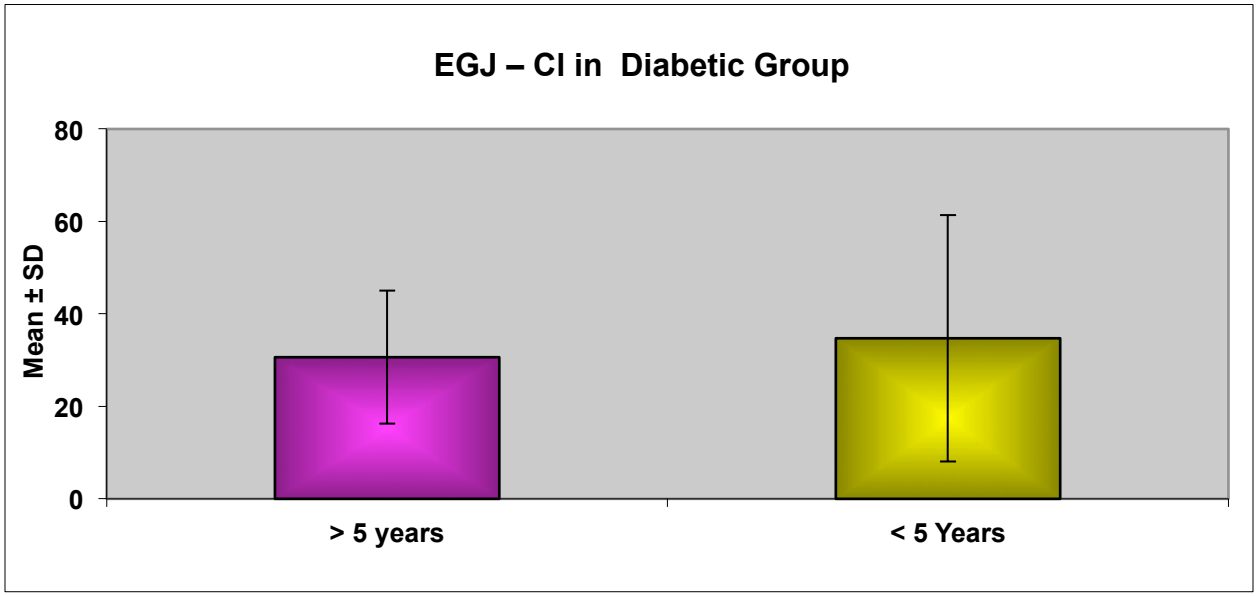
Mean Basal Expiratory Pressure in Duration of Diabetes > 5 years and < 5 years



P value **0.041***

CHART 17

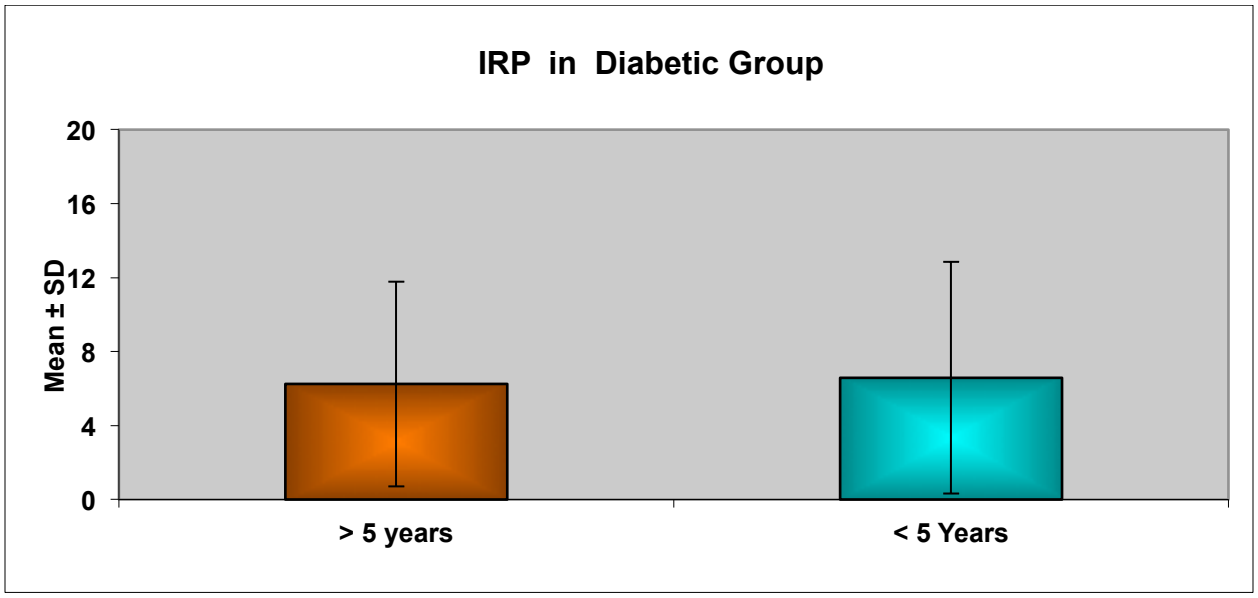
EGJ -CI in Duration of Diabetes > 5 years and < 5 years



