An-Najah National University

Faculty of Graduate Studies

UPPER GASTROINTESTINAL COMPLICATIONS AND TREATMENT AMONG PATIENTS WITH CHRONIC DISEASES: A CROSS SECTIONAL STUDY FROM PALESTINE

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Dedication

First, I dedicate this project to God Almighty, my creator, my strong pillar, and my source of inspiration.

I dedicate this to my wonderful, deeply missed Mom. Forever you will remain in my soul. To my rock and backbone from the start of my educational journey, my beloved husband and best friend,

Dr. Montaser,

to my lovely daughter Nada.

To my whole family, thank you all.

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Declaration

I, the undersigned, declare that I submitted the thesis entitled:

UPPER GASTROINTESTINAL COMPLICATIONS AND TREATMENT AMONG PATIENTS WITH CHRONIC DISEASES: A CROSS SECTIONAL STUDY FROM PALESTINE

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Deema Mahmoud Mustafa Tu'meh

Signature: _____

Date: 23/10/2022

Table of Contents

List of Tables

List of Figures

List of Appendices

UPPER GASTROINTESTINAL COMPLICATIONS AND TREATMENT AMONG PATIENTS WITH CHRONIC DISEASES: A CROSS SECTIONAL STUDY FROM PALESTINE

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Abstract

Background: Most people, older than 60, have at least one chronic disease. Therefore, these people have no choice but to use, multiple drugs. Gastrointestinal complications occur because of the harmful effects of these chronic drugs on the stomach.

Objectives: The study has assessed the prevalence of patients taking chronic drugs and suffering from upper gastrointestinal complications, the severity of these symptoms, and their taking of any gastro-protective drugs or not.

Methodology: This is a cross-sectional study. A questionnaire was developed and administered format outpatient clinics at a specialized hospital. Patients with chronic diseases who were taking at least one medication were included in the study. A form was used for data collection. The Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) was used to evaluate the severity of the upper gastrointestinal symptoms. Statistical analysis was performed, using the Statistical Package for Social Sciences (SPSS) version 21.

Results: A total of 400 patients with chronic diseases and using multiple medications participated in the study. Of these 53.8% were females and 56% were married, 58.5% were unemployed, and 70% were non- smokers.The mean age was 54.7±17.5. The most common comorbid diseases among the patients were diabetes, hypertension, and arthritis: 44.3%, 38%, and 27.3%, respectively. Most patients used between 2 and 4 medications daily. The most commonly used medication was aspirin. It was used by 50%, followed by atorvastatin, bisoprolol, and insulin: 29.5%, 25%, and 20.3%, respectively. Among the 400 participants, 362 (90.5%) suffered from upper gastrointestinal side effects like indigestion (66%), heartburn (77.5%), nausea (49.3%), and regurgitation (52.3%). Based on SF-LDQ scoring, of the 400 respondents, 235(58.8%), 109(27.3%) and 18(4.5%) suffered from mild, moderate and severe

dyspepsia, respectively. In addition, 38 (9.5%) had no dyspepsia. About 81.3% of participants were prescribed gastro-protective medications. Proton pump inhibitors were the most prescribed group for 209 (52.3%) patients. Older age, marriage health insurance, education, smoking and ≥ 5 medications were all associated with a higher possibility of having dyspepsia; (p-value <0.05).

Conclusion: Upper gastrointestinal complications among patients with chronic diseases were very common. Fortunately, the symptoms were mild in most cases. The risk increased with age and with the use of high number of medications. The use of gastro-protective agents, when needed, is important.

Keywords: Chronic disease; upper gastrointestinal side effects; stomach irritation; dyspepsia;Palestine

Chapter one
Background and literature review

1.1 Background

In recent years, the number of chronic diseases has increased as a consequence of the increased number of elderly people and life style [1]. In addition, it is noticed that older population is more susceptible to multiple drug therapy [2]. For example, in England, the number of medications for each patient had a mean of 11.9 in 2001 and increased to 18.3 in 2011 for 53.8% of patients above 65[3].

In a study from Palestine among patients ≥ 60 years old, many patients had multiple chronic conditions with a mean number of 2.33 diseases per patient. The most common diseases were cardiovascular (mainly hypertension; 54%), followed by endocrine conditions (mainly diabetes; 38.2%), followed by musculoskeletal conditions (mainly arthritis; 13.7%). Furthermore, the average number of medications per patient was 4.54, including different types of medications including prescribed and over the counter. The maximum number for medications prescribed for one patient was 17 [4].

The gastrointestinal tract, especially the stomach, has protective defense mechanisms that can withstand the harmful effects, but chronic exposure is the problem. The mucosal lining of the stomach, the generation of prostaglandin and the repair effect are the main protective mechanisms. Some drugs like aspirin and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) can inhibit the synthesis of prostaglandins by inhibiting the cyclooxygenase enzyme and so the mucosal defense. In addition, chronic use of any drug may produce cytotoxic compounds that irritate the mucosal lining of the stomach and cause dyspepsia and ulcers. This condition almost always happens in the elderly who take multiple medications including pain relievers and aspirin [5].

To reduce these effects, some patients take agents that block acid secretion and enhance repairing like proton pump inhibitor which block the acid production. Other medications that reduce the amount of acid release in to the stomach are H2 blockers which reduce gastritis pain and improve healing. In addition, agents that neutralize stomach acidity like bicarbonates are useful [6].

