TOPIC OF THE THESIS:

"TO EVALUATE PATIENTS OF CHRONIC KIDNEY DISEASE FOR GASTRO-ESOPHAGEAL REFLUX DISEASE AND ESOPHAGEAL DYSMOTILITY".

December 2012 Year

“TO EVALUATE PATIENTS OF CHRONIC KIDNEY DISEASE FOR GASTRO-ESOPHAGEAL REFLUX DISEASE AND ESOPHAGEAL DYSMOTILITY ”.

A THESIS

PRESENTED TO THE SOUTH BRANCH OF KYRGYZ STATE MEDICAL INSTITUTE OF POSTGRADUATE AND CONTINUOUS EDUCATION IN FULFILLMENT OF THE THESIS REQUIREMENT FOR THE DEGREE OF **DOCTOR OF PHILOSOPHY (PhD)**

IN THE SPECIALTY

“NEPHROLOGY”.

BASED ON THE STUDIES CONDUCTED IN THE DEPARTMENT OF NEPHROLOGY OF OSH REGIONAL INTEGRATED CLINICAL HOSPITAL, AND

OSH CITY TERRITORIAL CLINICAL

HOSPITAL.

BY

DR. SUBODH KUMAR PANDEY

December 2012 Year

DECLARATION

I, hereby declare that contents of the thesis have not been submitted earlier in candidature for any degree. I give my written consent for permitting availability of the thesis for photocopying and library loan to other institutions.

DR. SUBODH KUMAR PANDEY

DECEMBER 2012

CERTIFICATE

ACKNOWLEDGEMENT

I am heartily thankful to my mentor and guide, Dr.Zakirove U.A.Professor and Head, Department of nephrology his encouragement, guidance and support from the initial to the final level which enabled me to develop an understanding of the subject. His valuable advice and suggestion at each and every step helped me a lot in completing this mammoth task. He has been a source of constant inspiration for me.

I am also indebted to my co-guide Dr. Muzaffar U.A,Associate Professor Department of Nephrology, for extending his valuable guidance and support in completion of this project.

I would also like to express my gratitude towards my co-guide Dr.Kuljohn B.O. Professor Department of Nephrology, Dr.Gulnaz J.J. Professor Department of Nephrology, without whose unconditional support it would have been difficult for me to complete this works He was always available for help at any time of the day and provided his valuable assistance throughout the project.

I thank my colleagues, my juniors,my friends .

Special thanks to Mrs Elena B.B., Sister in charge Endoscopy unit, Mr. Kulagin U.A, for their technical assistance and help throughout the activities performed during the work. I would also like to thank all my ECG technicians who helped me even during odd hours of work with a smile-on their face.

My utmost thanks to my parents who are my constant source of inspiration and motivation. it will be highly unfair not to mention of all my patients who happily and willingly rendered their full cooperation, expressed full faith in my judgment and without whom this thesis would not have taken the final shape.

Above all, 1 would like to thank the Almighty who gave me the strength courage and determination to complete this ardours task.

DECEMBER 2012 Dr.SUBODH KUMAR PANDEY

TABLE OF CONTENT

TITLE PAGE NO.

INTRODUCTION

REVIEW OF LITERATURE

OBJECTIVES OF RESEARCH

MATERIALS AND METHODS

RESULTS & OBSERVATION

DISCUSSION

CONCLUSIONS AND RECOMMENDATIONS

INDEX OF REFRENCES

APPENDICES

PROFORMA FOR THESIS

CONSENT FORM

KEY

SUMMARY

Abbreviations

CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
GER	Gastro esophageal reflux
GERD	Gastro esophageal reflux disease
EE	Endoscopic esophagitis
LES	Lower esophageal sphincter
TLESRRs	Transient lower esophageal sphincter relaxations
UGIE	Upper gastrointestinal endoscopy
LA	Los Angles
PPI	Proton pump inhibitors
AN	Autonomic Neuropathy
ANS	Autonomic Nervous System

INTRODUCTION

INTRODUCTION

Chronic kidney disease (CKD) is a debilitating condition responsible for morbidity and mortality. It's a financial burden on the government and the society. According to a latest study, the prevalence of CKD in United States is 16.8%. However in Kyrgyz Republic its prevalence is 0.785%. In a CKD patient several complications are known to occur such as loss of renal function, cardiovascular disease, and complications' arising as a result of uremia, one of them is involvement of the autonomic nervous system. Involvement of autonomic nervous system in the form of autonomic neuropathy in the region of esophagus leads to gastro esophageal reflux (GER) and esophageal dysmotility. Due to high prevalence of GER in such patients there's alteration of dietary pattern which leads to poor oral intake and thus predisposing the patient to malnutrition. Henceforth treatment of GER in such patients leads to better nutritional status and thus a favorable outcome. However there's paucity of knowledge and studies regarding the exact pathogenesis of gastro esophageal reflux and dysmotility in CKD patients. Main mechanisms postulated are delayed gastric emptying and increased production of gastric acid.

Gastroesophageal reflux disease (GERD) describes clinical manifestations of reflux into the esophagus4. It is a common

condition in which stomach acid or occasionally bile flows back into esophagus. GERD is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents in the esophagus which is severe enough to impact the patient's daily life5. It is a complex, chronic and relapsing condition that carries a risk of morbidity and the potential for resultant complications. Heartburn and acid regurgitation are the classic symptoms of GERD. Heartburn describes a burning feeling, rising from the stomach or lower chest and radiating toward the neck, throat, and occasionally, the back. It occurs postprandially, particularly after large meals or after eating spicy foods, citrus products, fats, chocolates, or drinking alcohol. The effortless regurgitation of acidic fluid, especially after meals and worsened by stooping or the supine position is suggestive of GERD.

The current-study focuses on evaluation of CKD patients for the presence of GERD, esophageal dysmotility and autonomic dysfunction, and possible correlation between them, if any.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

In this modern era incidence of chronic kidney disease is increasing day by day and constitutes a major public health problem. The major outcomes of chronic kidney disease, regardless of the specific diagnosis include progression to kidney failure, complications from decreased kidney function, and development of cardiovascular disease. There is increasing evidence which shows that early detection and treatment can prevent or delay some of these adverse outcomes. However, sometimes opportunities for prevention may get lost because chronic kidney disease is not diagnosed or is being treated insufficiently. One of the reasons is the lack of agreement about the definition of chronic kidney disease, as well as the classification of its stages. Another reason is lack of uniform application of simple tests for the detection and evaluation of the disease. In February 2002, the Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published clinical practice guidelines on chronic kidney disease. The goals of the Work Group that developed the guidelines were as follows: to define chronic kidney disease and classify its stages, regardless of the underlying cause; to evaluate laboratory measurements for clinical assessment of kidney disease; to associate the level of kidney function with

the complications of chronic kidney disease; and to stratify risk for the loss of kidney function and the development of cardiovascular disease. The leaders of the NKF recognized the role of family physicians in providing medical care for patients with chronic kidney disease (particularly during the early stages when interventions might slow disease progression) and therefore wanted the guidelines to be practical and easily accessible to primary care physicians. To meet these ends, a family physician was invited to be an active participant in the guidelines Work Group and a member of the K/DOQI Advisory Board, which oversees all guidelines developed under its auspices.

NKF Definition of Chronic Kidney Disease

Kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests or GFR < 60 mL per minute per 1.73 rn2 for three months or more, with or without kidney damage.

Kidney failure is defined as a GFR below 15 ml per minute per 1.73 m2, usually accompanied by signs and symptoms of

uraemia, or need for initiating kidney replacement therapy for the management of the complications of a decreased GFR.

Kidney failure is not synonymous with end-stage renal disease (ESRD). In the United States, “end-stage renal disease” is an administrative term based on the conditions for health care payment by the Medicare ESRD Program for patients treated with dialysis or transplantation. However, the term does not include patients with kidney failure who are not treated with dialysis or transplantation.

EPIDEMIOLOGY

More than 20 million adults in the United States have chronic kidney disease, and millions more are at risk of . developing the disease. Patients who have diabetes mellitus and hypertension are at highest risk. As the number of patients with diabetes and hypertension continues to increase, the number of patients with chronic kidney disease also will increase. In Kyrgyz Republic it is estimated that 10,000 new patients of and stage renal disease (ESRD) enter renal replacement programs annually.

CLASSIFICATION

It's required to have a uniform consensus among the primary care physicians and to have a proper communication between the physician and a nephrologists so that specific interventions as needed can be done at each and every stage so as to provide maximum benefit to the patient and preventing progressive renal damage and ultimately renal failure from developing.

COMPLICATIONS:

CKD is associated with several complications particularly when GFR is less then I 5m1/minll .73m2. Some of the complications are anemia, metabolic disturbances such as hypocalcemia, hyperphosphatemia, GI complications such as peptic ulcer, GERD, neurological complications such as peripheral neuropathy and uremic complications such as uremic pericarditis and autonomic neuropathy.

AUTONOMIC NERVOUS SYSTEM

The autonornic nervous system (ANS or visceral nervous system) is a part of peripheral nervous system that acts as a control system functioning below the level of consciousness controlling visceral functions. It is classically divided into two subsystems: the parasympathetic nervous system and

sympathetic nervous system. Recently, a third subsystem of neurons that have been named ‘nonadrenergic and non-cholinergic’ neurons (because they use nitric oxide as a neurotransmitter) have been described and found to be integral in autonomic function, particularly in the gut and the lungs.

After the autonomic nervous system receives information about the body and external environment, it responds by stimulating body processes, usually through the sympathetic, division, or inhibiting them, usually through the parasympathetic division. An autonomic nerve pathway involves two nerve cells. One cell, is located in the brain stem or the spinal cord. It is connected by nerve fibres to the other cell; which is located in a cluster of nerve cells (called an autonomic ganglion). Nerve fibres from these ganglia connect with internal organs. Most of the ganglia for the sympathetic division are located just outside the spinal cord on both sides of it. The ganglia for the parasympathetic division are located near or in the internal organs. function The automomic nervous system controls blood pressure heart and breathing rates body temperature digestion metabolism (thus affecting body weight) the balance of water and electrolytes (such as sodium and calcium) the production of body fluids (saliva, sweat, and tears), urination, defection, sexual response, and other processes.

many organs are controlled primarily by either the sympathetic or theparasympathetic division. Sometimes the two division have opposite effects on the same organ. For example, the sympathetic division increases blood pressure, and the parasympathetic division decreases it. Overall, the two divisions work together to ensure that the body responds appropriately to different situations thus maintaining homeostasis of the body.

Generally, the sympathetic division prepares the body for stressful or emergency situations— fight or flight. Thus, it increases heart rate and the force of cardiac contractions and widens (dilates) the airways to make breathing easier. It causes the body to release stored energy. Muscular strength is aincreased. This division also causes palms to sweat, pupils to dilate, and hair to stand. It slows down body processes that are less important in emergencies, such as digestion and urination.

The parasympathetic division controls body process during ordinary situations. Generally, it conserves and restores. It slows down the heart rate and decreases blood pressure. It stimulates the gastrointestinal tract to process food .and eliminates waste. Energy from the processed food is used to restore and build tissues. However both the sympathetic and parasympathetic divisions are involved in sexual activity.

Two chemical messengers (neurotransrnitters), acetyicholine and nor epinephrine, are used to commu1jcate within the autonornic nervous system. Nerve fibres that secrete acetylcholine are called cholinergic fibres. Fibres that secrete norepinephrine are called adrenergic fibres.

Generally, aetylcho1ine has parasympathetic (inhibiting) effects and nor epinephrine has sympathetic (stimulating) effects. However, acetyleholine has got some sympathetic effects; for example, it sometimes stimulates sweating or makes the hair stand on end.

Symptoms

1. Ortho static hypotension: dizziness or light-headedness due to an excessive decrease in blood pressure when a person stands.

2. Dry eyes, dry mouth

3. Heat intolerance: due to absence of sweating

4. Gastroparesis

5. Urinary incontinence/retention

6. Constipation

7. Lack of pupillary response to light

8. Erectile dysfunction: difficulty in initiating and maintaining an erection can be an early symptom of an autonomic disorder

Diagnosis If patients have symptoms and signs suggestive of autonomic insufficiency, sudomotor, cadiovagal, and adrenergic testing.. is usually done to help determine severity and distribution of the insufficiency.

1. **Sudomotor** testing includes the following

a) **Quantitative sudomotor axon-reflex test**: This test evaluates intergity of postganglionic neurons using iontophoresis. In this test electrodes filled with acetylchline areplaced on the legs and wrist to stimulate sweat glands and the volume of sweat is then measured. The test can detect decreased or absent sweat production.

b) **Thermoregulatory sweat test:** This test evaluates both preganglionic and postganglionic pathways Here a dye is applied to the skin and patient is made to enter a closed compartment which is heated to cause maximal sweating, Sweating causes the dye to change its colour, so that areas of anhidrosis and hypohidrosis are apparent and can be calculated as a percentage of BSA.