P value 0.445

CHART 18

IRP in Duration of Diabetes > 5 years and < 5 years



P value 0.868

Discussion

Discussion

It is within human nature and for the betterment of science that controversial findings or statements are not ignored. May the findings that one comes will create more controversy finally down the timeline, these are the foundations that get created for one to make a discovery and end the controversy giving rise to a new proven theory. It is the scientist within each one of us who tries to come up with this new proven theory that can maybe even change the world one day.

One of the longest autonomic nerves present in the human body is the tenth cranial nerve, the vagus Nerve. It has been known to be historically cited as the pneumogastric nerve. Its supply to the digestive tract and has proven to be imperative for many physiological functions. Gastrointestinal symptoms have been attributed due to motor dysfunction, which results from autonomic (vagal) neuropathy. [65] Vela et al reinforces by stating that the esophagus is part of the alimentary tract that is highly supplied by the vagus, but whose functional activity in those with diabetes has been neglected. [66]

Diabetes has been present for centuries, and within this long duration many advances have been seen with regard to treatment and control of this disease. Likewise Gastro esophageal Reflux Disease has also been prevalent for countless years, with treatment ranging from something as simple as home remedies to something as complex as surgical intervention. Tying up these two diseases and seeing if there lies a correlation between GERD and the presence of Diabetes was the

aim of our study. Nishida et al comments that the incidence of GERD in patients with Diabetes Mellitus remains controversial. [67] It is this controversy that has led us into this study.

Age in Relation to Non Diabetics and Diabetics with GERD

In our study, there was no statistical significant difference in mean age of the subjects who were present in both groups. This shows that both the groups are age matched. The mean age was found to be 51 in non-diabetics and 54 in diabetics, which seemed to be similar to a study conducted by Wang et al and team in a population based study to see the prevalence of GERD in southern India. Wang et al found that 22.2% of the general population from southern India there was significant association between presence of GERD with increasing age. [68]

Sex in Relation to Non Diabetics and Diabetics with GERD

In our study, there was no statistical significance found between males and females within each group. Nishida et al found there was no significant difference in the incidence of reflux symptoms between males and females. [67] Mayne et al found that GERD associated with diabetes occurs three to four times more often than in the general population of a similar age and sex. [69] On the contrary Janatuinem et al demonstrated that the spectrum of gastrointestinal symptoms in diabetes is similar and does not differ from that in the general population. [70]