1.1.1 Gastrointestinal defense mechanisms

The gastrointestinal tract considers a tube with muscular cells, which nearly reach 9 meters. The important role of the gastrointestinal tract is food digestion, absorption, and excretion of unimportant products. Following the oral administration of any material (food or drug), it passes through the esophagus and then to the stomach (upper gastrointestinal tract), this process is compromised with peristaltic contractions. The stomach usually acts as the precursor reservoir for ingested materials before they go to the duodenum and lower gastrointestinal tract [7].

GI function is regulated by hormones as well as by the autonomic nervous system (ANS). Entero- endocrine hormones are buried substantially by the stomach and duodenum. As ingested food and fluids move through the GI tract, these hormones similar as gastrin, secretin, cholecystokinin(CCK), and gastric inhibitory peptide(GIP)) are released to either stimulate or inhibit peristalsis, and to beget substances that grease digestion to be buried. For illustration, gastrin stimulates gastric juice Product and smooth muscle compression in the stomach, small bowel, and large intestine, and controls the pyloric sphincter,CCK also facilitates digestion by relaxing the hepatopancreatic ampulla, which allows corrosiveness and pancreatic authorities to flow into the duodenum. [8]

.Secretin is released in the duodenum and small intestine and leads to Product of bicarbonate, which neutralizes the acidity of chyme, corrosiveness product by the liver, and inhibits gastric motility to decelerate digestion and gastric evacuating. GID also acts to drop gastric motility.[9]

The ANS includes nerves that are both extrinsic and intrinsic to the gastrointestinal tract . Extrinsic nerves, include sympathetic and parasympathetic, are distributed through the GI tract. Intrinsic (enteric) nerves are grouped into multiple nerve networks including the myenteric and submucosal plexuses. Intrinsic nerves integrate input from the GI tract and extrinsic nerves to facilitate the GI motility, blood flow, and secretions. Gastric tumors that decrease production of gastric inhibitory peptide (GIP) may lead to gastric stasis, nausea and emesis, and anorexi.[10]

GI tract organs admit arterial blood from the esophageal, gastric, celiac, hepatic, and superior mesenteric highways. Venous drainage from the bowel empties into the hepatic

portal system and, latterly, the liver. This system allows nutrients and other composites to be reused by the liver before entering the general rotation via the hepatic tone.[11]

The stomach usually secret nearly 2.5 liters of gastric juice every day, the main component is proenzymes like prorennin and pepsinogen which are produced by the peptic cells, also hydrochloric acid and some intrinsic factors secreted by the parietal cells. Acid production is very important in the proteolytic digestion of food, drugs and for pathogen killing [12].

The four distinct concentric layers of the gut wall are the mucosa, the submucosa, the muscularis externa, and either the adventitia or the serosa . The mucosa layer and the innermost layer of the gut wall, lines the entire GI tract and consists of epithelium, lamina propria, and muscularis mucosa. The mucosal epithelium is differentiated along the GI tract; tissue specialization relates with the regional function of the tract. At the upper and lower ends of the GI tract (the mouth, esophagus, and anal canal) the mucosal epithelium is protective and composed of stratified squamous epithelial cells. [13]

On the other hand, the mucosal epithelium in the stomach, small intestine, and colon are composed of simple columnar or glandular epithelial cells. The cells in these regions secrete mucous, enzymes, and other biochemicals that either protect the mucosa or aid in digestion. The gastrointestinal mucosa is considered the main defense mechanism to protect the epithelial cells from endogenous substances like low PH and gastric acids and exogenous substances like chemicals and foodstuffs. Each plays an important role in this defense.[14]

The lamina propria and muscularis mucosa are outside the mucosal epithelium. The lamina propria contain connective tissue, as well as blood and lymphatic vessels that reach nutrients to the mucosal epithelium, transfer hormones secreted by the endocrine epithelium, and absorb essential end products of digestion from the lumen of the GI tract. In addition, the lamina propria is infiltrated with lymphocytes and lymph nodules, all known as the GALT that protect the GI tract wall from resident bacterial flora and any foreign substances or ingested pathogens. The tonsils, appendix, and Peyer's patches in the ileum are aggregates of lymph nodules that comprise GALT in the GI tract, and are part of the larger mucosal-associated lymphoid tissue (MALT) that contribute 50% of the body's total immunity and 70% of antibody production.[15]

The premucosal layer is responsible for mucus secretion and HCO3- which trapped in the mucosa, making a gel like barrier, the mucosal layer regulates the intracellular PH with ion transporter and enzyme activities, and the submucosal plays an important role in regulation of blood flow through afferent nerves and mediator release. The submucosa is a connective tissue layer that lies outside of also it supports the mucosa, furthermore the submucosa layer compromise blood vessels, lymphatic vessels, submucosal glands, and Meissner's (submucosal) plexus (a nerve network that influences the smooth muscle of the muscularis). [16]

After that, The next outer layer of the gut wall is the muscularis externa. In the mouth, pharynx, and upper esophagus the muscularis externa is composed of striated muscle cells in order to facilitate swallowing. In the rest of the GI tract the muscularis externa contains two smooth muscle layers: an inner circular layer and an outer longitudinal layer. Auerbach's (myenteric) plexus lies between the two layers, and this nerve network coordinates contractions of the layers resulting in rhythmic peristalsis. The outside layer of the gut wall that lies farthest from the lumen is the serosa. If the outermost layer is attached to surrounding tissue, it is adventitia, connective tissue that supports the organ it surrounds.[17]