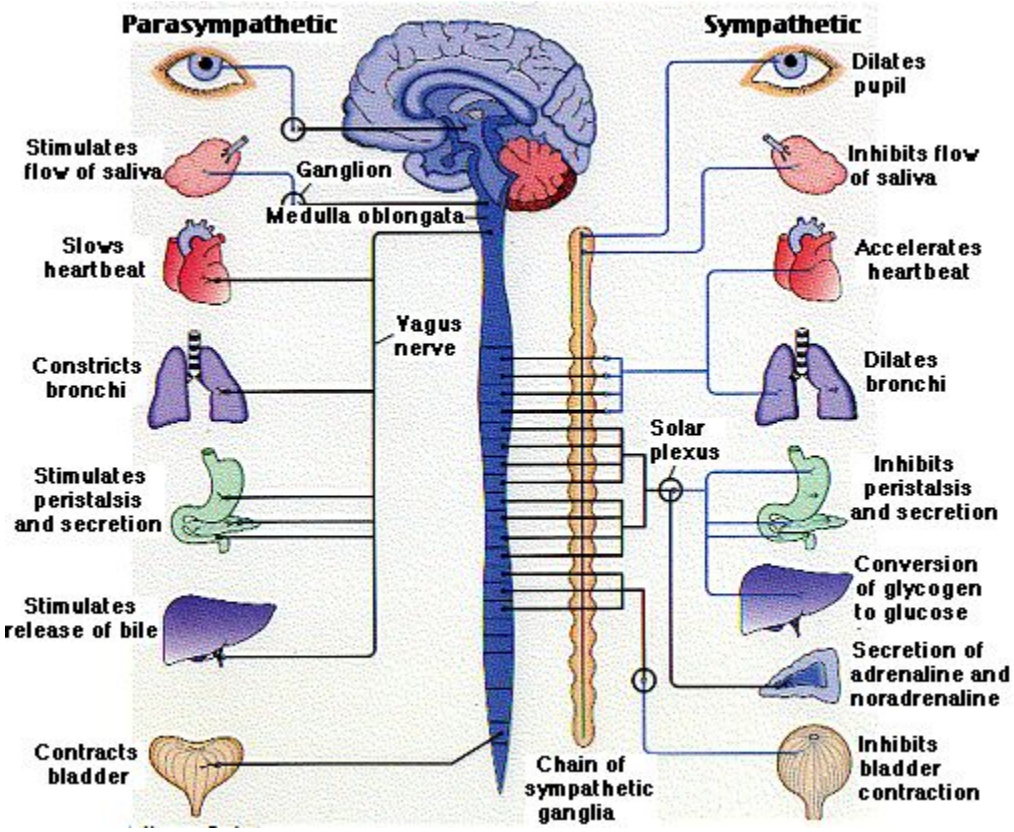
2. **Cardiovagal tests:** it evaluates heart rate response (via ECG rhythm strip) to deep breathing and Valsalva manoeuvre. If the ANS is intact, heart rate varies with these manoeuvres.

3. **Adrenergic:** It evaluates response of beat-to -beat BP to the following:

a) **Head-up tilt**: Blood is shified to dependent parts of the body, causing reflex responses in BP and heart rate. This test helps differentiate autonomic neuropathies from postural tachycardia syndrome.

b) **Valsalva manoeuvre:** This manoeuvre increases intrathoracic pressure and reduces venous return, causing BP changes and reflex vasoconstriction.

ORGANISATION OF ANS



UREMIA AND AUTONOMIC NEUROPATHY

Involvement of the autonomic nervous system may occur in patients with chronic kidney disease. its prevalence varies from 45-59% it may have a number of clinical sequel but the pathogenesis remains unknown. It has been seen that parasympathetic neuropathy appears more frequently than sympathetic damage.. Parasympathetic dysfunction was demonstrated in 14 to 34% of patients and sympathetic neuropathy in 18 to 24% of subjects'6. The presence ajzdeverity of autonomic neuropathy (AN) do not seem to be related with either the duration orenal failure or with the duration of dialysis. Bolton CF et al have proposed that in the initial stages autonomic neuropathy is so the what reversible by hemodialysis and renal transplantation

PATHOLOGY

In 1971, Dyck and his colleagues established the concept of uremic neuropathy based on extensive nerve conduction studies as well as light and electron microscopy studies . On histopathology, they demonstrated axonal shrinkage but myelin sheaths appeared to be affected out of proportion to the axons. It's the neuronal dysfunction and not the involvement o Schwann cell which results in decrease in the diameter of the

axon, rearrangement of myelin, and ultimately, complete degeneration of the axon.

PATHOPHYSIOLOGY

Uremic neuropathy is considered a dying-back neuropathy or central-peripheral axonopathy. The exact mechanism of uremic neuropathy remains unclear. Fraser and his colleagues have postulated that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fibre enzymes required for the maintenance of energy production 19. It's seen that the longer axons are the first to undergo degeneration since longer is the axon; greater is the metabolic load. Energy deprivation within the axon may be especially critical at nodes of Ranvier, since these nodes demand more energy for impulse conduction and axonal transport.

Nielsen hypothesised that peripheral nerve dysfunction was due to an interference with the nerve axon membrane function and inhibition of Na^+/K^+ -activated AT Pase by the toxic factors present in the uremic serum

Krishnan and his colleagues investigated axonal membrane properties by measuring nerve excitability in chronic renal failure patients and suggested that motor and sensory axons

in patients with uremic neuropathy were depolarized, and hyperkalemia which is responsibl4 for uremic depolarization could contribute to the development of neuropathy,.

CAUSES: A number of mechanisms have been put forward which can play a role in the development of peripheral neuropathy of which autonomic neuropathy is an integral part. The various mechanisms are as follows:

1. **Uremic toxins:** A variety of toxins have been proposed to play role in the development of uremic neuropathy as given below.

i . Small water-soluble compounds

a. Guanidines

b. Asymmetric dimethylarginine

c. Creatinine

d. Purines

e. Phosphorus

f. Urea

ii . Middle, large molecules

a. Advanced glycosylated end products

b. Parathyroid hormone (Spallone V et a1)

c. Oxidation products

d. Peptides (beta-endorphin, methionine-enkephalin, beta-lipotropin, adrenomedullin)

e. Beta 2-microglobulin

iii . Protein-bound compounds

a. Indoles

b. 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid

c. Hippuric acid

d. Homocysteine

e. Polyamines

2) **Hypoxemia:** It's another mechanism proposed for the development of autonomic neuropathy in patients of uremia. Zoccali C et a! in their study on 25 patients showed that nocturnal hypoxia could be a causative factor for autonomic dysfunction in patients undergoing dialysis.

3) **Baroreceptor Hyposensitivity**: On the basis of an abnormal amyl nitrate inhalation test (a functional index of the entire baroreceptor reflex arc) and of a normal cold pressor test (a proposed index of the efferent pathway) some investigators postulated that the lesion may reside in the baroreceptors.

4) **End organ resistance to Nor Epinephrine**: On the other hand other researchers have found that plasma nor epinephrine (NE) levels are elevated in patients with renal failure. The association of elevated levels of NE and ANS dysfunction could suggest end-organ resistance to the action of NE26. However none of these factors have been proven conclusively in the generation of neuropathy in patients with uremia and further studies are needed.

Spectrum of AN disease in patients of uremia

Nayak KC et a1 in their study at PBM Hospital, Bikaner showed that there's higher incidence oL erectile dysfunction in patients with uraemia as compared to controls and prevalence increases with the duration of the disease.

Heidbreder E et a1 compared autonomic dysfunction in non diabetics and diabetics chronic renal failue patients with or without dialysis and seen that autonomic dysfunction was more pronoun ed in those with diabetes in the pre dialysis stage. It was also seen that dialysis was found to improve some degree of autonomic dysfunction in non diabetics as compared to patients with diabetic kidney disease

Studies done by **Malik S et al** at University Department of Medicine and Medical Renal Unit, Royal Infirmary, Edinburgh, UK, assessed autonomic function in 67. patients with chronic renal failure using a standardized battery of five cardiovascular reflex tests. The results showed that 38 (65%) had early. or definite parasympathetic abnormalities, while 14 (24%) had additional sympathetic damage and there were no significant differences between those treated conservatively (n = 19), those on continuous ambulatory peritoneàl dialysis (n = 8) and those on intermittent hemodialysis (n = 40).

Agarwal et a1have reported a slight improvement of some autonomic indices six months following renal transplantation. However it failed to demonstrate any benefit of hemodialysis on recovery of autonomic dysfunction. The Swedish Huddinge group also. found no significant change of AN t 6 and 12 months after renal transplantation however, they documented a slight improvement of parasympathetic function 48 months following kidney transplantation. Few studies conducted by Vit et al also showed that the autonomic neuropathy is reversible in early stages by prolonged bicarbonate hemodialysis. Tory K et al in their study on children demonstrated that the prevalence of autonomic dysfunction was low in renal transplant recipients as compared to the patients on dialysis.

Dumitrascu et al demonstrated that patients with CRF had delayed gastric emptying if parasympathetic andsympathetic neuropathy were both present. Diabetics are at increased risk of autonomic neuropathy, and they do constitute a large proportion of patients with CRF Thus CRF patient certainly experience delayed gastric emptying.

Thus recognition of autonomic dysfunction early in CKD patients could lead to its reversal by taking appropriate measures thereby improving the prognosis in such patients.

UREMIA AND ESOPHAGEAL DYSMOTIL1TY

The main function of the esophagus is to transport swallowed food into the stomach. The esophagus consists of 2 different parts; the cervical esophagus composed of striated muscles and the thoracic esophagus composed of smooth muscles, The striated muscle esophagus is innervated by the lower motor neurons and peristalsis in this segment is due to sequential activation of the motor neurons in the nucleus ambiguous. Both primary and secondary peristaltic contractions are centrally mediated.. The smooth muscle of esophagus is innervated by intramural inhibitory (nitric oxide releasing) and excitatory (acetylcholine releasing) neurons that receive inputs from separate sets of preganglionic neurons located in the dorsal motor nucleus of vagus. The primary peristalsis in this segment involves both central and peripheral mechanisms. The primary peristalsis consists of inhibition (called deglutitive inhibition) followed by excitation. The secondary peristalsis is entirely due to peripheral mechanisms and also involves inhibition followed by excitation. The lower esophageal sphincter (LES) is characterized by tonic muscle that is different from the muscle of the esophageal body. The LES, like the esophageal body smooth muscle, is also innervated by the inhibitory and excitatory neurons. The LES maintains tonic closure because_ of its myogenic property. The LES tone is modulated by the inhibitory and the excitatory nerves.

RK Goyal et al have shown that the sympathetic nerves were not found to exert a major effect on LES tonic contraction and relaxation. A systematic study of the effect of vagus nerve suggested that the vagus nerve exerts a tonic inhibitory effect on the sphincter pressure so that vagotomy was found to cause LES contraction and vagal efferent stimulation caused frequency-dependent LES relaxation. It now appears that the vagus nerve provides both inhibitory and excitatory innervations to the LES.

In CKD patient's autonomic neuropathy is seen. Such abnormality in the region of gastroesophagus could lead to decreased LES tone and several esophageal motility disorders either in the form of diffuse esophageal spasm or biphasic / triphasic esophageal contractions.

In one study conducted by K.C. Siamopoulos et al esophageal motility was studied in hemodialysed patients and they found out a higher incidence of esophageal dysmotility in the form of biphasic and triphasic contractions in cases than in controls. They attributed this to uremic induced neuropathy of vagus nerve and smooth muscle myopathy.

In another experimental study on rats done by Laken et al they have found a higher incidence of esophageal smooth muscle dysfunction leading to gastro esophageal reflux in CKD

induced rats as compared to controls38. They supported the notion that uremia in CKD patients may lead to autonomic neuropathy. causing reflux and esophageal dysmotility.

Ledermann SE studied esophageal and gastric motor function in 12 children (age 7 months – 6.8 years) with severe CRF not undergoing dialysis having persistent anorexia and vomiting. Eight of 12 patients had significant gastro-esophageal reflux (mean 11.3% controls <5%) 7/10 had altered gastric half emptying times for 5% glucose or milk. Gastric antral electrical control activity was abonrmal in 6/11 patients as compared to controls and showed that all CRF patients with anorexia and vomiting had one or more disorder of foregut motility.

Lin X et al in their study concluded that patients with chronic renal failure as compared to healthy controls have abnormal gastric myoelectrical activity on electrogastrography leading to dysmotility and delayed gastric emptying.

Patients with CKD frequently develops upper GI complications41, although both patients and doctors are now aware of the increasing prevalence of GERD but little is known about its pathophysiology in CKD patients. Esophageal motility disorders and delayed gastric emptying have been postulated to play an important role.

UREMIA AND GERD

GERD has been seen in patients with chronic kidney disease. The condition is believed mainly to be due to an increase in the number of normally occurring transient lower esophageal sphincter (tLESR) relaxations. Other mechanisms include decreased clearance of esophageal contents and refluxate owing to impaired peristalsis, decreased gastric emptying with resultant back pressure into the esophagus, and increased gastric acid production with a resultant increase in the potency of the refluxed. Studies have shown that gastroparesis and hyperacidity play an important role in the pathogenesis of GERD in such patients but some work has been done-determining the role of transient LES relaxation or esophageal clearance in CRF.