Body Motility in Relation to Non-Diabetics and Diabetics with GERD

88.6% of the study group and 88.6% of the control group showed propagative movements and 11.4% in both the groups showed ineffective motility and on comparison there was no statistical significance. In a study conducted by Jorge et al, comparison of esophageal motor characteristics between diabetics and healthy individuals were conducted. It was found that maximum active tension in healthy individuals reduces due to age and in other words the esophagus becomes stiffer with age. Increased stiffness is associated with reduction in primary and secondary peristalsis in a healthy individual after the age of 40 years. [71] The mean age in both groups in our study was 51 in the control group and 54 in the study group. Vela et al found in his manometric examination of the esophagus that significant change was present in diabetics who had esophageal motor alterations. He felt that these motor alterations would add to a functional obstruction, which affects the transport of esophageal contents thereby delaying the esophageal emptying. Despite the high incidence of esophageal motor disturbances the patients in the study conducted by Vela had no referable symptoms. [66] Feldman et al found in a study that 22% of asymptomatic diabetic patients had radiologic evidence of gastric retention, due to delayed gastric emptying. This is attributed to various causes; one of such is poor or no esophageal peristalsis. The only logical reason behind this being damage to the vagus due to autonomic neuropathy. These findings are found to be similar with that of ones seen after truncal vagotomy. [59]

Basal lower esophageal sphincter pressure between non-diabetic and diabetic group

The basal lower esophageal sphincter pressure is classified according to a range. The normal value falls within the pressure range of 10-35 mm of Hg. A value above 35 mm of Hg is considered as elevated and a value below 10 mm of Hg is considered as reduced. More than 70 % of the non-diabetic and diabetic group showed pressures to be within the normal range. Elevated pressures were found to be 5.7% in the control group and 8.6% in the study group. Reduced pressures were 22.9% in the control group and 17.1% in the study group.

Mean Basal Inspiratory Pressure in Relation to Non-Diabetics and Diabetics with GERD

In our study, there was a statistically significant p value obtained while comparing the mean basal inspiratory pressures in both control and case groups. The mean basal expiratory pressure is the standard pressure recording taken for lower esophageal sphincter pressure readings; therefore no studies have discussed the values and significance of mean basal inspiratory pressures. However, due to its statistical significance its value may hold significance. The mean value for the study group was increased, when compared to the control group but still within the normal range of pressures.

Mean Basal Expiratory Pressure in Relation to Non-Diabetics and Diabetics with GERD

The mean basal expiratory pressure recorded in this present study showed there to be statistical significance between the two study groups. However, the control group showed mean values to be of 17 mm of Hg when compared to the diabetic group, which had a mean of 23 mm of Hg. Both these values come under the normal range of 10-35 mm of Hg for basal expiratory pressure. In a study conducted by Stewart et al the lower esophageal sphincter pressure was significantly reduced in all groups of diabetics when compared with non-diabetics. Stewart et al and team however conducted the study in diabetics with known neuropathic complications and went one step further to find out that there was no difference in those who had diabetes with and without autonomic symptoms. [(72)] In a study conducted by Lluch et al found that there was a higher prevalence of abnormal gastro esophageal reflux in asymptomatic diabetics when compared to the general population. [(73)] However, in our study both the groups were symptomatic that could be the reason for the control group having a low value of mean basal expiratory pressure.

Comparison of EGJ-CI between non diabetics and diabetics

In our study, the mean value for the EGJ – CI was found to be 29.920 mm of Hg in the control group and slightly higher around 31.68 mm of Hg in the diabetic study group. This showed no statistical significance when subjected to t test as well as Mann Whitney test. Ham et al in a study conducted between patients with GERD and

healthy individuals found that the EGJ –CI value was lower in patients with GERD (around 22.6 mm of Hg) when compared to those without GERD having a value of 50.3 mm of Hg. [74] There is no other study evidence, which discusses the effect of diabetes on the EGJ – CI. However in our study it shows that the diabetic group had a slightly raised value of 31.68 mm of Hg when compared to the control group.

Comparison of the Median Integrated Pressures between non diabetics and diabetics

In our study the median integrated pressure was found to be 7.87 mm of Hg in the control group and a slightly lower value of 6.33 mm of Hg in the diabetic group. Upon comparison there was no statistical significance found. A value above 15 mm of Hg is considered to be pathologic. [34] In our study, in both groups it falls within the normal range.

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

In our study, the mean basal expiratory pressure was found to be statistically insignificant, when comparison was done between males and females in the control group. The mean age for males in our study was for the control group was 44 years and for females was 38 years. In a study conducted by Kim et al, he states that the prevalence of reflux esophagitis is significantly increased only as age increases in females, and this may be due to the decrease in estrogen levels post menopause. [64]

Since the mean age of women in our study was within the reproductive age group it maybe the reason for normal expiratory pressures.