The esophagus is nearly 10 inches (25 cm) long and traverses through the diaphragm . furthermore it connects the pharynx to the upper end of the stomach, and work to complete swallowing. The upper esophageal sphincter, the cricopharyngeal muscle, prevents entry of air into the esophagus through respiration. The lower esophageal sphincter, the cardiac sphincter, contribute as a barrier between the esophagus and stomach. The innermost esophageal surface is stratified squamous epithelium that protects the esophagus from trauma, and submucosal mucous glands that produce mucus facilitating the passage of food.[13]

The J-shaped stomach which lies below the diaphragm and has threeareas : the fundus, the body, and the antrum. The stomach is a temporary storage place that mixes food with water and gastric juices to generate chyme, breaks food physically and chemically, and controls release of the chyme into the small intestine through pyloric sphincter. Blood is supplied to the stomach by a branch of the celiac artery. Specialized cells located throughout the gastric mucosa produce various substances. For example, goblet cells is responsible for mucus secretion that protects the gastric mucosa. Parietal and

chief cells occur in the oxyntic and pyloric glands of gastric pits which lie in the fundus and the body of the stomach. Parietal cells make hydrochloric acid, which damage proteins and kills bacteria, as well as intrinsic factor necessary for the absorption of Vitamin B12. Chief cells are responsible for the secretion of pepsinogen, an enzyme precursor that is converted to the proteolytic enzyme, pepsin, in gastric juice.Pyloric glands contain the gastrin producing G cells and mucous cells.[18]

Furthermore, this mucosal defense is found in the esophageal, duodenal, and gastric tract; any disruption or break in these layers leads to peptic ulcers, gastro-oesophageal reflux disease and other severe injury caused by non-steroidal anti-inflammatory drugs(NSAIDs) [19].

Any changes in the acid secretions lead to peptic ulcers that are targeted by different drugs, the pH of the parietal cell secretions is less than 1, and the hydrogen ions concentration will be one million higher than that in plasma, to make this acid, chloride ions transported through canaliculi which links the gastric glands and the stomach. This process is attached to potassium production, which is then exchanged by hydrogen ions through K+_H+_ATPase (the proton pump). After that, in the cell, the carbonic anhydrase enzyme catalyzes the water and carbon dioxide combination to produce carbonic acid, which in order produces bicarbonate ions and hydrogen ions. Further exchange is for chloride ions through the basal membrane of the parietal cells [20].

Also there is multiple mediators that control the parietal cells production in direct or indirect manner, there are: histamine which considered an stimulatory local hormone, gastrin that is a stimulatory peptide hormone, acetylcholine which considered a stimulatory neurotransmitter, prostaglandins E2 and I2 that considered local hormones which inhibit acid secretion and finally, somatostatin which considered an inhibitory peptide hormone [21].

In addition, the main components of the gastric mucosa are prostaglandin E2 and PGI2. They play a main role in mucus and bicarbonate secretion, and in keeping the epithelial cell surface more hydrophobic with good blood flow [22].

On the other hand, the esophagus has a strong correlation with the stomach, and keeping them in normal condition is very important. The esophagus has two sphincters: the

upper, which is near the pharynx and prevents aspiration, and the lower, which is in contact with the stomach and contains smooth muscle that prevents gastric contents from refluxing into the esophagus. Any disruption of this mechanism, like inappropriate contraction or relaxation of the sphincter, leads to reflux and dysphagia [23].

Furthermore, dyspepsia is considered a problem in most patients; they suffer from pain or burning in the epigastric region, fullness sensation after meals or early satiety. This is related to multiple factors like smoking, sex, drugs, acute gastroenteritis, and H. pylori. However, the accurate pathophysiology is still not understood, but it mainly results from incorrect communication between the brain and gut due to changes in gut microbiota, mucosa, and immune function [24].

1.1.2 Chronic diseases and their influence on patient's life

Chronic disease has multiple definitions according to different policy, public health, academic and medical conditions. For example, according to the Centers for Disease Control (CDC), the following conditions are chronic diseases: cardiovascular disease, stroke, cancer, obesity, arthritis, and type 2 diabetes. However, the Centers for Medicare and Medicaid Services added 19 chronic conditions to the chronic disease list, like depression, HIV, and Alzheimer's disease [25].

According to the World Health Organization (WHO) report in 2020, chronic diseases caused 70% of all deaths in the world. WHO defines chronic diseases as a collective of disorders that include stroke, cancer, diabetes, heart disease, and chronic lung disorders. They also reported that 82% of these deaths occur in middle and low-income countries before reaching 70 years old. Furthermore, multiple risk factors, such as smoking, physical activity, alcohol, and an unhealthy diet, increase the occurrence of chronic diseases. Otherwise, they cost the government a lot, so WHO makes the control and prevention of them an urgent job and needs good cooperation and leadership [26].

The presence of chronic diseases increases with age. In America, 95% of people older than 65 years old and above have at least one chronic condition, but only 23% of young people have one or more chronic conditions. Also, age had an important role in developing multiple chronic disorders for the same patients. As an example, 62% of Americans above 65 years had more than one chronic disease, but 5% of children had

more than one chronic disease. On the other hand, men had a lower percentage than women, 40% for men and 50% for women [27].

According to the Health Annual Report on 2020, the population of Palestine was 5,101,152. Among them, 3.05 million were in the West Bank with a percent of 59.9% of the Palestinian population and 2.04 million in the Gaza Strip with a percent of 40.1%. The Palestinian population is considered a young community as only 3.3% of Palestinians are over 65 years old, with a life expectancy of 74.1 years. Chronic diseases contribute to a risk factor for deaths. Of all the deaths in Palestine in 2020, 24.7% were due to cardiovascular diseases, 14.6% due to diabetes mellitus, 10.7% due to cerebrovascular diseases, and 1.6% due to chronic obstructive pulmonary disease [28].