Orlando RC et al at Tulane University Medical Centre, New Orleans, Louisiana showed that there's increased frequency of transient lower esophageal sphincter relaxations in patients of CKD which could lead to increased frequency of GERD in such patients.

Ravelli et a139 found that 70% of CRF patients (7 of 10) experienced delayed emptying with 5% glucose or milk. Kao et a143 found 80% of non dialyzed uremic patients had delayed gastric emptying of radiolabelled solid meals. Schoenmakere

GD et a144 in their study evaluated 56 hemodialysis patients by radio isotopic examination for gastric emptying time and demonstrated that gastric emptying is significantly delayed in end-stage renal disease patients. Studies done by Fallone CA et a13 in patients with gastroparesis due to cronic renal failure have also shown a predisposition to gastroesophageal reflux.

However few studies have shown conflicting results; one such study was conducted by Mcnamee et a1 where no difference in gastric emptying was seen among CKD and normal controls. Another study done by Richard A et a146 showed that CKD patients receiving hemodialysis showed no difference in gastric emptying when compared with controls. Viem VB et al47showcd that there was no significant difference in gastric emptying between dyspeptic hemodialysis patients and healthy volunteers.

In a recent publication, Strid and his colleagues have found delayed gastric emptying in 36% of their patients with ESRD, with a higher prevalence in peritoneal dialysis patients compared to chronic renal failure patients who are not on dialysis. This might be explained by the increased intra-abdominal pressure induced by the intraperitoneal dialysis fluid along with other factors.

The presence of an autonomic neuropathy has also been postulated to play a role. Dumitrascu et al demonstrated that patients with CRF had delayed gastric emptying if parasympathetic and sympathetic neuropathy were both present. Diabetics are at increased risk of autonomic neuropathy and they do constitute a large proportion of patients with CRF. Thus CRF patients certainly experience delayed gastric emptying. Delayed gastric emptying can increase gastric reflux and can therefore potentially be a mechanism for GERD in these patients.

Another mechanism by which uremia can potentially lead to GERD is increased acid production. Higher acid production can occur secondary to hypergastrinemia, which is a consequence of decreased calescence of gastrin owing to reduced excretion and impaired metaholism. Hypergastrinemia is present49 in CRF patients, but may be partly due to increased secretion, because- the density of G cells is increased in CRF patients50, possibly owing to a hyper parathyroid state.

Straathof etal5 ‘reported that postprandial plasma concentrations of gastrin are high in CKD patients which in turn decreases LES pressure and increase the transient LES relaxations leading to reflux. These factors may explain the higher prevalence of GERD in patients with ESRD. Elevated

serum gastrin also causes an increase in acid production by the parietal cells. The resulting elevation in gastric acid would increase the potency of the refluxate. Thus some patients certainly have, increased acid production, and this increase' may potentially be a mechanism by which CRF can be associated with GERD.

In a study done by Kawaguehi y et a152 at Tokai University School of Medicine evaluating patients of CKD for GERD endoscopically, 156 CRF patients underwent endoscopic examination and the prevalence of GERD was found to be 34.0%. In the early stages of CKD the prevalence of GERD was seen to be 4411%, whereas in hemodialysis patients, the prevalence of GERD was 50.0%. Thus the prevalence of GERD tends to increase as the renal function become worse.

Ibraheim S Abdulrehman et al at King Fahad University Hospital Saudi Arabia, studied prevalence of GERD and its association with H. Pylori in CKD and Renal Transplant patients by performing endoscopies and biopsy and showed that though prevalence was equal in both groups it was significantly higher than the control group and duration of ESRD correlated significantly with the prevalence of GERD in the CKD group as compared to the renal transplant recipients.

In a study done by Edward J. Ruley et al at Department of Nephrology, Children's Hospital Natiopal Medical Center, George Wnshington University School of Medicine, twenty-two infants (mean age 7.5 months) with chronic renal failure were studied for their nutrition, growth, and upper gasfrintestinal function. Most infants had, a history of poor caloric intake and 7 had received supplemental feeding (SF) prior to. the investigation. Sixteen of 22 infants (73%) had significant gastroesophageal (GE) reflux demonstrated by 24-h esophageal pH monitoring. Infants with GE reflux were significantly younger and more often required SF than those without GE reflux. There were no significant differences in the degree of renal failure, growth failure, caloric intake, protein intake, or nutritional status between the infants with and without, GE reflux. From these studies it was concluded that GE ..reflux should be considered as one of the factors contributing to the feeding problems of infants with CRF.

In a study done by Herman Darmawan et al at King Fahad Hospital of the University, the prevalence of gastroesophageal reflux disease (GERD) in chronic renal failure patients and in renal transplant recipient (RTR) and its relation to Helicobacter pylori infection was studied . The results showed that the prevalence of GERD in the first two groups was similar (77.5vs 75.0% P = 0.412) while it was significantly lower in the control group (38.6%, P < 0.01) Multivariate

logistic regression analysis in groups I and II showed that high serum creatinine immunosuppressive therapy and absence of H. pylori infection were significantly associated with GERD. The duration of ESRD also correlated significantly with the prevalence of GERD in group I.

METHODS TO DIAGNOSE GERD

1 **History:** Clinical experience suggests strongly that the patterning of reflux-induced - . symptoms has considerable diagnostic utility. Different researchers have used different .methods or scoring systems for symptom analysis, developing a uniform criterion based on ,composite score of typical reflux symptoms will be useful in the diagnosis of GERD, pion questionnaire and scoring techniques are an important step in this analysis. For patients with a moderate or severe composite score, the diagnosis of GERD can be made . without further tests in most situations.

Studies had shown that the prevalence of GER based on symptom analysis in general population ranged from 5-30%.

Therapeutic trial with PPI's: In patients presenting with uncomplicated but suspected GERD a 6 week trial of empiric acid suppressive drugs can be tried. Symptom resolution with

therapy initiation & recurrence with therapy cessation provides presumptive evidence of GERD. An empirical trial of proton pump inhibitor therapy has a sensitivity of around 75% and a specificity of about 80% for GERD. This form of diagnostic modality is much more comfortable and cost effective for the patients as compared to other diagnostic methods.

3) UPPER – GI ENDOSCOPY

UGIE is a standard diagnostic test' for GERD. On upper GI Endoscopy patulous LS, Hiatus hernia and esophagitis can be observed directly. Around 40 to 60% patients with GERD have esophagitis on upper Gi Endoscopy of which majority had low grade involvement. Severity of esophagitis is graded according to different systems like Los Angeles grading system & Savary-Miller grading system.

Table 1: Los Angles Classification

SI	Grade	Definition
1	A	One or more of mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds.
2	B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds.
3	C	Mucosal breaks that extend between the tops of two or more mucosal f: involve less than 75% of the esophageal circumference.
4	D	Mucosal breaks which involve at least 75% of the esophageal circumference.

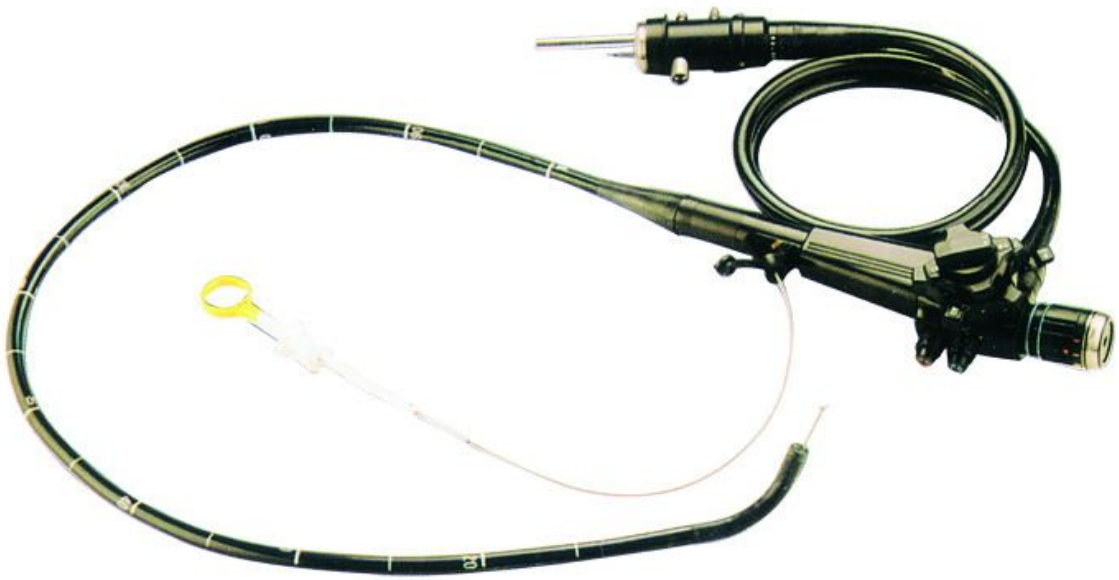


Figure 1: Flexible Fiberoptic Endoscope

Figure 2: Portable pH measuring unit

4) **Ambulatory 24 Hr pH metry**

Ambulatory 24-hour pH monitoring is the gold standard in establishing a diagnosis of GERD. it has got a sensitivity of 96% and a specificity of 95%.

Esophageal pH is traditionally monitored using a catheter inserted transnasally into the esophagus. The procedure is uncomfortable, inconvenient, and unsightly, and interferes with the patient's normal activities and diet during ambulatory pH monitoring.

Disadvantage of ambulatory 24 hours pH monitoring is that normal 24 hr record can be seen in a qual [or of patients with otherwise typical reflux esophagitis and in about one third of patients with endoscopy negative reflux disease. Also 24 hour pH recording is always not reproducible.

5) NEWER MODALITIES

1. RADIOTELEMETRY CAPSULE MONITORING:

A capsule is attached to esophageal mucosa and pH monitored without the discomfort of nasogastric tube.

It decreases patient's discomfort and allows longer monitoring (48hrs), may improve accuracy by allowing the patient to carry out their usual activities.

2. COMBINED IMPEDANCE AND ACID TESTING

Allows measurement of both acid and non acid (volume) reflux. May be particularly important in the patient with persistent symptoms despite adequate medical trial and allow more efficient monitoring of reflux in patients on therapy.

METHOD TO DIAGNOSE ESOPHAGEAL DYSMOTILITY

ESOPHAGEAL MANOMETRY

The ability of the Lower Esophageal Sphincter (LES) to protect against gastric reflux depends on its resting pressure, length exposed to abdominal pressure & overall length. DeMeester and coworkers showed that mechanical incompetence of the LES occurs when one or more of these components fail.

It's used to measure the pressure within the esophagus. It's used to evaluate the action of the muscle waves in the main portion of the esophagus as well as the muscle valve at the end of esophagus. The equipment for manometry consists of

thin tubing with openings at various locations. This tube is positioned in the esophagus; the various openings sense the pressure in various parts of the esophagus. As the esophagus squeezes on the tube, these pressures are transmitted to a computer analyzer that records the pressures on moving graph paper. The physician can evaluate these wave patterns to determine if they are normal or abnormal.

The three most widely used methods to measure LES pressure are

1. A sleeve sensor.

2. Rapid pull through of sensors across the sphincter during suspended respiration

3. Station pull through of side hole sensors recording pressure at every 1cm increments while withdrawing the catheter.

Esophageal pressure waves are typically single-peaked, although doub1e-peaked waves are not uncommon. Waves with three or more peaks are considered to-be abnormal.

Normal resting LES pressure is 10-25mm Hg.

Esophageal manometry has a limited role in suspected GERD because of low test sensitivity & is recommended only to evaluate a patient with GERD before antireflux surgery to exclude an alternative diagnosis, to evaluate the LES, and to assess esophageal body function.

Studies have shown wide variations in the basal LES pressure in obese patients with GERD, Koppman JS etal, Jaffin BW etal have documented hypotensiv LES (<10mm hg) in 3-50% of obese patients with GERD. Studies by Scheffer RC etal, Holloway RU etal have shown that it is not the basal LES pressure that is important but the transient LES relaxations have been implicated as the cause for GERD.

OBJECTIVES OF RESEARCH

AIMS AND OBJECTIVES

1) To evaluate patients of chronic kidney disease for gastro esophageal reflux disease and esophageal dysmotility using clinical symptoms and investigative tools like pHmetry, manometry and upper GI endoscopy.

2) To assess autonomic-dysfunction in such patients using bed side clinical methods.

3) To find a possible correlation between GERD, esophageal motility and autonomic dysfunction.

MATERIALS AND METHODS

MATERIALS AND METHODS

SELECTION OF CASES

Fifty three CKD patients with stage Il-V presenting to medicine OPD. and medicine emergency Osh city territorial clinical Hospital are taken up for the study and were divided into two groups based on their creatinine clearance based on KJDOQI17 clinical practice guidelines.

