

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders, and its prevalence is increasing worldwide. It is a condition that develops by reflux of the stomach contents into the esophagus, and causes troublesome symptoms, such as heartburn and regurgitation. The aim of this work is to evaluate the serum level of IL4 in patients with GERD and patients with refractory GERD.

Patients and methods: The study included two groups of patients, Group-1 including 25 patients with GERD symptoms who didn't receive treatment or who received treatment for less than 8 weeks with improvement of symptoms and Group-2 including 25 Patients with refractory GERD and who received PPIs for more than 8 weeks without improvement of symptoms.

Results: Serum Interleukin-4(IL4) level was elevated in patients with refractory GERD more than patients with GERD, Serum IL4 level was elevated in patients with Barrett's esophagus more than patients with Reflux oesophagitis.

Conclusion: The study has concluded that : Serum Interleukin-4(IL4) level was elevated in patients with refractory GERD more than patients with GERD, Serum IL4 level was elevated in patients with Barrett's esophagus more than patients with Reflux oesophagitis, Pathological features that we found in patients with GERD were moderate reflux oesophagitis (52%), mild reflux oesophagitis (40%) and severe reflux oesophagitis (8%), while in patients with refractory GERD there were severe reflux oesophagitis (56%), Barrett's esophagitis (28%) and moderate reflux oesophagitis (16%).

Key words: GERD, Refractory GERD, Interleukin-4, IL4, Reflux oesophagitis, Barrett's esophagus.

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List of Abbreviations

5-HT45-hydroxytryptamine-4
AL2+Aluminum
ALTAlanine Aminotransferase
APCArgon Plasma Coagulation
ASTAspartate Aminotransferase
ATPAdenosine Triphosphate
B cellsB Lymphocytes
BEBarrett's Esophagus
CaCalcium
CanDysCanadian Dyspepsia
CBCComplete Blood Count
CBTCognitive Behavioral Therapy
CCBCalcium Channel Blocker
ClChloride
CmCentimeter
COPDChronic Obstructive Pulmonary Disease
CreatCreatinine
CYP2C19 (P450 2C19)Cytochrome P450 2C19
D2Dopamine 2
DGERDuodenogastroesophageal Reflux
DISDilated Intercellular Spaces
DNADeoxyribonucleic Acid
EACEsophageal Adenocarcinoma
EEErosive Esophagitis
EGDEsophagogastroduodenoscopy
ENTEar, Nose, Throat
EoEEosinophilic Esophagitis

List of Abbreviations

EST	Electrical Stimulation Therapy
FDA	Food and Drug Administration
g/dL	Grams Per Deciliter
GEJ	Gastroesophageal Junction
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GIT	Gastrointestinal Tract
H	Hydrogen
H. pylori	Helicobacter Pylori
H2RAs	Histamine-2 Receptor Antagonists
HCL	Hydrochloric Acid
HCO₃	Bicarbonate
HDL-C	High Density Lipoprotein Cholesterol
HH	Hiatus Hernia
HRQL	Health-Related Quality of Life
IBS	Irritable Bowel Syndrome
IFN-γ	Interferon- γ
IL	Interleukin
INR	International Normalized Ratio
IPG	Implantable Pulse Generator
K	Potassium
LES	Lower Esophageal Sphincter
LESP	Lower Esophageal Sphincter Pressure
M receptors	Muscarinic Receptors
mEq/L	Milliequivalents Per Liter
Mg²⁺	Magnesium
Mii	Multichannel Intra-Luminal Impedance