On the other hand, 80% of deaths, which are caused by chronic disease, will be in developing and low-income countries, while the rest of the deaths (20% only) will occur in rich countries.. In addition, the rates of deaths from these preventable diseases occur mainly among 30-60 years old in low and middle-income countries compared with high-income countries. Therefore, there is a special new effort concerned to reduce deaths caused by Non-communicable diseases through those who are worried about international public health. The main effort aims to minimize the deaths caused by chronic disease by 2% per year; this will save 36 million deaths by 2015. A further advantage of this goal will conserve nearly 500 million years of life between 2006 and 2015, and most of these preserved deaths and these protected life –years will happen in low and middle-income countries, mainly among older people [29].

Nowadays, many efforts were concerned to determine the burden of chronic diseases and minimize them, the World Bank as an example uses its exchequer to develop prevention and control efforts in low-income countries. Both the UK's Department for International Development and AusAID (the Australian Government's overseas aid program) implement in their strategic documents the importance of chronic diseases, this effort translated to financial support and corroboration for these countries. Global agencies, ranging from the World Health Organization and the Food and Agriculture Organization to the World Trade Organization and World Bank, must be incorporated and help the global policies which as a result determine and reduce the development of chronic diseases, especially in neglected public health in developing countries. Despite this international effort, many low and middle-income countries still improving plans to

control chronic diseases. As an example, India determines small funds for programs concerned with the prevention of multiple chronic diseases like cardiovascular disease, diabetes, and stroke. Furthermore, Vietnam has improved different plans from outside donors to prevent, and control the chronic diseases, Pakistan improved major public health programmed in 2003 which implements a national plan on Non-communicable Diseases [30].

Multiple processes in our bodies produce harmful compounds called free radicals, like breathing, digesting food, drug metabolism, and converting fats into energy. These Free radicals convert into a non-toxic compound in our bodies by a natural antioxidant mechanism. If this system not working well or is over-saturated, the free radical will accumulate and trigger harmful processes in the body, a reaction can damage the cell membrane, inhibit the normal cell division, block the energy production, damage deoxyribonucleic acid, and prevent the action of major enzymes and the necessary processes in the cell, which in order develop oxidative stress. The new lifestyle associated with low physical activities, unhealthy food, heavy meals, air pollution, food additives, and exposure to multiple chemicals mainly pesticides can improve oxidative stress. These excessive amounts of free radicals lead to cell damage and apoptosis which as a result incorporated with multiple metabolic and chronic diseases, cancer, stroke, myocardial infarction, diabetes, and other conditions [31].

Many studies connected the influence of chronic diseases on people's quality of life. They reported that there is a significant influence on three domains (psychological, social functioning, and physical) [32].

The quality of life in people with chronic disease differs with age, and young adults are mainly affected. Young adults are especially affected by chronic diseases because they affect their mobility and as a result affect their functional status, physical activities, emotional feelings and affect their self-confidence because of their need and dependence on other people in order to help them, and this will be incorporated with unhappiness which reduces the quality of life, on the other hand, older people usually accept the chronic disease and this will not decrease the quality of life compared with younger people [33].

On the other hand, Patient education is important in many disciplines as a valid component of chronic disease control, education teaches the patient about the chronic disease and its available treatment, the patient who receives instruction is presumed to be in a better in his own health care control and, as a result maximize the therapeutic benefit. However, a patient education program prepared to help patients cope with their unique self-management plan is much more likely to improve the course of chronic disease than is a standard medical facts and treatment rules which is famous for hypertensive, or all diabetics, or all asthmatics should know.[34]

1.1.3 Medications used in chronic diseases

A study examined the drugs prescribed for chronic diseases among adults. Nearly 1/3 of non-elderly adults had one chronic disease at least and needed 2/3 of the drugs prescribed. However, among the elderly, 36% had more than two chronic diseases and needed 57% of the drug consumption [35].

According to recent studies, it has been shown that cardiovascular drugs like (Beta blockers, statin, ACE-inhibitors, warfarin and clopidogrel) were used largely with the highest percentage (26.7%), followed by analgesics and NSAIDs with a percent of (20.8%), then hematopoietic drugs like (darbepoetin alfa, Aransep, ancestim and epoetin alfa) with a percent of (14.8%), followed by gastrointestinal drugs (12%), then endocrine drugs, diuretics, vitamins, respiratory drugs, psychiatric drugs, CNS drugs, antibiotics, genitourinary drugs, dermatologic drugs, ophthalmic drugs and otic drugs with the least percent (0.9%) [36].

NSAIDs are usually called aspirin-like drugs, most of them inhibit cyclooxygenase enzymes (both COX 1 and COX2) which are responsible for prostaglandin synthesis and are called traditional NSAIDs, while selective ones inhibit only COX2 which are called coxibs. Furthermore, the inhibition of COX2 is responsible for the anti-inflammatory, analgesic, and antipyretic effects; however, the harmful side effects of these drugs are related to COX1 inhibition [37].

Aspirin, naproxen, paracetamol, indomethacin, ibuprofen, and piroxicam are considered the most important NSAIDs. Celecoxib and etoricoxib were considered selective COX2 inhibitors [38].

Using NSAIDs to treat a specific disease that needs high doses, will increase the risk of unwanted side effects, particularly gastrointestinal tract complications, also liver, spleen, kidney, bone marrow, and blood are adversely affected. Because all NSAIDs inhibit prostaglandin synthesis which is involved in platelet aggregation, renal vascular, gastric cytoprotection, and labor induction, they all share the same unwanted side effects [39].