K/DOQLEQUATION FOR CALCULATION OF CCR:

$$CCR = \frac{(140 - AGE') \times BODY\ WEIGHI}{72 \times PLASMA\ CREATIMNE}$$

In case of females, multiply the equation by a FACTOR OF 0.8

CKD STAGE

CKD STAGE	Creatinine Clearance Rate
STAGE V	1 5-3OmlImin
STAGE I	<1 5m1/min
STAGE II	>90m1/min
STAGE III	60-90m1/min
STAGE IV	3 0-60m1/min

They are divided into two groups one with creatinine clearance; >30m1/min but <90m1!min (stage2-3) and other, <30m1/min (stage 4-5) containing 26 and 27 patients respectively. These patients are kept free from anti secretory agents and other drugs affecting GI motility for a period of 7 days.

STUDY DESIGN

Observational cross sectional study.

INCLUSION CRITERIA

1. Patients with established C stage25(creatinine clearance 1 59Oml/min).

2. Patients of age group >15 but <6Oyrs.

3. Willing for informed consent.

EXCLUSION CRITERIA

1. Patients with diabetes, chronic liver disease, COPD.

2. Taking drugs affecting GI motility or LES tone.

3. Neurological disorder.

4. Known psychiatric illness.

5. Not willing for informed consent.

CONSENT

Written informed consent was taken before enrolment into the study

Finally 53 patients with established CKD and fulfilling inclusion and exclusion criteria were included in the study.

Sympatom quantification

The severity, frequency and duration of heart bum were measured on Likert-stale and frequency of regurgitation was also noted.

Lekert ca1e (Table 1)

Grade	Severity	Frequency	Duration
0	No pain	None	None
1	Mild	<2/wk	<10min
2	Moderate	>3/wk	10-30min
3	Severe	Daily intermittent	>30
4	Very severe	Daily continuous	continuous

Mild	Can be ignored when not thinking about it.
Moderate	Cant be ignored, but not influencing daily activities.
Severe	Influence concentration on daily activities
Very severe	Markedly influencing daily activities or requires rest

Symptom scores for individual symptoms were calculated and added up to give the total symptom scores of the patient

Total symptom score. (Table 2)

S No	Total score	Grade
1	1-4	mild
2	5-8	Mod
3	>8	Severe

UPPER GASTROINTESTINAL ENDOSCOPY

Endoscopy was performed by a flexible fiber optic endoscope after overnight fasting, The procedure was performed after the throat had been anaesthetized with a 2% lignocaine spray.

Olympus endoscope was used. Esophagitis, if found was graded according to Los Angles classification.

AMBULATORY 24 HR LOWER ESOPHAGEAL PH MONITORING

24 hr pH monitoring was performed in all the 53 subjects with a portable pH measuring unit consisting of a single channel antimony electrode and a portable solid-state memory unit. The antimony-electrode was passed through the nose and positioned in the esophagus 5cm above the LES, previously located by manometry. The pH probe was connected to a digital memory box that was worn on a waist belt. The system was standardized at pH values of pH 7.0 and 4.0 with known pH solutions. All patients were fully ambulatory and followed no restrictions in diet or habits.

The data was analyzed for the following parameters:

1. Percentage reading <pH4.0

2. Reflux time (%) in both sitting and supine positions

3. Number of reflux episodes

4. Number of reflux episodes longer than 5 minutes (long refluxes)

5. Duration of the longest reflux episode

6. Percentage of time th pH is less than 4 for the total duration of the study

Patients having acid reflux 5.45 % of the total times were classified as pH monitoring positive.. The data was stored on the computer using the Win reflux software. Severity of Distal sophagea1 Reflux based on pH metry is categorized into mild, moderate and severe depending upon the % of total time pH is < 4.

Duration of Time (%)	Grade
5.5-8.5	Mild
8.6-11.5	Mod

>11.5	Severe

ESOPHAGEAL MANOMETRY

Esophageal manometi5iras perfonned using the Griffon esophageal manometry program on the MK2 gastrointestinal motility apparatus with water perfused four lumen catheter in which perfusion was maintained by a hydraulic capillary infusion system. The patients were kept fasting overnight prior to the test. For the test, the patients were kept in the supine position, and the transducer height was adjusted to keep it at the mid-axillary level. After applying a lubricating jelly, the catheter was inserted nasally into the stomach till the 70 cms mark. Catheter placement in the stomach was verified by visualization of the pressure tracings and effect of respiration and of compression over the stomach on the pressure tracings. The intragastric baseline pressure was taken as zero.

The LES was evaluated by the station-pull through method, gradually withdrawing the

catheter by 0.5 cm distances, after minimum 5-6 respiratory excursions. All ancillary activity like swallowing, coughing

during the manometric testing was noted in each patient, and such events were discounted from final analysis. LES was identified an increase in the respiratory variations and persistent rise in pressure above the end-expiratory gastric baseline. Maximum end expiratory pressure reading was noted as the resting LBS pressure. End expiratory pressure is more indicative of the true LES pressure, as this is the point in the respiratory cycle the diaphragmatic contribution to the observed pressure is at a minimum.. Repeat pull-through with the pressure channels that followed were done to obtain a total of at least three readings, the average of which was taken finally as the resting LES pressure. Normal resting LES pressure is taken as between 10-25 mm Hg.

Peristalsis and LBS relaxation are normally assessed-in response to 5-mL water swallows. At least 10 swallows were tested to provide an adequate sample for assessing esophageal body motility. These swallows were spaced at least 15 seconds apart to avoid disturbance of the peristaltic response by the adjacent swallow. - Normal esophageal pressure wave is single peaked and propagates at a rate of 2-4cm/sec.

AUTONOMIC FUNCTION TESTS

1. PARASYMPATHETIC FUNCTION TESTS

a) Standing to lying ratio(SJL Ratio): ECG Limb leads are attached to the subject using cardiac jelly and the procedure is explained. Activity in limb lead II is obtained. Patient is asked to stand quietly and then lie down without any support. A continuous ECG is recorded from 20 beats before and 60 beats after lying down. The procedure is repeated 3 times with a gap of 5mm each.

Calculation: Longest R-R interval during 5 beats before lying down to shortest R-R interval during 10 beats after lying down; i.e.

$$\text{S/L Ratio: } \frac{\text{Longest R-R interval during 5 beats before lying down}}{\text{Shortest R-R interval during 10 beats after lying down}}$$

The maximum ratio of thee trials is taken and any abnormal ratio is suggestive of parasympathetic damage.

Normal : >1.04

Abnormal: <1.0

Indeterminate: 1.0-1.04

b) 30:15 ratio: Subject is asked to lie supine quietly for 15 minutes and ECG leads are attached. Initially resting ECG is obtained in lead II and baseline heart rate is calculated. The subject is then asked to stand and remain motionless and a continuous ECG is obtained for 1- 3min and a mark is made on ECG record to identify the time of standing. HR at 15th and 30th beat is noted after standing and 30:15 ratio is calculated and compared with the baseline.

Normal : >1.04

Abnormal: <1.0

Indeterminate: 1.0-1.04

c) Valsalva ratio: procedure is explained to the patient so as to ensure maximal Co operation. Subject is sitted comfortably on a stool with ECG leads attached. His nose is clipped with the help of a nose clip and a mouth piece is inserted between the teetlT and lips and allowed to relax. Baseline HR is calculated. The other end of mouth piece is attached to a mercury manometer. Subject is then asked to strain by blowing against closed glottis into the mouth piece attached to the manometer and maintaining a pressure of 40mm Hg for I 5sec. A continuous ECG is recorded: 1 mm before the strain

(resting period); during the maneuver (strain period, 1 5sec); and 45 sec following the release. The procedure is repeated 3 times with a gap of 5mm and ratio is calculated and maximum value is taken for the activity.

Valsalva ratio: Longest R-R interval after the strain

Shortest R-R interval during the strain

Normal :>1.45

Abnormal: <1.20

Indeterminate: 1.20-1.45

2) SYMPATHETIC FUNCTION TESTS:

Hand grip test: Procedure is explained to the patient and base line BP is measured. subject is asked to hold the dynamometer in the dominant hand and compress the hands with 1naximum effort and tension developed is measured.

Whole procedure is repeated twice and 2' and 311 reading are taken. Mean of all 3 readings is obtained; this is referred to as maximal isometric tension (T max). Now subject is asked to maintain a pressure of 30% of T for 5mm. during this

procedure BP is recorded every 30 seconds on the non exercising arm. The rise in diastolic BP just before the release of hand grip is taken as an index of response.

Normal: > 15mm Hg rise in diastolic BP

Abnormal: 10mm Hg rise in diastolic BP

b) Cold pressor response: after explaining the procedure to the patient he's sitted comfortably in chair and baseline BP is recorded. He's then asked to immerse his hand in cold water maintained at a temp of 4-6°C and BP is recorded from the other arm at 30 sec intervals for a period of 2 mm. after a period of two mm he's allowed to remove his hand and maximal rise in systolic and diastolic BP is noted and compared with the normal.

Normal : >1 5-2OmmHg rise in systolic BP

>lOmmHg rise in diastolic BP.

Both groups of patients were compared after all these tests were performed.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

This study titled as "To evaluate patients of chronic kidney disease for gastroesophageal reflux disease and esophageal dysmotility" was carried out in Department of Medicine and Department of nephrology, Osh Regional Integrated Clinical Hospital, Osh City Territorial Clinical Hospital, Osh, from January 2010 to December 2012.

SELECTION OF PATIENTS

Fifty three cases of CKD were selected for the study on the basis of strict exclusion and inclusion criterion mentioned previously. Written and informed consent was taken of them to participate in the study.

A detailed history about the reflux symptoms was taken and physical examination was performed of the patients. The patients then underwent upper gastro intestinal endoscope, esophageal manometry, 24-hour pH monitoring and bed side autonomic function tests. Results obtained were compared to look for any conflation between GERD, esophageal dysmotility and autonomic dysfunction.

AGE

Mean age of the study group was 36.85 years. The mean age of females was 39.29 yrs while that of males was 36.27 years with standard deviation of 13.69. This difference was not statistically significant. (p> 0.05),

Table 1

AGE GROUP	NUMBER OF PATIENTS (n=53)
<20	5
21-30	15
31-40	13

41-50	10
>50	10

SEX

Out of 53 patients 29 were males and 24 were females constituting 54.7% and 45.3% of the patients respectively.

STAGE OF CKD

CKD stage is defined according to Kidney: Disease Outcome and Quality Initiative (K/DOQI) classification system based on creatinine clearance which is as follows:

Table 2

CKD STAGE	Creatinine Clearance
STAGE I	>9OmiJmin
STAGE II	60-90m1!min
STAGE Ill	30-6OmlImin
STAGE IV	15-3OmlJmin
STAGE V	<I5miImin

Each stage of CKD included equal number of patients in each age group.

DEMOGRAPHIC DISTRIBUTION (Table 3)

CKD STAGE	MALE	FEMALE	TOTAL
STAGE II	10	1	11
STAGE III	5	10	15
STAGE IV	1	1	2
STAGE V	13	12	25

The following graph represent the above distribution:

SYMPTOMS

Likert scale was used to quantify GER related symptoms. The severity, duration and frequency of heart burn were measured on Likert scale. Symptom scores for heartburn was calculated and added up to give the total heartburn score (0-12) for each patient and depending on the total score subjects were divided into mild (1-4), moderate (5-8) and severe (>8) categories respectively. The frequency of regurgitation was also noted using the Likert scale.

Of 53 patients, 44 patients had symptoms suggestive of GERD. Out of these 39 patients (73.6%) had heart burn, of which 23

cases (60%) had low scores, 9 cases had moderate scores (23.07%) and 7 cases (17.94%) had severe scoring. 34 patients (64.15%) had regurgitation symptoms, of which 21 cases (61 .76%) had low scores, 7 cases (20.58%) had moderate scores and 6 patients (17.64%) had severe scores.

Thirty patients had both the symptoms of heart burn and regurgitation while 9 patients had only heartburn and 5 patients only regurgitation.

UPPER GI ENDOSCOPY

Only 34 patients out of 53 had evidence of esophagitis on Upper GI Endoscopy. Majority of 25 out of 34 (73.52%) had Grade A esophagitis by Los Angles classification, followed by Grade B seen in 7 patients (20,58%), and only 2 patients (5.88%) had Grade C esophagitis. No patient had Grade D esophagitis. 19 patients were normal for Upper GI Endoscopy.

24HOUR pH MONITORING

The 24 hours pH test results were interpreted in respect to the following variables:

1. Time Percentage when pH was less than 4.0 during 24 hour period (FT-fractional time).

2. Number of reflux episodes.

3. Number of reflux episodes 1ating longer than 5 minutes (PR-pathological refluxes).

4. Duration of the longest reflux episode.

Reflux is considered significant on pH metry when p11 of < 4 is present for> 5.5 % of the duration of recording.

Of 53 patients, 41 patients (77.35%) had significant reflux on pHmetry while other 12 had no significant reflux.

