Role of IL-6 in GERD Patients with and without Obesity

Thesis

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانكَ لاَ عِلمَ لَنَا إِلاّ مَا

عَلّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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List of Abbreviations

BMI	**:** Body Mass Index
CCK	**:** Cholecystokinin
CNS	**:** Central nervous system
DEXA	**:** Dual-energy X-ray absorptiometry
FDA	**:** Food and drugs administration
GABA	**:** Gamma Amino Buteric Acid
GERD	**:** Gastroesophageal reflux disease
H+	**:** Hydrogen Ion
H2RA	**:** histamine-2 receptor antagonist
HDL	**:** High density lipoprotein
IL 6	**:** Interleukin 6
K+	**:** Potassium Ion
LDL	**:** Low density lipoprotein
LES	**:** Lower esophageal sphincter
LESRs	**:** Lower Esophageal Sphincter Relaxations
MRI	: Magnetic resonance imaging
NERD	**:** Non erosive reflux disease
RDAs	**:** recommended daily allowances
TNF	**:** Tumor necrosis factor
WHO	**:** World Health Organization
5-HT_3	**:** Histamine

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Introduction

Gastroesophageal reflux (GERD) is a normal physiological phenomenon experienced intermittently by most people, it occurs when the amount of gastric juice that refluxes into the esophagus exceeds the normal limit causing symptoms either with mucosal injury i.e. esophagitis (GERD) or without remarkable oesphageal lesion i.e. non erosive reflux disease (NERD) ***(Loots et al., 2013).***

GERD is a disorder that affects the lower esophageal sphincter (LES), and causes injury to the esophagus due to chronic exposure to acid. Several factors contribute to the weakening of the LES as some food and smoking but one of the most common causes of GERD is obesity ***(Janeway et al., 2007).***

Obesity is a medical condition in which excess fat has accumulated to the extent that it may cause an adverse effect on health, leading to reduced life expectancy and/or increased health problems. BMI is one of the methods used to estimate obesity where the subject considered obese when his BMI exceeds 30kg/m^2 ***(Haslam and James, 2005).***

Studies proved that; GERD and its complication is highly related to high BMI. Therefore, the pathophysiology of GERD in patients who are morbidly obese might differ from that of patients who are not obese So that the correction of reflux in patients who are morbidly obese might be better achieved with a procedure that first controls obesity ***(Kaplan, 2008).***

The mechanism by which a high BMI increases GERD is not completely understood. Increased intragastric pressure and gastroesophageal pressure gradient, incompetence of the lower esophageal sphincter (LES), and increased frequency of transient LES relaxations may all play a role in the pathophysiology of GERD in patients who are morbidly obese ***(Kaplan, 2008).***

Studies have focused that visceral fat is metabolically active and produce variety of cytokines including IL-6 and TNF which may affect osephagogastric motor activity ***(Friedenberg, et al., 2008).***

Interleukin-6 (IL-6) is a protein that in humans is encoded by the *IL6* gene. It is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, other tissue damage leading to inflammation. In terms of host response to a foreign pathogen during infection, IL-6 has been shown, to be required for resistance against the bacterium, *Streptococcus pneumoniae*. IL-6 is also a "myokine," a cytokine produced from muscle, and is elevated in response to muscle contraction ***(Febbraio and Pedersen, 2005).***

AIM OF THE Work

The aim of this study is to assess the possible role of IL-6 in GERD patients with and without obesity.

Chapter (1)
Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux is a normal physiologic phenomenon experienced intermittently by most people, particularly after a meal. Gastroesophageal reflux disease (GERD) occurs when the amount of gastric juice that refluxes into the esophagus exceeds the normal limit, causing symptoms with or without associated esophageal mucosal injury (i.e., esophagitis) ***(Loots et al., 2013).***

Gastroesophageal reflux disease is the failure of the normal anti-reflux barrier to protect against frequent and abnormal amount of gastric content moving retrograde effortlessly from stomach to esophagus. GERD itself is not a disease but rather physiological process. It occurs multiple times each day especially after large meals without producing symptom of heartburn or mucosal damage. In contrast GERD is a spectrum of disease usually producing symptoms of heartburn and acid regurgitation. Most patients have no visible damage at the time of endoscopy (non-erosive GERD),whereas others have esophagitis, peptic stricture, Barrett's esophagus, or have chest pain or evidence of extra esophageal manifestation such as pulmonary or near, nose, and throat symptoms. GERD is multifactorial process and most common disease of mankind ***(Orenstein et al., 2002).***