The median integrated relaxation pressure is a metric used in HRM in order to assess the adequacy of esophagogastric junction. The integrated relaxation pressure has been defined as the lowest pressure through the EGJ for four contiguous or non-contiguous seconds within the relaxation window. This value incorporates both a measure of the completeness of relaxation and the duration of time for which this relaxation is sustained. [(75)] In our study the median IRP was decreased in males compared to females. This is attributed to the presence of estrogen in females, which increases smooth muscle contraction. Upon performing the Mann Whitney test for median IRP among males and females in the control group a p value of 0.030 was obtained showing statistical significance. Costa et al found that the IRP in women and men had no statistical significance. [(76)] Like in our study Costa also found no statistical significance between men and women for median IRP, this he attributed to the possibility of decreased number of subjects, which could also be the same in out study. Only upon the Mann Whitney non-parametric comparison did the median IRP show statistical significance between male and female.

None of the same parameters showed statistical significance in the diabetic study group, in the current study. This may be attributed to the fact that in the control group the mean age for women was found to be 38, which is within the reproductive age group showing their presence of estrogen; however the males in the control group

were older with a mean age of 56. In the study group the mean age for women was calculated to be 51, which mean they have entered the menopausal age group with reduction in estrogen function. The males in the study group had a mean age of 56, therefore when comparison was carried out between both male and female with all manometric parameters in the study group no statistical significance was found.

Comparison of Manometric Parameters between those with HbA1c Values < 6.5 or ≥ 6.5

In our study more than 80 % of the study group had an HbA1c value of greater than 6.5 and were not in glycemic control. Nishida et al comments that the incidence of GERD is higher in patients with diabetes regardless of the complications of diabetes. Based upon a questionnaire study the HbA1c was positively associated with the incidence of symptomatic GERD. [67]

However in our study upon comparison of various manometric parameters, mean expiratory pressure and IRP showed no statistical significance, but the EGJ- CI showed statistical significance. There are no studies that comment on the EGJ –CI of diabetic individuals regardless of their glycemic control.

Comparison of Manometric Parameters between Diabetics whose duration of the disease is < 5 years and ≥ 5 years

Nishida et al states that the incidence of GERD is related to the duration of diabetes mellitus. [67] The mean expiratory pressure was increased in those who were diabetic

for more than five years when compared to those who were diabetic for more than five years. This increase was significant in both t test and Mann Whitney test. More than 70% of diabetic patients had diabetes for more than 5 years. Less than 30% of the individuals were within duration of 5 years. However there was no statistical difference in the EGJ-CI and IRP values in relation to the duration of diabetes mellitus.

Conclusion

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.

Regarding the duration of diabetes, mean expiratory pressures were lower in diabetics less than five years duration 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 an impact on these manometric parameters, and age related changes occur irrespective of glycemic control. 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 undergo high-resolution esophageal manometry in order to come to a definite conclusion.

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Annexures

ANNEXURE I

DATA COLLECTION TOOL:

OP NO: **IP NO:**

PHONE NUMBER:

Name:

Age:

Sex:

BMI: **HT:** **WT:**

Type II DM : **YES** **NO**

DURATION OF TYPE II DM:

HbA1c Value: **Date last checked:**

ON ANY MEDICATION: **YES** **NO**

NAME OF DRUGS:

OTHERS:

ANNEXURE II

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I / We (write name of the investigator(s) here), **Dr. R Pavitra Vyshnavi Yogisparan_**, am / are carrying out a study on the topic: **Lower Esophageal Sphincter Pressure in patients with type II Diabetes Mellitus presenting with heartburn** as part of my / our research project being carried out under the aegis of the Department of: **Physiology & Gastroenterology**

(*Applicable to students only*): My / our research guide is: **Dr. T. Umamaheshwari**

The justification for this study is:

To find out the association of upper gastrointestinal symptoms in patients with type II diabetes who live in India. There are not many studies done to see this association in the Indian Phenotype of type II Diabetes Mellitus Patients.