Severity Grading On 24 Hour pHmetry

Significant reflux is further divided into 3 grades of severity based on total fractional time. Out of 41 patients with significant reflux7majority had mild reflux 27 patients(65.85%), 5 patients (12.2%) had moderate grade while 9 patients (21.9%) had severe reflux.

Duration of Time (%)	**Severity of Reflux**	**No. of Patient (n=41)**
5.5-8.5	Mild	27 (65.85%)
8.6-11.5	Mod	5 (12.2%)
>11.5	Severe	9(21.9%)

Correlation between symptoms of GERD and Endoscopy

When symptoms of GERD were compared with endoscopic findinit was seen that all the 34 patients with symptomatic GERD had esophagitis on endoscoy. And 10 patients who were symptomatic for GERD have normal upper GI study. The result was statistically significant (p value= 0.000).

UGIE AND GERD SYMPTOMS (Table 4)

GERD Symptom	UGIE Normal	UGIE Abnormal	P value
Present	10	34	0.000
Absent	9	0	

34 patients, of 44 symptomatic GERD had endoscopic esophagitis which constitutes 77.2% of the patients.

Correlation between symptoms of GERD and Ph metry

When pHmetry findings were compared with symptoms, it was seen that all the 41 patients who had significant reflux on pH metry had symptomatic GERD in the form of either heart burn or regurgitation or both.Only 3 patients symptomatic for GERD did not reveal any significant reflux on pH metry. The result was statistically significant (p value = 0.000)

PH METRY AND GERD SYMPTOMS

GERD symptom	Non Significant reflux (n=12)	Significant Reflux (n=41)	P value 0.000
Present	3	41	
Absent	9	0	

41 patients with significant reflux constitutes 93% GERDof the total patients symptomatic for

Correlation between Endoscrpy and Ph metry

When pHmetry findings were compared with endoscopic findings, it was seen that 32 patients who had significant reflux on Ph metry had esophagitis on endoscopy as well., while 9 patients who had positive results on pHinetry had normal endoscopic findings. Only 2 patients who were negative on pHmetry had esophagitis on UGI Endoscopy. The result was statistically significant ($p < 0.05$) as shown in Table 5.

Table 5

UGIE	Non – Significant reflux (n=12)	Significant Reflux (n=41)	P value
Normal	10	9	
Abnormal	2	32	<0.05

0f 41 patients wjih significant reflux on pH metry, 32 patients (78.04%) had evidence of endoscopic esophagitis.

To study the correlation between stage of CKD and GERD, the patients were divided into two groups based on the stage of CKD, Group I (CKD Stage 11-Ill) and Group II (CKD Stage IV-V) each including 26 and 27 patients respectively as shown in Table 6.

Table 6

GROUP I	GROUP II	TOTAL NO. OF PATIENTS (N=53)
GROUP I	STAGE II-III	26
GROUP II	STAGE IV-V	27

CORRELATION BETWEEN GERD SYMPTOMS AND CKD STAGE

Of 26 patients in Group I, 17 patients (65.3 8%) had symptomatic GERD and in Group II, all the 27 patients (100%) had symptoms. It was seen that all the patients with severe scores belong to stage IV-V. The difference was statistically significant (p= 0.000).

CORRELATION BETWEEN ENDOSCOflESOPBAGIT1S AND CK1) STAGE

On UGI Endoscopy in Group I (stage lI-Ill), 8 patients (30.76%) have positive findings diagnostic of GERD whereas it's seen in 26 patients (96.29%) belonging to Group II (stage lV-V). The difference was statistically significant (p value= 0.000)

CORRELATION BETWEEN PH METRY AND CKD STAGE

On ph metry 14 patients (53.84%) in Group I tage Il-Ill) have significant reflux while in Group II (stage IV-V), 27 patients (100%) have significant reflux. The difference was statistically significant (p =0.000)

The above findings are summarised in the Table No.7

CORRELATION BETWEEN GERD AND STAGE OF CKD (TABLE 7)

GERD	GROUP 1 C STAGE II III(n26)	GROUP II CKD STAGE IV-V(n=27)	p value
SYMPTOMS(n=44)	17 (65.38%)	27 (100%)	0.000
UGI ENDOSCOPY cn=34)	8 (30.76%)	26 (96.29%)	Cooo
Ph-METRY (w=4l)	14 (53.84%)	27 (100%)	0.000

The GERD symptoms, endoscopic esophagitis and positive pH metry documenting reflux was seen in nearly all the patients of group II (stage IV-V).

RESULTS OF OESOPHAGEAL MANOMETRY

It was done to see Esophageal body motility pattern and Lower esophageal sphincter (LES) tone using Griffon esophageal manometry program on the MK2 gastrointestinal motility apparatus

A) ESOPHAGEAL MOTILITY:

It was done to see esophageal body motility pattern and Lower esophageal sphincter .(LES) tone. Abnormal esophageal motility patterns inclü&d triphasic contractions and irregular to diffuse oesophageal contractions.

Of 53 patients who underwent oesophageal manometry 25 patients (47.16%) showed abnormal results, of these 17 patients (68%) showed abnormality in the form of triphasic contractions whereas 8 patients (32%) have irregular to diffuse oesophageal contraction1 while 28 patients (52.83%) showed no abnormality in the test result. This is shown in Table

MANOMETRIC STUDY (Table 8)

Esophageal Motility		No. of patients (n=53)
Normal		28 (52.83%)
Abnormal	Triphasic	17 (32.07%)
	Irregular/Diffuse	8 (15.09%)

CORRELATION BETWEEN STAGE OF CKD AND ESOPHAGEAL MOTILITY:

It's seen that in stage II-III, 2 patients (7.69%) had abnormal manometric results while in stage IV-V, 23 patients (85.18%) had abnormal results. The difference was statistically significant (p value = 0.000)

STAGE OF CKD AND ESOPHAGEAL MOTILITY (table 9)

Manometry	GROUP I (CKD. STAGE II-III(n=26))	GROUP II (CKD STAGE -IV(n=27))	p value
NORMAL	24 (92.3%)	4 (24.82%)	
ABNORMAL	2(7.69%)	23 (85.18%)	0.000

CORRELATION BETWEEN ESOPHAGEAL DYSMOTILITY AND GERD

a) ESOPHAGEAL DYSMOTILITY AND SYMPTOMS

Of 44 patients with symptomatic GERD 25 patients (56.8 1%) had abnormal esophageal motility and rest had normal results. This difference was statistically significant (p<0,05). (Table 10)

Table 10

Symptom	Motility normal (n=28)	Motility abnormal (n=25)	P value 0.001
Present (n=44)	19 (43.18%)	25 (56.81%)	
Absent (n=9)	9	0	

ESOPHAGEAL DYSMOTILITY AND PH METRY

Of 41 patients with significant reflux only 22 patients (53.65%) were abnormal for esophageal motility. Only 3 patients with dysmotility had normal pH metric findings. The difference was statistically significant (p<O.O5) as shown in Table 11.

Table 11

PH metry	Motility normal	Motility abnormal	P value(0.0245)
Significant	19 (46.35%)	22 (53.65%)	<0.05
Not significant	9	3	

ESOPHAGEAL DYSMOTILITYAND UPPER GI ENDOSCOPY

Of 34 patients of endoscopic esophagitis, 22 patients (64.7%) had abnormal manometry. 3 patients with dysmotility had normal Endoscopy. The difference was statistically significant

Table 12

UGIE	Motility normal	Motility abnormal	P value (0.001)
Normal	16	3	
Abnormal	12 (35.29%)	2 (64.7%)	<0.05

LOWER ESOPHAGEAL SPHINCTER TONE (LES TONE)

LES is considered to be hypotensive when LES tone is < l0miuHg. It was seen that out of 53 patients, 34 patients (64.15%) had decreased LES tone i.e. < 10mm Hg.

CORRELATION BETWEEN LES TONE AND STAGE OF CKD:

1n stage Il-Ill patients (Group I), out of 26 patients 10 patients (3 8.46%) had hypotensive LES and in 27 Stage TV-V (Group TI) CKD patients 24 (88.88%) had hypotensive LES. The difference was statistically significant (j value = <0.05) as shown in Table 13

Table 13

LES TONE	CKD STAGE Il-Ill (N=26)	CKD STAGE IV-V (N=27)	P value
NORMAL	16 (61.54%)	3(11.13%)	
HYPOTENSIVE	10 (38.46%)	24 (88.88%)	<0.05

CORRELATION BETWEEN LES TONE AND GERD

a) LES TONE AND GERD SYMPTOMS: Of 44 symptomatic patients for GERD hypotensive LES was seen in 29 patients (65.9%). 14 patients had normal LES tone. This difference was statistically significant ($p<0.05$) as shown below.

Table 14

Symptoms	LES tone normal	LES. tone decreased	P value
Present (n=44)	14 (34.1%)	29 (65.9%)	<0.05
Absent (n=9)	4	5	

b) LES TONE AND ENDOSCOPIC ESOPHAGITIS: Of 34 patients with endoscopic esophagitis, 26 patients (76.47%) had decreased tone and rest of the patients had normal LES tone. The difference was statistically significant ($p<0.05$) as shown in Table 15.

Table 15

Abnormal (n=34)	8 (23,53%)	26 (76.47%)	P value
UGI Endoscopy	LES tone normal	LES tone decreased	<0.05
Normal (n=19)	11	8	

C) LES TONE AND P11 METRY: It was seen that of 41 patients with significant reflux, 32 patients had hypotensive LES (78.04%) and 9 patients with positive pH metry had normal LES tone. The difference was statistically significant ($p < 0.05$)

Table 16

Ph-METRY	LES TONE NORMAL	Les Tone Abnormal	P value
Significant (n41)	9(21.96%)	3278.04%)	<0.05
Not significant (n=l2)	10	2	

AUTONOMIC FUNCTION TESTS

RESTING HEART RATE: In 53 patients studied heart rate ranged between 58/mm to 1 12/mm (mean 91 ± 8.85).

a) PARASYMPATHETIC FUNCTION TESTS: These tests are based on ECG recordings.

The various tests results are as follows:

1. **STANDING / LYING RATION** Of 53 patients studied 28 patients (51.9%) had abnormal test results whereas 20 patients (36.5%) showed no abnormality and 5 patients were indeterminate (1 1.5%).

2. **30:15 RATIO**: 26 patients (49.1%) showed abnormality in the test and almost equal no. of patients showed normal test results and one was indeterminate (1.9%).

3. **VALSALVA RATIO**: Among 53 patients studied 26patients (49.1%) showed abnormal results and 23 patients (43.4%) performed normally whereas 4 patients (7.5%) were indeterminate for the test.

b) SYMPATHETIC FUNCTION TESTS: These tests are based on the measurement of Blood Pressure, The various tests results are as follows:

1. **HAND GRIP TEST:** Out of 53 patients studied 26 patients (49.1%) showed abnormality in the test whereas 27 patients (50.9%) were normal for the test.

2. **COLD PRESSOR RESP.NSE:** Out of 53 patients studied 26 patients (49.1%) showed abnormality m the test whereas 27 patients (50.9%) were normal for the test.

3. **Autonomic Function Tests (table 17)**

Tests	PARASYMPATHETIC SYSTEM (N= 53)			SYMPATHETIC SYSTEM (N= 53)	
	NARMAL	ABNORMAL	INDETERMI NATE	NORMAL	ABNORMAL
S/L RATION	20	28	5	-	-
30:15 RATIO	26	26	1	-	-
VALSALVARATION	23	26	4	-	-
HAND GRIP TEST	-	-	-	27	26
COLD PRESSOR RESPONSE	-	-	-	27	26

CORRELATION BETWEEN AUTONOMIC DYSFUNCTION WITH CKD STAGE

Of 53 patients, 28 patients showed abnormality in parasympathetic nervous system while rest were normal. Of these26 patients (96.29%) belonged to CKD Group II (Stage IV-V) and 2 patients (7.69%) were in Group I (Stage Il-Ill). The difference was statistically significant (p= 0.000). In advanced stage of CKD the parasympathetic dysfunction was seen in significantly higher number of patients as shown in Table 18.

STAGE OF CKD AND PARASYMPATHETIC SYSTEM (Table 18)

PARASYMPATHETIC SYSTEM	CKD STAGE II III(n=26)	CKD STAGE IV- V(n=27)	P value
NORMAL	24(92.32%)	1 (3.72%)	
ABNORMAL	2(7.69%)	26(96.29%)	0.000

NORMAL	-24 (92.32%)	1 (3.72%)	
ABNORMAL	2 (7.69%)	26 (96,29%)	0.000

26 patients showed sympathetic dysfunction and all of them belong to stage IV-V and none in CKD stage Il-Ill. The difference was statistically significant p=0.000). All these patients also had parasympathetic dysfunction.

STAGE OF CKD AND SYMPATHETIC SYSTEM (Table 19)

SYMPATHETIC SYSTEM	CKD STAGE II- III(n=26)	CKD STAGE IV- V(n=27)	p value
NORMAL	26	1 (3.72%)	
ABNORMAL	0	26 (96.29%)	0.000

Of 53 CKD patients, parasympathetic neuropathy occurred in 28 patients and among them 26 patients had sympathetic dysfunction as well. Rest of the CKD patients i.e. 25 patients did not show any peripheral evidence of autonomic neuropathy.