Epidemiology

Although GERD is widely reported to be one of the most prevalent diseases of gastrointestinal tract, prevalence and incidence data for it based more on estimates than actual data. Furthermore estimating the prevalence of GERD differs depending on whether the analysis based on symptoms (usually heartburn) or sign of disease (i.e., esophagitis) ***(Ohara et al., 2011).***

On basis of symptoms GERD is common in western countries. In nationwide population-based study by Gallup Organization in United States, 44% of respondents reported heartburn at least once a month ***(Locke et al., 1997).***

In contrast the true prevalence of esophagitis is very difficult to define as healthy person rarely undergo upper endoscopy. Studies suggest that 7% of American have erosive esophagitis, whereas Europeans studies identify prevalence rate ranging from 2% to10% ***(McCord and Clouse, 1981).*** The gender ratio of GERD show nearly equal proportion of affected men and women, but a male predominance occurs in esophagitis and Barrett's esophagus. Increasing age is important factor in prevalence of GERD complications, probably the result of cumulative acid injury over time to esophagus ***(Johnson and Fennetry, 2004).***

Studies suggest that many patients with H-pylori induced gastritis have involvement of both the antrum and corpus decreasing parietal cell mass, reducing acid secretions no

elevating gastric PH. (El-serage HB,Sonnenberg A 1998) This may have a protective effect on esophageal mucosa in patients susceptible to GERD. Additionally, the epidemic increase in obesity may be another contributing factor for GERD ***(Mokdad et al., 2001).***

Along with environmental factor, the epidemiology of GERD may be affected by genetics. Families clustering of GERD and its complications, especially Barrett's esophagitis have been reported ***(Romero et al., 1997).*** The genetic mechanisms are unknown but may be related to smooth muscle disorder associated with hiatal hernia, lower esophageal sphincter (LES) pressure and impaired esophageal motility ***(Orenstein et al., 2002).***

Health care impact

Although rarely a cause of death, GERD is associated with considerable morbidity and complications such as esophageal ulceration (5%), peptic stricture (4%to 20%) and Barrett's esophagitis (8%to20%) ***(Johnson and Fennetry, 2004).*** Not surprisingly the burden of GERD on health care use is great. In study using national ambulatory medical care survey for year 2000, heartburn and dyspepsia were identified as the fifth most gastrointestinal complaint, prompting more than 1.8 million outpatient visits. Abdominal pain was the leading outpatient gastrointestinal diagnosis followed closely by GERD with 4.5 million visits ***(Edwards et al., 1992).***

Pathogenesis

The pathogenesis of GERD is complex, resulting from an imbalance between defensive factors protecting the esophagus (antireflux barriers, esophageal acid clearance, tissue resistance) and aggressive factors from stomach (gastric acidity, volume, and duodenal content).

Antireflux Barriers

The first tier of the three-tiered esophageal defense against acid damage consists of the antireflux barriers. This is an anatomically complex region including the intrinsic LES, diaphragmatic crura, and the intra-abdominal location of the LES, the phrenoesophageal ligaments, and the acute angle of His (fig. 1).

The LES involves the distal 3 to 4 cm of the esophagus and at rest is tonically contracted ***(Liebermann-Nleffert et al., 1979).*** It is the major component of the antireflux barrier, being capable of preventing reflux even when completely displaced from the diaphragmatic crura by a hiatal hernia ***(Sloan et al., 1992).***

The proximal LES border is normally 1.5 to 2 cm above the squamocolumnar junction, whereas the distal segment, about 2 cm in length, lies within the abdominal cavity. This location maintains gastro esophageal competence during intra-abdominal pressure events. Resting LES pressure ranges from 10 to 30 mm Hg with a generous reserve capacity, as only a pressure of 5 to 10 mm Hg is necessary to prevent GERD ***(Dodds et al., 1981).*** The LES maintains a high pressure zone