The main side effect is gastrointestinal tract complications including (dyspepsia, nausea, vomiting, constipation, gastric bleeding, and ulceration), which can lead to perforation and hemorrhage. This effect mainly resulted from the inhibition of gastric COX1 [40].

On the other hand, taking selective COX2 inhibitors will give anti-inflammatory in addition to analgesic effects but with minimum gastric damage. Taking oral prostaglandins analogs like misoprostol with these medications will decrease the gastric damage produced by insufficient prostaglandins [41].

NSAIDs also caused skin reactions with unknown mechanism, reversible renal insufficiency, especially in patients with compromised renal function, and cardiovascular side effects (like hypertension, stroke, and myocardial infarction) which is related to COX2 inhibitors, they also cause nephropathy after a high dose regime with long term use, also they cause liver diseases, bone marrow suppression, and bronchospasm. Furthermore, all NSAIDs prolong bleeding by inhibiting of platelet aggregation except selective COX2 [42].

Coxibs are usually used for individuals whose treatment with the traditional NSAIDs induces severe gastrointestinal complications, however, these complications still occur but they can improve the healing of previous ulcers. During the treatment with NSAIDs, cardiovascular risk should be evaluated [43].

Aspirin (acetylsalicylic acid) consider the oldest NSAID; it works by inhibiting both COX 1 and COX 2 irreversibly. It can inhibit platelet aggregation as well as its anti-inflammatory effect, while its platelet aggregation is long-lasting due to its irreversible action. 75 mg/day is the required aspirin dose for platelet aggregation inhibition, so it is recommended to take aspirin daily even when there is no risk as primary prevention, this criteria will increase the incidence of gastrointestinal complications. large doses of

aspirin can induce dizziness, deafness, and tinnitus, also aspirin is related to a rare disorder called Reyes syndrome in children following acute viral infections [44].

Aspirin can interact with some concomitant medications, it displays warfarin from protein binding sites on plasma that will increase the warfarin effect, in addition, aspirin antagonizes some uricosuric agents and antihypertensive drugs, and it should not use in gout because low doses of aspirin decrease urate excretions [45].

Paracetamol or acetaminophen is a widely used medication as a non-narcotic analgesic and antipyretic agent over the counter, this excellent effect is resulted from the inhibition of prostaglandin synthesis in the CNS, despite their weak anti-inflammatory effect. The inhibition occurs mainly on CNS COX enzymes, so it does not show any gastric or platelet adverse effect [46].

To treat dyslipidemia, statin drugs almost used (also called HMG-COA reductase inhibitors), which are considered the rate-limiting enzyme through cholesterol production, simvastatin, and pravastatin are reversible and specific for HMG-COA reductase inhibition, while rosuvastatin and atorvastatin are long-acting inhibitors. They mainly reduce LDL, and triglyceride and increase HDL. Statin is also used as an antithrombotic agent, fibrinolysis, immune suppression, and protection against sepsis. Also, statins usually are tolerated with mild side effects like myalgia, insomnia, rash, gastrointestinal side effects, liver problems, and some rash. There are some rare side effects including muscle damage or myositis (in severe cases called rhabdomyolysis) and angioedema, myositis also occurs with other lipid-lowering agents called fibrates, these agents reduce circulating LDL and increase HDL but less than statins. Fibrates include bezafibrate, gemfibrozil, ciprofibrate, fenofibrate, and colifibrate, they are sometimes used in combination with other lipid-lowering drugs in severe resistant conditions, but this increase the risk of unwanted side effects [47].

1.1.4 Polypharmacy and Adverse Drug Reaction

There is a high and increasing percentage of people who have been prescribed drugs for their chronic conditions especially the elderly (often termed polypharmacy), While polypharmacy usually defined as taking five medications or more (including OTC and complementary medications), another definition would be who at least taking one drug that is not clinically indicated because of lack of indication, effectiveness or duplication

of another medication, so it is very import to minimize the inappropriate medications, and to emphasize using appropriate medications. Aging patients with a high risk of co-morbidity (having two or more chronic conditions) would increase the risk of using multiple medications. The main and cutoff point is that using more than 5 medications would increase the risk of Adverse Drug Reactions, especially in older adults [48].

There are different definitions for Adverse Drug Reactions, one defines it as a harmful or unwanted reaction, caused by an intervention correlate with the medicinal product, it can presage danger from another use of the drug in the future, or changing of the dosage regimen, or removing of the drug. Other definitions, including a medication error and drug abuse or misuse [49].

The main classification of adverse drug reactions according to Rawlins and Thompson, divided the drug reactions into two types: type A reactions and type B reactions. Type A reactions are mainly characterized as the excess manifestation of the pharmacological drug action (augmentation), also there are dose-dependent, reversible reactions, and less fatal (often called Pharmacological reactions). On the other hand, type B reactions are uncommon, unpredictable, dose-independent, irreversible and can be fatal (often called idiosyncratic) [49].

Type A reactions contribute about 80% of all reactions, and they are less severe and not related to fatal conditions compared to type B reactions. In addition, they can result from primary or secondary pharmacological reactions of the drug, there are multiple factors related to type A reactions including pharmacokinetics or pharmacodynamics, dose, different drug formulations, drug-drug interactions, and finally food- drug interactions. So as a result type A reactions occur when there is a high level of drug concentrated on plasma and tissue which surpasses the acceptable therapeutic window [50].

As concluded, the people who are highly affected by type A reactions will suffer from impairment of clearance of the drug, or high sensitivity resulting from diseases, aging, concomitant medications, concomitant food, or some polymorphism or combination of all [51].