The objectives of this study are:

Primary Objective:

To evaluate the Lower Esophageal Sphincter Pressure in patients with Type II Diabetes Mellitus, presenting with heartburn, by esophageal manometry studies and 24 hour esophageal pH monitoring.

Secondary Objective:

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.**

Sample size: **60**

Study volunteers / participants are (specify population group & age group): **30 Type II Diabetic patients and 30 Non-diabetic patients presenting with heartburn.**

Location: **Gastroenterology Dept, PSGIMSR, Coimbatore**

Benefits from this study: **To find out for future patients with type II diabetes how to prevent and manage heartburn.**

Risks involved by participating in this study:**NIL**

How the **results** will be used: **For my dissertation study.**

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings-including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date: Witness:

Contact number of PI:

Contact number of Ethics Committee Office: 0422 2570170 Extn.: 5818

ANNEXURE III

ஒப்புதல் படிவம்

தேதி:

டாக்டர். பவித்ரா வைஷ்ணவி யோகீஸ்பரன் ஆகிய நான் PSG மருத்துவக்கல்லூரியில் **உடலியங்கியல்** துறையின் கீழ் **"நீரிழிவு நோயாளிகளில் நெஞ்செரிச்சல் அறிகுறி உள்ளவர்களுக்கு குறைந்த உணவுக்குழாய் சுருக்கத்தசை அழுத்தத்தை கண்டறிதல்"** என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி: **டாக்டர். டி. உமா மகேஸ்வரி**

ஆய்வு மேற்கொள்வதற்க்கான அடிப்படை: **மேல் இரைப்பை அறிகுறிகளுக்கும் நீரழிவு நோய்க்கும் சம்பந்தம் உள்ள ஆய்வுகள் இந்தியாவில் மிக குறைவாகவே உள்ளன. அதனால் இந்த ஆய்வை மேற்கொள்கிறேன்.**

ஆய்வின் நோக்கம்: **மேல் இரைப்பை அறிகுறிகளுக்கும், நீரழிவு நோய்க்கும் சம்பந்தம் உள்ளதா என்பதை ஒப்பிட்டு பார்த்து கண்டுபிடிக்க வேண்டும்.**

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை: **60 (அறுபது)**

ஆய்வு மேற்கொள்ளும் இடம்: **உடலியங்கியல் மற்றும் இரைப்பை குடலியில் பிரிவு.**

ஆய்வின் பலன்கள்: **நீரழிவு நோயாளிகளில், மேல் இரைப்பை அறிகுறிகளை வராமல் தவிர்க்க முடியும் மற்றும் அதை நன்முறையில் குணப்படுத்த முடியும்.**

ஆய்வினால் ஏற்படும் அசௌகரியங்கள் / பக்க விளைவுகள்:

எந்த விதமான பக்க விளைவுகளும் இல்லை.

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் **ஐந்து** வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்க்கும் பயன்படுத்தப்பட மாட்டாது. ஏந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்படமாட்டாது. அவை ரகசியமாக வைக்கப்படும்.

இந்த ஆய்வின் கேள்விகளுக்கு பதிலளிப்பதிலோ, இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுப்பதிலோ உங்களுக்கு ஏதேனும் அசௌகரியங்கள் இருந்தால், எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. எப்பொழுது வேண்டுமானாலும் ஆய்விலிருந்து விலகும் உரிமை உங்களுக்கு உள்ளது. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சை முறையில் எந்த வித பாதிப்பும் இருக்காது என்று உங்களுக்கு உறுதியளிக்கிறோம். மருத்துவ மனையில் நோயாளிகளுக்கு அளிக்கப்படும் சேவைகளை நீங்கள் தொடர்ந்து பெறலாம். இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் வேறு எந்த விதமான கூடுதலான பலனும் உங்களுக்குக் கிடைக்காது. நீங்கள் அளிக்கும் தகவல்கள் இரகசியமாக வைக்கப்படும். ஆய்வில் பங்கேற்பவர்கள் பற்றியோ அவர்கள் குடும்பத்தைப் பற்றியோ எந்தத் தகவலும் எக்காரணம் கொண்டும் வெளியிடப்படாது என்று உறுதியளிக்கிறோம். நீங்கள் அளிக்கும் தகவல்கள் / இரத்த மாதிரிகள் / திசு மாதிரிகள் அங்கீகரிக்கப்பட்ட ஆய்விற்கு மட்டுமே பயன்படுத்தப் படும். இந்த ஆய்வு நடைபெறும் காலத்தில் குறிப்பிடத்தகுந்த புதிய கண்டுபிடிப்புகள் அல்லது பக்க விளைவுகள் ஏதும் ஏற்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இதனால் ஆய்வில் தொடர்ந்து பங்கு பெறுவது பற்றிய உங்கள் நிலைப்பாட்டை நீங்கள் தெரிவிக்க ஏதுவாகும்.