List of Abbreviations

mins	Minutes
mm of Hg	Millimeters of Mercury
mm	Millimeter
MUSE	Medigus Ultrasonic Surgical Stapler
Na	Sodium
NAB	Nocturnal Acid Breakthrough
NERD	Non Erosive Reflux Disease
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
P value	Probability Value
Pg	Picogram
PGE	Prostaglandin E
PMNLs	Polymorphonuclear Leukocytes
PPIs	Proton Pump Inhibitors
PT	Prothrombin
PTT	Partial Thromboplastin Time
QOL	Quality of Life
RE	Reflux Esophagitis
ROC curve	Receiver Operator Characteristic Curve
SD	Standard Deviation
SSR	Sustained Symptom Response
SSRI	Selective Serotonin Reuptake Inhibitors
T cells	T lymphocytes
TCAs	Tricyclic Antidepressants
TEA	Transcutaneous electrical acustimulation
Th cells	T Helper Cells
TIF	Transoral Incisionless Fundoplication

List of Abbreviations

TLESR	Transient Lower Esophageal Sphincter Relaxation
TNF-α	Tumor Necrosis Factor- α
U/L	Unit per Liter
vs	Versus

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders, and its prevalence is increasing worldwide. It is a condition that develops by reflux of the stomach contents into the esophagus, and causes troublesome symptoms, such as heartburn and regurgitation (*Yu-Min et al., 2017*).

Heartburn and regurgitation are the cardinal and most common symptoms of GERD. They are the typical symptoms of GERD (*Orlando, 2010*).

GERD may manifest atypically with extra-oesophageal symptoms as respiratory symptoms (cough, wheezes like asthma and recurrent upper respiratory tract infections), ENT symptoms (hoarseness of voice, globus sensation, postnasal drip, otitis media, dental erosions, sore throat, gingivitis, halitosis, aphthous ulcers and water brash), cardiac symptoms like pericordial or chest pain that may mimic anginal pain and multiple unexplained symptoms, which may be associated with psychological distress (*Richard et al., 2015*).

Patients with GERD, especially with chronic disease, may present complications as esophagitis, Barrett's esophagus and peptic stricture (*Sudha et al., 2018*).

Although PPIs are currently the most effective treatment for GERD and its complications, patients with nonerosive reflux disease (NERD) and patients with erosive esophagitis (EE) may remain symptomatic on standard therapy after 8 weeks of treatment. Patients with continued symptoms despite PPI treatment are considered to have refractory GERD (*Mermelstein et al., 2018*).

Recently refractory GERD is generally defined as the persistence of typical symptoms that do not respond to stable, twice-daily PPI dosing during at least 12 weeks of treatment. Up to 30% of GERD patients experience refractory GERD (*Mermelstein et al., 2018*).

There are many potential causes and factors related to refractory GERD that vary in incidence, clinical importance, and symptom severity and frequency. Poor compliance and adherence should first be assessed before further evaluation is decided. The most common mechanisms for refractory GERD include functional bowel disorders, weakly acidic reflux, and residual acid. Factors related to metabolism and bioavailability play a limited role in PPI failure. GERD-like symptoms may also be due to a variety of other disorders, such as eosinophilic esophagitis (EoE), pill-induced esophagitis, infectious esophagitis, and achalasia, which should be considered in the differential diagnosis of patients with unremitting symptoms (*Mermelstein et al., 2018*).

Barrett's esophagus is the condition in which a metaplastic columnar mucosa replaces an esophageal squamous mucosa damaged by gastroesophageal reflux disease (GERD). Barrett's esophagus are major risk factors for esophageal adenocarcinoma (*Stuart and Rhonda, 2014*).

Cytokines are a peptide signaling molecules, play an important role in the damage of tissues and can demonstrate pro-inflammatory as well as anti-inflammatory activity (*Vladimir et al., 2015*).

In addition to direct stimulation by intraluminal reflux contents, the esophageal epithelial layer is also exposed to factors produced by chronic inflammatory cells from the basal side (*Jing et al., 2016*).

Studies have shown an increase in proinflammatory TH1 cytokines in reflux esophagitis compared to BE, whereas TH2 cytokines are predominant in BE. There is increase in IL-4 in BE (*Jing et al., 2016*).

AIM OF THE WORK

The aim of this work is to evaluate the serum level of IL4 in patients with GERD and patients with refractory GERD.