As result polypharmacy or polytherapy individuals have a likelihood of developing type A reactions, as increasing the number of drugs will increase the chance of the interactions, but unfortunately, this problem has largely appeared in younger patients with multiple chronic conditions and taking multiple medications [52].

The occurrence of multiple diseases and chronic conditions often is related to age, and multiple conditions may present in the same individual. So as a result, the elderly are the most people exposed to multiple medications, 90% of them in low and middle-income countries were taken at least one drug, also the occurrence of adverse drug reactions will increase with using multiple medications [53].

As the elderly use multiple medications, there is a high chance for drug-drug interactions, so in some countries, they used computer alerts program in hospitals for possible drug-drug interactions. Increasing age will change the pharmacokinetic process in the body, the rate and extent of the absorption in the gastrointestinal extract will decrease, and the gastrointestinal motility, acid secretion, gastric emptying, and blood flow also will decrease the absorption. Furthermore, increasing age will increase the adipose tissue and decrease the body water, so this will increase the distribution of lipid-soluble drugs will increase, in contrast, the distribution of lipid insoluble drugs will decrease [54].

Further changes with increasing age, there is a minimal decrease in serum albumin, the further decrease will happen with poor nutrition, immobility, and some diseases, so this increase the percent of free drugs(but this always overcame by increased clearance), which as a result needs dose adjustment, especially in low therapeutic index drugs [55].

In addition, the elderly who have surgeries or injuries will have a slow metabolizing enzyme activity, which resulted in a higher drug concentration in the blood and increased the adverse drug reaction, also the clearance of high hepatic extraction ratio drugs will decrease because the hepatic blood flow in healthy elderly is 35% lower than young individuals [56].

In addition, every decade, the glomerular filtration rate will decrease by 8ml/min, so it will reduce by 40-50% with the age of 70 years old, so if the elderly take the usual dose of the drug, it will accumulate in a toxic manner, especially drugs that depend on renal

excretion. on the other hand, multiple drugs with use will negatively affect renal function, so it is important to monitor the drug level in the body [57].

Other changes in pharmacodynamics in the elderly occur including sensitivity, some drugs will have high sensitivity, while others will have low sensitivity[58]. However, despite all these changes, female gender, self-medication, unnecessary or interacting medications, drugs with contraindications, and multiple chronic diseases will increase the incidence of adverse drug reactions [59].

Therefore, the appropriate medications must be emphasized from time to time in each patient especially when new treatments were initiated, and when the patients move to other health care professionals. Beers criteria were developed to identify inappropriate medications in older individuals, these criteria provide a list of Potentially Inappropriate Medications, intended for adults above 65 years old and used by researchers, consumers, pharmacists, and other healthcare providers. The main purpose of American Geriatric Society (AGS) Beers Criteria is to maximize medication selection, improve the education level of clinicians and patients, minimize the unwanted adverse drug reaction and it is important for older adults in the evaluation of the quality of care, cost, and other matters related to drug use [60].

So the healthcare providers should prescribe drugs more carefully to avoid risks associated with multiple medications, like drug-drug interaction, inappropriate medications, drug side effects, drug overdose, drug underdoes, drug-disease interaction, non-adherence, and inappropriate dosing regimen [61].

Drug utilization reviews by the pharmacist are important because they will optimize the regimen and identify the inappropriate drugs, after that an intervention is required, for example, the pharmacist will contact the physician who prescribed the drug. Also, it is important to ensure that the patient especially the elderly understands their medication regimen, to avoid problems related to nonadherence, medication error, and unintentional dose changes. So elderly patients with memory loss should frequently be evaluated [62].

In some high-income countries, all the healthcare providers use electronic prescribing or computerized physician order entry (CPOE) system, which provides information related to dosing, drug-drug interactions, and contraindicated drugs [63].

There are multiple quality problems related to drugs that should be minimized to achieve the desired outcome of medications. The first of them is underdoes, it defined as failure of the medication to provide a favorable outcome, secondly one is overdose, it defined as the potential harm from medication use exceeding the benefit or when there is no need for the drug. Thirdly, misuse happened when an appropriate drug has been used but a problem happened and prevents the desired benefits of the drug [64].

1.1.5 Influence of drugs on the upper gastrointestinal tract

The number of elderly people above 60 years old worldwide in 1950 was 205 million, and the expected number in 2050 is 2 billion, so the number of drugs used to treat chronic diseases will increase because the elderly use drugs three more times than young people, and therefore the influence of these drugs on the gastrointestinal tract will increase [65].

Dyspepsia and heartburn are considered the main consequences of chronic drug use. Recent studies show that the prevalence of dyspepsia associated with aspirin and NSAIDs annually was 15%, upper GI symptoms including dyspepsia also occur in patients whose taking NSAIDs—at a relative risk of about 1.5 to 2 compared with that in patients do not use NSAID [66]. Heartburn, also recognized as a retrosternal burning sensation, it had a prevalence among the elderly with aspirin and NSAIDs of 12.9%. Furthermore, aspirin was considered a risk factor of dyspepsia and/or heartburn with (OR = 1.6, 95% CI 1.2, 1.2, 2.2) and with NSAIDs (OR = 1.8, 95% CI 1.3, 2.6) [67].