ஆய்வுக்குட்படுபவரின் ஒப்புதல்: இந்த ஆய்வைப் பற்றிய மேற்கூறிய தகவல்களை நான் படித்து அறிந்து கொண்டேன் / ஆய்வாளர் படிக்கக் கேட்டுத் தெரிந்து கொண்டேன். ஆய்வினைப் பற்றி நன்றாகப் புரிந்து கொண்டு இந்த ஆய்வில் பங்கு பெற ஒப்புக்கொள்கிறேன். இந்த ஆய்வில் பங்கேற்பதற்கான எனது ஒப்புதலை கீழே கையொப்பமிட்டு / கை ரேகை பதித்து நான் தெரிவித்துக் கொள்கிறேன்.

பங்கேற்பாளரின் பெயர், முகவரி :

பங்கேற்பாளரின் கையொப்பம் / கை ரேகை / சட்டபூர்வ பிரதிநிதியின் கையொப்பம் :

தேதி :

ஆய்வாளரின் கையொப்பம் :
தேதி :

ஆய்வாளரின் தொலைபேசி எண்:

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்: 0422 2570170 Extn.: 5818

ANNEXURE IV

Non-diabetic (Control) Group

S. NO	AGE	SEX	Basal LOS Pressure	Mean Basal Insp Pr	Mean Basal Exp Pr	EGJ-Cl	Median Integrated Relaxation Pressure	Body Motility
1	55	M	Normal	34.2	11.4	25.6	4.1	Propagative
2	37	M	Normal	19.5	20.2	22.3	12.1	Propagative
3	57	M	Normal	38.5	16.5	31.1	5.2	Propagative
4	40	M	Normal	30.1	16.6	24.9	6.1	Ineffective
5	57	F	Reduced	14.7	17.6	18.2	0.5	Propagative
6	76	F	Normal	28.2	22.9	29.8	0.1	Propagative
7	47	M	Normal	34.8	11.7	30.8	7.3	Propagative
8	65	M	Normal	22.8	27.8	38.2	12.6	Propagative
9	37	F	Elevated	45	45.2	95.1	8.6	Propagative
10	44	F	Normal	14.1	25.8	27.1	4.6	Propagative
11	53	M	Normal	14	19	18.8	9.9	Propagative
12	53	M	Normal	22.3	15.1	18.9	1.7	Propagative
13	42	M	Normal	33.9	27.6	37.9	13.3	Propagative
14	42	M	Reduced	11	8.5	3.1	1.6	Propagative
15	44	M	Reduced	9.4	10.5	10.9	9.5	Propagative
16	62	M	Normal	40.6	18.2	51.2	9.3	Propagative
17	57	F	Reduced	47.7	5	17.9	2.8	Ineffective
18	40	F	Normal	31.9	22.3	50.5	6.5	Propagative
19	59	M	Reduced	15.7	5.2	8.5	3.6	Propagative
20	50	M	Reduced	35.1	8.6	22.7	11.3	Propagative
21	37	M	Reduced	17.3	9.2	21	10.5	Propagative
22	51	M	Normal	21.1	11.8	12.7	4.5	Propagative
23	52	F	Elevated	52.8	41	73.4	23.1	Propagative
24	40	F	Reduced	32.5	9.9	20.4	3.4	Propagative
25	39	M	Normal	40.6	23.2	45.5	25.9	Propagative
26	54	F	Normal	21.9	10.3	17.5	5.6	Propagative
27	74	M	Normal	33.2	17	59.9	16	Propagative
28	51	M	Normal	20.5	10.1	18.6	6.8	Propagative
29	59	F	Normal	19.9	28.1	16.1	4	Ineffective
30	52	M	Normal	34.1	12.8	31.1	13.2	Propagative
31	44	F	Normal	29.8	12.7	19.3	3.3	Propagative
32	72	M	Normal	16.9	13.8	21.3	4	Propagative
33	57	M	Normal	22.3	15.1	18.9	1.7	Propagative
34	46	m	Normal	34.4	17.1	51.4	10.4	Ineffective
35	48	M	Normal	47.8	28.8	36.6	12.6	Propagative