CORRELATION BETWEEN AUTONOMIC DYSFUNCTION AND GERD

a) CORRELATION BETWEEN AUTONOMIC DYSFUNCTION AND GERD SYMPTOMS

of 44 patients with symptomatic GERD, 28 patients (63,63%) had parasympathetic dysfunction and 26 patients (59.1%) had sympathetic involvement also. 9 symptomatic cases were normal for ANS. The difference was statistically significant ($p<O.O5$) as shown in Table no. 20. It was also seen that patients with severescores on Likert scale had autonomic dysfunction ($p<O.O5$)

Table 20

Symptoms	PARASYMPATHETIC DYSFUNCTION (N=28)		SYMPATHETIC DYSFUNCTION (N=26)		P value
	Present	Absent	Present	Absent	

Table 21

UGIEE	PARASYMPATHETIC DYSFUNCTION (N28)	SYMPATHETIC DYSFUNCTION (n=26)			p Value
	Present	Absent	Present	Absent	
Normal (n= 19)	1 (5.3%)	18(94.7%)	1 (5.3%)	18 (94.7)	
Abnonrmal	27 (79.4%)	7 (20.6%)	25 (73.5%)	9 (26.5%)	0.000

It can be concluded that 96.4% patients with autonomic dysfunction had endoscopic

b) CORRELATION BETWEEN AUTONOMIC DYSFUNCTION AND PH METRY

Of 4L patients with significant reflux, 28 patients (68.29%) had parasympathetic dysfunction and 26 (63.4%) had sympathetic involvement. 13 patients were normal for the test results. This difference was statistically significant Q=0.000) as shown in Table 22.

Table 22

REFLUX	PARASYMPATHETIC DYSFUNCTION (N28)	SYMPATHETIC DYSFUNCTION (n=26)			p Value
	Present	Absent	Present	Absent	
Present (n= 41)	28	13(31.7%)	26	15 (36.58%)	0.000
Abesent (n=12)	0	12	0	12	0.000

It can be seen that 100% patients with autononomic dysfunction had p11 metry findings

CORRELATION BETWEEN AUTONOMIC DYSFUNCTION AND DYSMOTILITY

Of 25 patients with dysmotilily on manometry, 19 patients (7 6%) had involvement of both parasympathetic and sympathetic system and remaining patients were normal. It was statistically significant (p=0.000). (Table 23)

Table 23

MANOMETRY	PARASYMPATHETIC DYSFUNCTION (N28)	SYMPATHETIC DYSFUNCTION (n=26)			p Value
	Present	Absent	Present	Absent	
Normal (n= 28)	9	19	7	21	
Abnonrmal (n = 25)	19(68%)	6 (32%)	19(68%)	6 (32%)	0.000

Nineteen patients (68%) out of twenty eight with autonomic dysfunction had esophageal dysmotiity

Thus from Tables 20-23 it can be observed that, of 28 patients of autonomic dysfunction 100% patients had GERD symptoms4 96% had endoscopic esophagitis and 100% patients had reflux on pH metry. 68% patients had esophageal dysmotility. The difference was statistically significant ($p<0.05$).

DISCUSSION

DISCUSSION

The present study "TO EVALUATE PATIENTS OF CHRONIC KIDNEY DISEASE FOR GASTROESOPHAGEAL REFLUX. DISEASE AND ESOPHAGEAL DYSMOTILITY" was Learned out in the Department of Nephrology, Osh Regional Integrated Clinical Hospital, and Osh City Territorial Clinical Hospital, Osh from January 2010 to December 2012.

Literature mentions a few reports which suggest chronic renal failure state is associated with higher prevalence of gastro esophageal reflux disease. The suggested mechanism include increased number of transient lower esophageal sphincter relaxations, delayed gastric emptying, decreased acid clearance from the esophagus due to impaired peristalsis and decreased LES tone. Presence of autonomic neuropathy may also contribute to delayed gastric emptying. The incidence of autonomic neuropathy in CKD ranges from 10-83% and it increases with the severity of the disease. Autonomic dysfunction can lead to both decreased LES tone as well as impaired esophageal motility as studied in diabetics but this phenomenon has not been studied in CKD.

The present study evaluated the patients of CKD for GERD, esophageal dysmotility and autonomic dysfunction, which

were also correlated with the severity of CKD. The severity of CKD was based on K/DOQI classification

53 Patients of CKD presenting to the Medicine Outpatient Department and Medicine Emergency of Osh Regional Integrated Clinical Hospital, and Osh City Territorial Clinical Hospital, Osh were taken up for the study after fulfilling inclusion and exclusion criteria. These patients were evaluated for GERD symptoms, namely Heart bum and Regurgitation.

All these patients' also underwent upper gastrointestinal endoscopy, esophageal manometry and 24 hour pH monitoring and subjected to a battery of five bed side autonomic function tests,

Among the study group out of 53 patients, 24 were male and 29 were female. Mean age of the study group was 36.85 years. The mean age of females was 39.29 yrs while that of males was 36.27 years. This difference was not statistically significant (p>O.O5).

Forty four patients (83.01%) had symptomatic GERD. In a study from King Fahad University Hospital Saudi Arabia by Ibraheim S Abdufrehman et al, prevalence of GERD in uraemia was found to be 77.5%. This is much higher than the

normal population. In normal population it's estimated that 20% to 44% have symptoms of GERD at least once a month and 20% had weekly symptoms. There is evidence that GERD is increasing in frequency across the globe. In Kyrgyz Republic only few studies have been conducted on GERD showing the prevalence to be varying from 16-35%.

On UGIE, esophagitis was seen in 34 (64.15%) cases, of these majority 25 (73.52%) had grade A esophagitis, 7 (20.58%) had grade B esophagitis and 2 (5.88%) had Grade C esophagitis according to LA classification. No patient had Grade D esophagitis. All these 34 patients(77.2%) were also symptomatic for GERD. A significant correlation was observed between the symptoms and endoscpy (p value=0.000). In normal population endoscopic esophagitis in patients with GERD symptoms varies from 25% to 35%, Studies by Wang et al and Torres et al have shown a good correlation between severe symptoms and esophagitis. In contrast Okamato et al and Nasi A et al did not reveal any significant correlation between the symptoms of GERD and esophagitis on UGIE.

On pH metry depending upon the duration for which pH <4 the patients showing significant reflux were divided into mild (5.5-8.5% time), moderate (8.6-11.5% time) and severe >11.5% time) categories respectively. It was seen that of 41 patients

having significant reflux on pH metry; 27 had mild, 5 had moderate and 9 had severe reflux.

All these patients with significant pH metry also had GERD symptoms. A highly significant corre1ation was found between the symptoms and pH metry. (p=O.000). Zerbib F et al and Sharma N et al have also reported a significant relationship between reflux symptomatology and 24 hr pH monitoring.

Few authors like Yorulmaz I et at, Colas E et al have not seen any significant correlation. They postulated that it could be due to the occurrence of alkaline/bile reflux in some patients which present with symptoms of GERD but have negative ph metry findings.

In the present study pH-metry findings correlated significantly with endoscopic esophagitis (p=O.000). 32 patients with significant reflux on pH metry also had endoscopic esophagitis. Only 2 patients with endoscopic esophagitis had normal pH metry. It's quite possible that on the day of 24 hr pH metry no reflux event was measured. Masclee AA et al, Kasapidis P et al have also reported a significant correlation between esophagitis and 24 hour pH monitoring.

Authors such as Arango L et al, Chan CC et al, Venegas S et al had found poor correlation between these two methods, Excessive bile exposure of esophageal mucosa has been proposed as the main cause of esophagitis with normal pH metry. It is also suggested that endoscopy-negative reflux disease should be treated as endoscopy positive GERD because long term acid exposure would rapidly damage esophageal mucosa.

In order to correlate GERD symptoms, endoscopic esophagitis and pH metry with severity of CKD; patients were divided into two groups: Group I CKD (Stage Il-Ill) and Group II CKD (Stage IV-V) each containing 26 and 27 patients, respectively.

Regarding reflux symptoms on Likert scale, the severity of reflux symptoms a significantly more in Group II i.e. stage IV-V as compared to patients in Group I i.e. stage l - II (p=0.000).

Similarly on upper GI endoscopy, only 8 patients (30.76%) in Group I had esophagitis and 26 patients (96.29%) in Group II had esophagitis. This difference was also highly significant (p=O.000). On pH metry all the 27 patients of Group II had significant reflux as compared to 14 patients (53.84%) of Group I (p=0.000). Thus it was seen that patients of stage IV-V CKD (Group II) had significantly more gastroesophageal reflux disease. Ibraheim S Abdulrehman et al at King Fahad

University Hospital Saudi Arabia, studied prevalence of GERD in CKD by performing endoscopies and biopsy. He found significantly higher prevalence of GERD in CKD patients as compared to the healthy control group and a significant correlation with the duration of end stage renal disease.

Kawaguchi Y et al has shown that the prevalence of GERD in early stages of CKD was 34.0% by endoscopy. Whereas the patients undergoing hemodialysis; the prevalence of GERD was 50.0%. They concluded that the patients with advanced disease might have specific risk factors for the development of GERD. Some have proposed that probably these factors are dialyzable

Esophageal manometry showed two major abnormalities: decreased LES tone in 34 patients (64.15%) and esophageal dysmotility in 25 patients (47.16%).

LES tone: LES tone is considered to be decreased when it's <10 mm Hg. Decreased LES tone is a known pathogenic mechanism for gastroesophageal reflux disease. The current study also showed that decreased LES tone correlated very well with the GERD symptoms, esophagitis and pH metry (p= <0.05). Koppman JS et al, Jafflu BW et al have also documented hypotensive LES (<10mm Hg) in 3-50% of obese patients with GERD.

In the present study significantly more number of patients in CKD stage IV-V i.e. Group II (88.8%) had decreased LES tone as compared to stage II-III i.e. Group I patients (38.46%) (p=0.000).

Esophageal dysmotility: showed two types of patterns- Triphasic contractions in 17 patients (32.07%) and diffuse esophageal spasm in 8 patients (15.09%). Esophageal dysmotility consisting of abnormal/slowed peristaltic waves can contribute to GERD by way of decreased clearance of refluxed acid. In the present study, a significant correlation between esophageal dysmotility and pH metric evidence of reflux was seen (p=<O.O5).

Esophageal dysmotility was seen in significantly more number of patients in stage IV-V CKD (85.18%) as compared to patients (7.69%) in stage II-Ill (p <0,05).

Experimental study by Laken et al in rats has shown a higher incidence of esophageal dysmotility in uremia. Ravelli AM in its study on children with CKD shows that a number of patients who are symptomatic for GERD have abnormality in their gastrointestinal motility system. No other study on esophageal motility in uremia was found.

On autonomic function tests 28 patients (52.83%) showed abnormality for parasympathetic nervous system and of these 26 patients (49.05%) also for sympathetic system tests Le. all the patients having sympathetic system dysfunction also had parasympathetic system dysfunction. Parasympathetic neuropathy occured more frequently then sympathetic neuropathy.

Studies done by Vita G et al showed that in uremia, parasympathetic neuropath appears more frequently than sympathetic damage. Malik S et a also showed that in chronic renal failure, 38 patients (65%) had early or definite parasympathetic abnormalities, while 14 of them (24%) had additional sympathetic damage.

It has been reported that with worsening of uremia, the prevalence of autonomic neuropathy increases. Autonomic Neuropathy in the current study correlated very significantly with the severity of CKD, 7.69% vs. 96.29% in Group I and Group II respectively (p=0.000). K.C. Siamopoulos et al in their study have also shown a higher incidence of autonomic dysfunction in CKD patients undergoing dialysis.

The third objective of this study was to find a correlation between autonomic dysfunction, GERD and esophageal dysmotility. 28 patients of 53 CKD patients had autonomic

dysfunction. Of these 28 patients, 100% patients had GERD symptoms, 96% patients had endoscopic esophagitis and 100% patients had significant pH metry. On manometry 19 patients i.e. 68% had dysmotility. Thus a very good correlation could be demonstrated between autonomic dysfunction, GERD and esophageal dysmotility. It is known that impaired esophageal clearance of gastric refluxate and decreased LES tone play an important role in the pathogenesis of gastroesophageal reflux disease and normal esophageal motility is dependent on an intact autonomic nervous system. Patients with autonomic neuropathy had a significant correlation with the severity of reflux symptoms ($p<O.05$)

In the present study autonomic neuropathy in the patients of chronic kidney disease led to decreased LES tone, impaired esophageal peristalsis which in turn contributed to the development of gastroesophageal reflux disease. Delayed gastric emptying due to autonomic. neuropathy has also been observed in patients of chronic renal failure which in turn predisposes to gastroesophageal reflux

Dumitrascu et al have shown that the patients of CRF had delayed gastric emptying if parasympathetic and sympathetic neuropathy were both present. In the present study 26 patients had both parasympathetic and sympathetic dysfunction. Even though we did not study gastric emptying in

our patients the problem of gastroesophageal reflux in all these patients may have been further compounded by delayed gastric emptying. All these 26 patients had symptoms of reflux, significant pH metry and 25 of them had esophagitis on endoscopy.