There is some drugs related to gastrointestinal side effects like (Anticholinergic agents, Aspirin, Benzodiazepines, Beta-blockers , Bisphosphonates ,Calcium channel blockers, Chemotherapy, Dopamine, Estrogens, Iron salts, Narcotic analgesics, Nitrates, Nonsteroidal anti-inflammatory drugs, Potassium, Progesterone, Tetracyclines, Theophylline, Tricylic antidepressants, Zidovudine).[68]

Nausea is also considered a main side effect of many drugs like analgesics, cardiovascular medications, digoxin, antiarrhythmic drugs, antihypertensive, beta blockers, calcium-channel antagonists, hormonal preparations/therapies, oral antidiabetics and many more. It is defined as a precursor sensation of vomiting, a desire to expel stomach contents [69].

Dyspepsia and heartburn are usually associated with diseases with GERD (gastro esophageal reflux. Even though they are considered distinct problems, there is some overlap through them, which result in further complication in diagnosis. On the other hand, dyspepsia is not considered a fatal problem, but it will affect daily activities, as a result, it affect the societies and economics [70].

Non-selective NSAIDs including aspirin can damage the mucosal layer in the stomach by two mechanisms: firstly they can directly irritate the topical gastric epithelium layer, secondly by indirect way through systematic inhibition of endogenous prostaglandins synthesis. Using COX-2 selective inhibitors medications decreases the risk of ulcers and other problems compared to nonselective ones. However, using aspirin and selective COX-2 inhibitors will mask its ulcer-sparing benefits and thus increase its ulcer effect. Also using corticosteroids alone will not induce ulcers, but using corticosteroids with NSAIDs will double the risk of ulcers [71, 72].

Using multiple drugs is common in the elderly population (more than 60 years old). In a previous study, 17.3% of the elderly used five or more drugs, 11.7% used four drugs, 18.5% used three drugs, 24.3% used two drugs, and 28.2% used one drug. Furthermore, there was a significant correlation between the use of multiple drugs and the appearance of different side effects (p 0.05), indicating that the doctor should use the fewest drugs possible. [36]

Some carbonated beverages and other food like milk, spices, coffee, tea, and beer induced dyspepsia not ulcers. Ethanol use will induce mucosal damage to the stomach and may induce upper gastrointestinal tract bleeding. Stress alone is not considered a risk of ulcers, but using medications it induced ulcers, in addition, also ulcer patients will be highly affected by the stressful lifestyle [73].

1.1.6 Treatment usually used for gastrointestinal complications

Patients with gastrointestinal complications or at high risk should receive protective therapy like H2 receptor blockers, proton pump inhibitors, anti-acids, and misoprostol. This is preferred when the NSAIDS must be continued over the ulcer because it improves ulcer healing. Omeprazole is considered the most effective, but additional studies are needed [74].

Histamine H2 receptor antagonist prevent histamine actions in all H2 receptor sites competitively. Cimetidine, ranitidine, nizatidine, and famotidine are the main drugs in this family, the histamine receptors located in the basolateral membrane of the acid-secreting parietal cell are of the H_2 type ,and so are not inhibited by traditional H_1 antihistamines such as diphenhydramine. The attachment of H_2 receptors by histamine, released from mast cells and possibly other cells, activates adenylate cyclase, increasing intracellular concentrations of cyclic AMP. The increased levels of cyclic AMP will as a result activate the proton pump of the parietal cell, a hydrogen, potassium-ATPase, in order to secrete hydrogen ions against a large concentration gradient in exchange for potassium ions. H_2 blockers competitively and selectively prevent the binding of histamine to H_2 receptors, thereby reducing both intracellular concentrations of cyclic AMP and so the secretion of acid. These cells also contain receptors for gastrins (particularly G_{17} and G_{34}) also contain receptors for acetylcholine (muscarinic type), both increase the intracellular calcium then activating the cells , there appears to be an in vivo interaction between the cyclic AMP pathway (which activated by histamine) and the calcium pathway activated by gastrin or acetylcholine or both. [75]

After therapy with H_2 blockers is stopped , the secretion of acid rapidly increases to the state before the treatment, or slightly above it for a few days or weeks (called rebound hypersecretion). [76].

Proton pump inhibitors are also used to treat stomach problems, omeprazole was the first one, they can irreversibly inhibit the H+_K+ _ATPase pump, which is considered the terminal point through acid secretion, so as a result, they can decrease the production of both basal and stimulated acid secretion, but the important and main goal of their use is for the inhibition of gastric acid secretion, also they can prevent the secretion of histamine, gastrin, and pepsin as a result of the decreased amount of gastric juice. [77]

Proton pump inhibitors (PPIs) considered weak bases composed of two parts, a substituted pyridine with a primary pK_a of about 4.0, which allows selective accumulation in the secretory canaliculus of the parietal cell, and the second one is a benzimidazole with a second pK_a of about 1.0. PPIs are acid-activated prodrugs that convert to sulfenic acids that react by covalent bonds with one or more cysteines

accessible from the luminal surface of the ATPase. Because of irreversible covalent binding, their inhibitory effects last longer time than their plasma half-life. However, the short half-life of the drug in the blood and the needs for acid activation impair their efficacy in acid suppression, particularly at night. PPIs with longer half-life promise to prolong the acid suppression.. [78]

These drugs can reduce 90% of the amount of acid secretion produced by food or in basal conditions, furthermore they can improve gastric and duodenal ulcer healing. This family is used to treat peptic ulcers, dyspepsia, reflux oesophagitis, in the treatment of Helicobacter pylori infection, and in the treatment of Zollinger –Ellison syndrome (which is caused by tumors secreting gastrin). Other proton pump inhibitors are esomeprazole, pantoprazole, lansoprazole and rabeprazole [79].