ANNEXURE V

Diabetic (Case) Group

S.NO	AGE	SEX	Basal LOS Pressure	Mean Basal Insp Pr	Mean Basal Exp Pr	EGJ-Cl	Median Integrated Relaxation Pressure	Body Motility	HbA1c	Duration
1	59	M	Normal	16.7	15.7	28.4	1.5	Propagative	12	10
2	64	F	Normal	22.5	21.2	22.7	0	Propagative	7.8	8
3	71	M	elevated	16.4	44.7	21.4	7.8	Propagative	6.3	7
4	49	M	Reduced	17.7	32.1	23.9	11.5	Propagative	9.2	20
5	55	M	Normal	25.7	27.7	44.2	12.8	Propagative	6.7	4
6	56	F	Normal	31	28.2	58.2	3.6	Propagative	7.9	12
7	62	M	Reduced	19.2	26.2	57	10.7	Propagative	8	5
8	63	F	Normal	26.4	27.8	43.9	7.6	Propagative	6.7	8
9	70	M	Normal	21.2	30.4	34.1	3.3	Propagative	8	10
10	48	M	Normal	24.2	29.5	30.8	19.3	Propagative	7.5	8
11	53	M	Normal	22.4	31.1	54.7	5.7	Propagative	7.9	5
12	37	F	Normal	38.1	23.3	55	4.4	Propagative	7.2	1
13	65	M	Normal	21.8	18.2	24.8	10.3	Propagative	10.9	15
14	67	F	Normal	24.8	11.7	22	5.1	Propagative	7	13
15	36	F	Normal	35.9	20.4	41.3	19.2	Propagative	9.3	2
16	33	F	Normal	14.8	11.5	22.1	2.4	Propagative	6.8	1
17	45	F	Normal	28.1	18.8	25.3	12.1	Propagative	7.2	15
18	37	M	Normal	19.1	15.1	21.1	9.3	Propagative	9	2
19	59	M	Normal	46.1	15.4	31.3	9.9	Ineffective	9	4
20	74	M	Normal	20.7	10.1	7.3	0.8	Ineffective	6.7	10
21	47	F	Normal	17.6	11.9	20.2	1.5	Propagative	9.8	4
22	63	M	Reduced	13.1	8.2	13	4.7	Propagative	6.1	8
23	42	M	Normal	24.5	15.8	41.3	-3.2	Propagative	8.8	4
24	67	F	Normal	45.5	22.1	30.5	4	Propagative	7.2	12
25	46	F	Normal	30.5	19.9	36.1	3	Propagative	7.3	3
26	54	M	Normal	34.7	23	47.2	7.8	Propagative	7.2	10
27	55	M	Normal	18	12.9	15	5.9	Propagative	10.5	7
28	65	F	Normal	20.4	36.6	43.5	14.5	Propagative	7.2	12
29	67	M	elevated	15.7	45.2	39.6	4.7	Ineffective	9.3	15
30	45	M	Reduced	12.7	22.4	17.9	6.4	Ineffective	12	10
31	60	M	elevated	11.8	43.4	35.8	5.5	Propagative	6.5	12
32	53	M	Normal	10.1	33.9	26.5	4.2	Propagative	6.4	8
33	52	F	Normal	21.8	24.5	42.9	2	Propagative	5.2	6
34	38	M	Reduced	11.6	23.9	11.2	0.7	Propagative	5	5
35	41	F	Reduced	11.5	20.2	18.8	2.8	Propagative	4.9	5