This study highlights that the Gastroesophageal reflux disease occurs in a large number of patients of chronic kidney disease. Autonomic neuropathy is also common in patients of chronic kidney disease and correlated well with the severity of disease. Presence of autonomic neuropathy correlated very well with the gastroesophageal reflux disease as well as esophageal dysmotility. Esophageal dysmotility is likely to contribute to gastroesophageal refiux disease. The outcome of this study also focuses on the fact that it's important to realize that patients of CKD stage IV-V are more likely to have autonomic neuropathy and esophageal dysmotility. While treating these patients for gastroesophageal reflux diseases with proton pump inhibitor's and other acid suppressing agents, one will also have to address the problem of impaired esophageal motility. Further studies are required on this issues

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS:

It is a first of its kind study which has comprehensively looked at the problem of gastroesophageal reflux disease, autonomic dysfunction and esophageal dysmotility in patients of chronic kidney disease. Most importantly this study shows that gastroesophageal reflux disease occurs commonly in patients of chronic kidney disease and has a direct correlation with the severity of CKD stage. Also esophagitis is more common in these patients. Autonomic dysfunction is common in patients of stage IV-V CKD. This autonomic dysfunction correlates significantly with GERD as well as dysmotility. In chronic kidney disease patients, esophageal dysmotility seen as decreased LES tone and impaired esophageal peristalsis are likely to contribute significantly to gastroesophageal reflux disease.

RECOMMENDATIONS:

Patients of CKD should be screened for GERD symptoms as well as autonomic dysfunction. Treatment of gastroesophageal

reflux disease should be initiated early as esophagitis is very common in these patients. In case patients of chronic kidney disease have GERD symptoms, they should be evaluated for autonomic neuropathy. In the presence of autonomic neuropathy the treatment modalities for GERD should address both acid suppression as well as esophageal dysmotility.

REFERENCES

REFERENCES

1. Coresh J, Selvin E, Lesley A, SJ Manzi et al JAMA ,2007;298(17):2038-47.

2. Giuseppe V, Bellinghieri G, Trusso A, Costantino G, Santoro D, Monteleone F,et al Kidney International (1999) 56, 232—237.

3. Carlo A. Fallone, Serge Mayrand. Gastroesophageal Reflux and Hyperacidity in Chronic Renal Failure; Peritoneal-Dialysis International, Vol. 21(2001), Supplement

4. Ala Kaila K. Upper GI findings in CRF. Scand J Gastroenterol 1987; 22:372-6.

5. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Praice Parameters Committee of the American College of Gastroenterology. Am J Gastitoenterol.1999; 94:1434-1442.

6. Vakil N, Van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence based consensus. Am J Gastroenterol 2006; 101:1900 - 20.

7. Carlsson R, Dent J, Bolling-Sternevold F, et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. Scand J Gastroenterol 1998; 33:1023—7.

8. National Kidney Foundation. K!DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(2 suppl 1) S1-266

9. Kher V. End stage renal disease in developing counte Kidney Int2002; 62: 350-62

10. Mani KM. Prevention of chronic renal failure at the community level. Kidney International 2003; 63: 586-9.

11. Modi GK, Jha V. The incidence of end-stage renal disease in India: A population based study. International Society of Nephrology 2006; 70; 213 1-3.

12. Agarwal SK, Dash SC, Mohammad I, Sreebhuasn R, Singh R, Pandy RM. Prevalence of chronic renal failure in adults in Delhi, India. Nephrology Dial Transplantation 2005; 20:1638-42.

13. Low Phillip. Autonomic Nervous System Disorders. Merck Manual.

14. Campese VM, RomoffMS, Jevitan D, Lane K, Massry SG. Mechanisms of autonomic nervous system dysfunction in uremia. Kidney Int 1981; 20: 246—253.

15. Heidbreder E, Schafferhans K, Heidland A. Autonomic neuropathy in chronic renal insufficiency. Nephron 1985; 41: 50-56.

16. Vita G, Messina C, Savica V,Bellinghieri G. Uraemic autonomic neuropathy, J Auton Nerv Syst 1990; 30: 179-14.

17. Bolton CF. Chronic dialysis for uremia. N Engl J Med Mar27 1980;302(l3):755

18. Dyck P3, Johnson WJ, Lambert EH, et al. Segmental deinyelination secondary to axonal degeneration in

uremic neuropathy. Mayo Clin Proc. Jun 1971 ;46(6):400-3 1.

19. Fraser CL; Arieff Al. Nervous system complications in uremia. Ann Intern Med. Jul 15 1988; 109(2):143-53.

20. Nielsen VK. The peripheral nerve funQtion in chronic renal failure. VI. The relationship betweeen sensory and motor nerve conduction and kidney function, azotemia, age, sex, and clinical neuropathy. Acta Med Scand. Nov 1973; 1 94(5):455-62.

21. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA Bostock EL. loaix MC. Altered motor nerve excitability in end-stage kidney disease. Brain 2005; 128:2164-74.

22. Nielsen VK, Winkel P. The peripheral nerve function in chronic renal failure. 3 A multivariate statistical analysis of factors presumed to affect the development of clinical neuropathy. Acta Med Scand. Jul-Aug 1971; 190(l-2):l 19-25.

23. Spallone V, Mazzaferro S, Tornei E, Maiello MR, Gentile F, Lungaroni et al. I Auton Nerv Syst. 1990 Jul;30:S149-51.

24. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA. Nephrol Dial Transplant 2001; 16:70-77.

25. Lilley JJ, Golden J, Stone RA. Adrenergic regulation of blood pressure in chronic renal failure. J Clin Invest 57:1190—1200, 1976.

26. Vito M. Campese, Mark S. Romoff, Daniel Levitan, Kenneth Lane, and Shaul G. Massry. mechanisms of autonomic nervous system dysfunction in uremia; Kidney International, Vol. 20 (1981), pp. 246- 253.

27. Nayak KC, Lal C, Singh VB, Verma KK, Saini MS, Verma SK. Prevalence of erectile dysfunction in non- diabetic uremia. Indian J Nephrol 2005; 15: 218-222.

28. Heidbreder E, Schafferhans K, Heidland AAutonomic Neuropathy in Chronic Renal Insufficiency. Comparative Analysis of Diabetic and Nondiabetic Patients. Nephron 1985;41:50-56

29. Malik S, Winney RJ, Ewing DJ. Chronic renal failure and cardiovascular autonomic function. Nephron 1986; 43: 191-195.

30. Agarwal A, Anand IS, Sakhuja V & Chugh KS. Effect of dialysis and renal transplantation on autonomic dysfunction in chronic renal failure. Kidney Int 1991; 40: 489-495.

31. Solders G, Tyden G, Persson A & Groth CG. Improvement of nerve conduction in diabetic neuropathy: A follow-up study 4 yr after combined pancreatic and renal transplantation. Diabetes 1992; 41: 946- 951.

32. Vita G, Savica V, Milone S, Trusso A Belliiighieri G & Messina C. Uremiel autonomic neuropathy: Recovery following bicarbonate hemodialysis. Clin Nephro 1996; 45: 56- 60.

33. Tory K, Sallay P. Toth-Heyn P, Szabo A, Szabo A, Tulassay T, Gyorgy S. Reusz.Signs of autonomic neuropathy in childhood uremia. Pediatr Nephrol (2001) 16:25-28.

34. Dumitrascu DL, Barnert J Kirschner T, Wienbeck M. Antral mptyinof semisolid meal measured by real time ultrasonograpy in chronic renal failure. Dig Dis Sci 1995; 40(3):636-44.

35. Goyal RK, Chaudhury A.J Clin Gastroenterol. 2008 May-Jun;42(5):610-9.Physioiogy of normal esophageal motility.

36. Goyal RK, Rattan S. Nature of the vagal inhibitory innervations to the lower esophageal sphincter. J Clin Invest. 1975; 5:1119-1126.

37. K.C.Siamopoulas; E.V.Tsianos; M.Dardamanis; C.Berecos.Nephronl 990; 55:389-93

38. A H Laken, Boyacioglu 5, Gursoy M, Bilezikei B, Gur G,E D Akin et al. Am J Gastroenterol 2002;97: 1352-56.

39. A M Ravelli, S E Ledermann, W M Bisset, R S Trompeter, T M Barratt, P J Milla Foregut motor function in chronic renal fa1ure. Arch Dis Child 1992;67:1343-1347

40. Lin X, Mellow MH, Southmayd L 3rd, Pan J, Chen JD. Impaired gastric myoelectrical activity in patients with chronic renal failure. Dig Dis Sci. 1997 May; 42(5):898-906.

41. Ala Kaila K. Gastic secretion kinetics in chronic renal failure. Scand J Gastroenterol 1987; 22:1185-92.

42. Orlando RC. The pathogenesis of gastroesophageal reflux disease: The relationship between epithelial defense, dysmotility and acid exposure. Am J Gastroenterol. 1997; 92:3s – 5S

43. Kao CH, Hsu YH, Wang SI. Delayed gastric emptying in patients with chronic renal failure. Nuci Medn Commun 1996; 17:164-7.

44. Schoenmakere GD, Vanholder R, Rottey S, Duym P and Lameire N. Relationship between &astric emptying and clinical and biochemical factors in chronic haemodialysis patients. Nephrol Dial Transplant (2001) 16: 1850-1855.

45. McNamee PT, Moore GW, McGeown MG, Doherty CC. Gastric emptying in chronic renal failure. Br Med J (Clin Res Ed) 1985; 291:310-11.

46. Richard A. Wright, MD; Rosa Clemente, MD; Ronald Wathen, PhD. Gastric Emptying in Patients With Chronic Renal Failure Receiving Hemodialysis. Arch Intern Med 1984; 144(3):495-496.

47. Van Viem B, Schoonjans R, Vanholder R, Dc Vos M, Vandamme W, Van Laecke S, Lameire N. Delayed gastric emptying in dyspeptic chronic hemodialysis patients. Am J Kidney Dis. 2000 Nov; 36(5):962-8.

48. Strid H, Simren M, Stitzer P0, Abrahamsson H, Björnsson ES. Delay in gastric emptying in patients with chronic renal failure. Scand J Gastroenterol. 2004; 39:516-20.

49. Korman MG, Layer MC, Hansky I. Hypergastrinaernia in chronic renal failure. Br Med 11972; 1(794):209-10

50. Carlei F, Caruso U, Lezoche E, Ruscitto G, Laukie P Casciani U, et al. Hyperplasia of antral G cells in uraemic patients. Digestion 1984; 29:26-30.

51. Straathof JW, Lamers CB, Masclee AA. Effect of gastrin-17 on lower esophage1sphincter characteristics in man. Dig Dis Sci. 1997; 42:2547-51.

52. Gastroesophageal Reflux Disease in Chronic Renal Failure Patients: Evaluation by Endoscopic Examination Tokai J Exp Clin Med., Vol. 34, No. 3, pp. 80-83, 2009.

53. Abduirabman IS, Al Quorain AA. Prevalence of gastro esophageal reflux disease and its association with H. Pylori infection in chronic renal failure patients and in renal transplant recipients. Saudi J Gastroenterol 2008 Oct; l4(4) 183-6.

54. Edward J. Ruley, Glenn H. Bock, Benny Kerzner, Ann W. Abbott, Massoud Majd and Irene Chatoor. Feeding disorders and gastroesophageal reflux in infants with chronic renal failure. Pediatric Nephrology. Volume 3, Number 4 / December, 1989. 424-429.

55. Fass R, Ofinan JJ, Gralnek TM, et al. Clinical & economic assessment of the omeprazole test in patients with symptoms suggestive of gastro esophageal reflux disease. Archives of Internal medicine 1999; 159:2161-2168.

56. Lundell L R, Dent J, Blum A L et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of Los Angeles classification. Gut 1999; 45:172-180.

57. Galmiche JP, des Varannes SB. Endoscopy-negative refiux disease. Curr Gastroenterol Rep 2001; 3:206-214.

58. Ollyo JB, Lang F, Fontolliet C, Monnier 1. Savary-Miller's new endoscopic grading of reflux-esophagitis: a simple, reproducible, logical, complete & useful classiflcation(abstract). Gastroenterology 1 990; 98: Al00.

59. Jamieson JR, Stein HJ, DeMeester TR. Ambulatory 24-H Esophageal pH Monitoring: Normal Values, Optimal Thresholds, Specificity, Sensitivity and Reproducibility. The American Journal of Gastroenterology 1992; 87(9): 1102-1111

60. Chan CC, Lee CL, Wu CH. Twenty-four-hour ambulatory esophageal pH monitoring in patients with symptoms of gastroesophageal reflux. J Formos Med Assoc. 1997 Nov; 96(l1):874-8.

61. Wenner J, Johnsson F, Johansson J, et al. Acid reflux immediately above the squamocolumnar junction and in the distal esophagus: simultaneous pH monitoring using the wireless capsule pH system. Am J Gastroenterol 2006; 101 (8):1734-41.

62. Zerbib F, Roman S, Ropert A. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study

in patients off and on therapy. Am J Gastroenterol. 2006 Sep; 101(9):1956- 59.

63. Klauser A, Schindbeck N, Muller-Lissner S. Esophageal 24h pH monitoring: is prior manometry necessary for correct positioning of the electrode. Ani J Gastroenterol 1990; 85:1463-7.

64. Bolton CF, Young GB. Neurological Complications of Renal Disease. Stoneham, mass: Butterworth-Heinemann; 1990:1-256.

65. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol 2007; 5:17-26.

66. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007; 41:131-7.

67. P SK, M KS, JV. Prevalence of symptoms of gastro-esophageal reflux amongst medical students. Indian J Gastroenterol 2006 25:168-9.

68. Sharma PK, Ahuja V, Madan Ketal. Prevalence of symptomatic GERD: interim analysis of an adult community-based cross-sectional study. indian J Gastroenterol 2004;23 (Suppl2): All

69. S. Nwokediuko, U. Ijoma, 0. Obienu & C. Agunyenwa : Gastroesophageal Reflux Disease A Clinical And Endoscopic Study Of Nigerian Patients. The Internet Journal of Gastroenterology. 2009 Volume 8 Number 2.

70. Mantynen T, Färkkilã M, Kunnamo I, Mecklin JP, Juhola M, Voutilainen M. The impact of upper GI endoscopy referral volume on the diagnosis of gastroesophageal reflux disease and its complications: a 1-year cross-sectional study in a referral area with 260,000 inhabitants. Am J Gastroenterol. 2002 Oct; 97(l0):2524-9.

71. Jin Hai Wang, Jin Yan Luo. Composite score of reflux symptoms in diagnosis of gastro esophageal reflux disease. World J Gastroenterol 2004 November 15; 10(22):3332-3335.

72. Peralta-Torres NM, Trujillo-Benavides OE, Paredes-Cnuz E. Obesity, symptoms of gastroesophageal reflux and

endoscopic findings in a referral hospital. Rev Gastroenterol Mex. 2007 Jul-i: Sep; 72(3):214- 21.

73. Okamoto K, Iwakiri R, Morietal M. Clinical Symptoms in Endoscopic Reflux Esophagitis: Evaluation in Adult Subjects Digestive Diseases and Sciences 2003 Dec; 48(12): 2237-41.

74. Nasi A, FilhO JP, Ziberstein B. Gastroesophageal reflux disease: clinical, endoscopic, and intraluminal esophageal pH monitoringevaluation. Dis Esophagus. 2001: 1 4(l):41 -9.

75. Yorulmaz 1, Ozugedik S, Kucuk B Gastroesophageal reflux disease: symptoms versus pH monitoring results. Otolaryngol Head Neck Surg. 2003 Nov; l25):582-6.

76. Colas-Atger E, Bonaz B, Papillon E. Relationship between acid reflux episodes and gastroesophageal reflux symptoms-is very inconstant. Dig Dis Sci 2002; 47: 645-651

77. Masclee AA, de Best AC, de GraafR. Ambulatory 24-hour-Ph-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to

endoscopy. Scand J Gastroenterol. 1990 Mar; 25(3):225-30.

78. Kasapidis P, Xynos E, Mantides A. Differences in manometry and 24- h ambulatory pH metry between patients with and without endoscopic or histological esophagitis in gastroesophageal reflux disease. Am J Gastroenterol. 1993 Nov; 88(11): 1893-9.

79. Arango L, Angel A,Molina RI. Comparison between digestive endoscopy and 24 hr esophageal pH monitoring for the diagnosis of gastroesophageal reflux esophagitis: presentation of 100 cases". Hepatogastroenterology. 2000 Jan-Feb;47(3l):174-8

80. Sanchez-Gey Venegas S, Yerro Paez VM. Relationship between endoscopic esophagitis and patterns of gastro esophageal reflux in ambulatory pHmetry. Rev Esp Enferm Dig. 1999 Feb; 91(2):l25-32.

81. Kawaguchi Y et al. Gastroesophageal Reflux Disease in Chronic Renal Failure Patients: Evaluation by Endoscopic Examination. Tokai J Exp Clin Md., Vol. 34, No. 3, pp. 80-83, 2009.

82. Bolton CF. Chronic dialysis for uremia. N Engl J Med. Mar27 1980; 302(l3):755.

83. Asbury AK. Recovery from uremic neuropathy. N Engl J Med. May 27 1971; 284(2):1211-2.

84. Dent J, Holloway R H, Touli J et al. Mechanisms of LES incompetence in patients with symptomatic gastroesophageal reflux. Gut 1988; 29:1020-8.

85. Kahlas PJ, Dodds WJ, .Hogan WJ. Effect Of Peristaltic dysfunction on esophageal volume clearance. Gastroenterology 1988; 94:73—80.

86. Mali1 S, Winney RJ, Ewing DJ. Chronic renal failure and cardiovascular autonomic function, Nephron 1986; 43: 191-195.

ANNEXURE

PROFORMA FOR THESIS

SUB: To evaluate patients of chronic kidney disease for gastroesophageal reflux disease and esophageal dysmotility

Patients Details:

- NAME
- AGE
- SEX
- CR.NO

Presenting complaints

- Generalised swelling
- Facial puffiness

- Decreased urine output
- Heart burn
- Regurgitation

Personal History:

- Smoking
- Alcohol
- Drug history

Examination

- Height
- Body weight
- BMI

Investigations

- Haemoglobin
- Blood urea
- S.Creatinine
- CCR
- 24 hr pH metry
- Upper GI endoscopy
- Esophageal manometry
    a. Esophageal Motility
    b. LES Tone
- Autonomic function tests:
        a. Resting heart rate
        b. Standing to lying down ratio

c. 30:15 ratio

d. Valsalva ratio

e. Hand grip test

f. Cold pressor response

INFORMED CONSENT

I _____ S/D/W of _____ R/O _____ _____ hereby declare that 1 give consent in the thesis study entitled To evaluate patients of chronic kidney disease for gastroesophageal reflux disease and esophageal dysmotility".

Dr. Subodh Kumar Pandey has informed me to my full satisfaction, in the language I understand, about the purpose, nature to the study and various laboratory investigations for the study to be carried out.

I give full consent for being enrolled in the above study and I reserve my rights to withdraw from study whenever I wish without prejudice of my rights to undergo further treatment at this hospital.

Patient/patient's relative's signature

Or thumb impression

name: Date;

We have witnessed that the patient signed the above form in the presence of his/her free will after fully understanding its contents.

1. Signature of the witness

Name

2. Signature of the investigator

Name

Designation:

CODES

1. Sympoms: Present: 1

   Absent: 2

2. pH metry Significant 1

   Not significant 2

3. Dysmotility: Normal 1

   Abnormal 2

4. LES tone Normal 1

   Decreased 2

5. UGI Endoscopy Normal 1

   Abnormal 2

6. S/L Ratio: >1.04: 1

1-1.04: 2

<1 : 3

7. 30:15 Ratio: >1.04:1

1-1.04: 2

<1 : 3

8. Valsalva Ratio: >1.45: 1

1.2-1.45:2

<1.20: 3

9. Hand grip/cold pressor: Normal 1

Abnormal: 2

SUMMARY

SUMMARY

The present study “TO EVALUATE PATIENTS OF CHRONIC KIDNEY DISEASE FOR GASTROESOPELAGEAL REFLUX DISEASE AND ESOPHAGEAL DYSMOTILITY” was carried out in the Department of Nephrology, Osh Regional Integrated Clinical Hospital, and Osh City territorial clinical Hospital, Osh, from January 2010 to December 2012.

53. Patients of CKD presenting to the Medicine Outpatient Department and Medicine Emergency of Osh Regional Integrated Clinical Hospital, and Osh City territorial clinical Hospital were taken up for the study after fulfilling inclusion and exe1uion criteria. These patients were evaluated for GERD symptoms, namely Heart burn and Regurgitation.

All these patients’ also underwent upper gastrointestinal endoscopy, esophageal manometry, and 24 hour pH monitoring and subjected to a battery of five bed side autonomic function tests.

1. Mean age of the study group ‘as 36.85 years. The mean age of females was 39.29 yrs while that of

males was 36.27 years with standard deviation of 13.69. This difference was not statistically significant. (p> 0.05).

2. Male: female ratio was 1.20.

3. Forty. four patients had symptoms suggestive of GERD. Out of these 39 patients (73.6%) had heart burn, of which 23 cases (60%) ha low scores, 9 cases had moderate scores (23.07%) and 7 cases (17.94%) had severe scoring.

4. Thirty four patients (64.15%) had regurgitation symptoms, of which 21 cases (61.76%) had low scores, 7 cases (20.58%) had moderate scores and 6 patients (l7.64%)had severe scores.

5. On UGIE, esophagitis was seen in 34 patients. Majority of patients, 25 out of 34 (73.52%) had Grade A esophagitis by Los Angles classification, followed by Giade seen in 7 patients (20.58%), and only 2 patients (5.88%) had Grade C esophagitis. No patient had Grade D esophagitis. 19 patients were normal for Upper GI Endoscopy

6. On pH metry, 41 patients (77.35%) had significant reflux on pH metry while other 12 had no significant reflux.

7. Out of 41 patients with significant reflux, majority had mild reflux 27 patients(65.85%), 5 patients (12.2%) had moderate grade while 9 patients (21.9%) had severe reflux.

8. When symptoms of GERD were compared with endoscopic findings it was seen that all the patients with esophagitis on endoscopy had GERD. Only few patients, who were symptomatic for GERD, have normal upper GI study. The difference was statistically significant (p value= 0.000).

9. It was seen that all the patients who had. significant refiux on pH metry had symptomatic GERD as well. Only 3 patients symptomatic for GERD did not reveal any significant reflux on pH metry. The difference was statistically significant (p value = 0.000)

10. When pHmetry findings were compared with endoscopic findings, it was seen that 32 patients

(78%) who had significant reflux on pH metry had esoplagitis, vhile 9 patients who had positive results on pH metry had normal endoscopic findings. Only 2 patients who were negative on pH metry had esophagitis. It was also statistically significant ($p< 0.05$).

11. To study the correlation, the patients were divided into two groups based on the CKD stage, Group I (CKD Stage II-III) and Group II (CKD Stage IV-V) each containing 26 and 27 patients respectively.

12. It was seen that all the patients with severe symptom scores belonged to Group II as compared to Group I CKD. This difference was statistically significant ($p=0.000$)

13. Endoscopic esophagitis also correlated significantly with the severity of CKD stage. ($p=0.000$)

14. Similarly pH metry findings in Group II patients were significantly higher than the patients in Group I ($p=0.000$)

15. Esophageal motility showed abnormal results in 25 patients (47.16%), of these 17 patients (68%) showed abnormality in the form of triphasic contractions whereas 8 patients (32%) have irregular to diffuse esophageal contractions. 28 patients (52.83%) showed no abnormal result

16. Patients in Group II CKD had higher number of patients with esophageal dysmotility as compared to patients in Group 1. The difference was statistically significant (p=0.000).

17. Of 44 patients with symptomatic GERD, 25 patients (56.81%) had abnormal esophageal motility and rest had normal results. This difference was statistically significant .($p<0.05$).

18. Patients with significant reflux had higher occurrence of esophageal dysmotility as compared to patients without reflux ($p<0.05$)

19. Similarly, in patients with endoscopic esophagitis, abnormal manometry was seen in a higher percentage of cases as compared to patients with normal endoscopy.

20. Thirty four patients (64.15%) had decrased LES tone i.e. < 10mm Hg.

21. Significantly more number of patients in Group II CKD had decreased LES tone as compared to Group I patients (p<O.O5)

22. A very significant correction was seen between decreased. LES tone and GERD symptoms, endoscopic esophagitis and pH metry evidence of GERD (p<O.O5)

23. Heart rate ranged between 58/mm to 112/mm with a mean of 91 ± 8.85.

24. Twenty eight patients showed abnormality in parasympathetic nervous system and 26 patients had sympathetic dysfunction.

25. All the patients with sympathetic dysfunction had parasympathetic involvement as well.

26. Autonomic neuropathy correlated very significant1 with the severity of CKD stage (p=0.000)

27. A very high correlation was observed between autonomic dysfunction and GERD symptoms, endoscopic esophagitis and significant reflux on pH metry (p=0.000)

28. A higher number of patients with esophageal dysmotility had autonomic dysfunction as compared to patients with normal motility. This difference was statistically significant

29. Esophageal dysmotility and decreased LES tone could be considered as a causative factor for gastroesophageal reflux disease.

30. Recognition of esophageal dysmotility in CKD patients therefore becomes essential as simple treatment of GERD in such patients would not be effective.

31. In addition to proton pump inhibitors for GERD, definitive therapy directed at dysmotility would be required for the optimum management of the chronic kidney disease patients.

32. Early treatment of GERD is also recommended in chronic kidney disease patients as esophagitis is quite common.