Proton pump inhibitors (PPIs) are among the highest selling drug in the United States, produce more than $13.9 billion per year. PPIs are also used for treating dyspepsia and prophylaxis of peptic ulcers in the intensive care setting, and among high-risk patients who used aspirin, NSAIDs, antiplatelets and anticoagulants . There is multiple adverse effects of proton pump inhibitors (PPIs) like nutritional deficiencies (especially B12 and magnesium), acute interstitial nephritis , rebound acid hypersecretion, , gastric carcinoid tumor, cardiovascular risk with clopidogrel and PPI coprescription, bone fractures, enteric infections and pneumonia. [80]

In the treatment of gastrointestinal problems, Antacids are considered the simplest way, they can neutralize the acid in the stomach, and this will inhibit the activity of other peptic enzymes which need a pH of 5. Magnesium and aluminum salt are used widely as antacids, magnesium salt cause diarrhea whereas aluminum salts cause constipation, to treat this, a mixture of them is used to maintain the bowel function [81].

The most effective and economical antacid regimens for the treatment of ulcer disease should include tablets or liquid that have acid neutralising capacity of 400 mmol/day given at least an hour after meals. As a long term therapy, antacids appear to work, but need be taken in multiple daily doses, a regimen which is unlikely to meet with long term patient compliance. On the other hand, the prophylactic administration of antacid aiming to have gastric pH between 3.5 to 7.0 has resulted in significant reduction of bleeding due to stress associated ulcers and/or erosive haemorrhagic gastritis in

critically ill patients. Antacid therapy, however, is controversial in the management of nonulcer dyspepsia or nonsteroidal anti-inflammatory drug related upper gastrointestinal mucosal damage. Antacids have clear advantages and disadvantages when compared with agents that inhibit acid secretion. New proton pump inhibitors have certainly be super than antacids and even the H_2-receptor antagonists in many respects. However, the long term safety of antacids remains unsurpassed by any of the new antisecretory agents.[82]

There are multiple salts of magnesium, magnesium hydroxide is widely used and it is an insoluble powder, another salt is magnesium trisilicate, which react with gastric acid and forms magnesium chloride and colloidal silica. Magnesium carbonate is another salt [83].

Aluminum hydroxide gel produces aluminum chloride in the stomach, which can increase the pH to 4 and adsorb pepsin. The colloidal aluminum hydroxide can bind with phosphates through the gastrointestinal tract and enhance its excretion in feces, these results in a decrease in the number of phosphates that are excreted through the kidney, which is used in treating individuals who have chronic renal failure. Another formulation is hydrotalcite which contains aluminum and magnesium salts [84].

Alginates and simethicone are often added to antacids, and simethicone considered an antifoaming agents that can reduce bloating and flatulence. Alginates can increase the viscosity and attachment of the mucus to the mucosa layer [85].

Several antiemetic drugs were used, each one used in a specific condition but sometimes overlapped, in our situation dopamine antagonist drugs were widely used, phenothiazine family including chlorpromazine, perphenazine, prochlorperazine, and trifluoperazine are used to treat severe nausea and vomiting resulted from several causes. Furthermore, they work by antagonizing the D2 receptors in the Chemo Receptor Trigger Zone (CTZ), but they also can antagonize histamine and muscarinic receptors producing unwanted side effects like sedation and hypotension in addition to extrapyramidal symptoms [86].

Metoclopramide is also used to treat nausea and vomiting by blocking the D2 receptors in the CTZ, in addition to its effect peripherally on the gastrointestinal tract

(esophagitis, stomach, and intestine) by increasing its motility, so it is used not only to treat emesis but also for the gastrointestinal tract, hepatic and biliary disorders. It produces several unwanted side effects because it blocks the dopamine receptor in the central nervous system, including motor restlessness, fatigue, problems in movements, especially in young, involuntary twisting of the neck, and galactorrhea(results from increasing prolactin production) [87].

Domperidone is considered similar to metoclopramide in treating vomiting and gastrointestinal tract problems, but it cannot cross the blood-brain barrier [88].

The pharmacists should always ascertain the appropriateness of self-treatment and find for possible drug interactions or contraindications before recommending any OTC products for heartburn or other conditions,. Individuals with preexisting medical conditions and pregnant or lactating women should be advised to have recommendations from their primary health care provider prior to using any of these products. In addition, Patients less than 12 years of age should be referred to their doctors before taking any OTC product for heartburn relief.[89]

Patients with frequent episodes of heartburn or with recurrent gastrointestinal side effects should always be referred for further medical consultations to prevent further complications. People who use these OTC products should be informed their doctors if their symptoms worsen or show no signs of improvement after 14 days of self-treatment. It also is important to remind patients that these products should not be used for more than 14 days unless directed by a doctor. [90]

In addition to providing patients with information about the proper use and adverse effects associated with the use of these products , pharmacists can also tell the patients about the nonpharmacologic measures that may be beneficial in decreasing the incidence of heartburn, such as avoiding eating late at night or eating large meals, stopping smoking, decreasing weight , not exercising immediately after eating, avoiding foods and drinks that may aggravate or contribute to heartburn and avoiding lying down within 30 minutes after eating.there is some Dietary Habits should be avoided to reduce these complications like eating less than 2 hours before bedtime, eating large meals, eating citrus fruits, chocolate, peppermint, tomatoes, raw onions, garlic, black pepper, and fatty or spicy foods, drinking alcoholic beverages particularly

before bedtime and drinking beverages such as coffee, tea, citrus juices, and caffeinated or carbonated beverages[91]

1.2 Problem statement

Elderly patients usually have multiple diseases which need multiple medications either prescribed by the doctor or bought without a prescription [92]. Multiple side effects may appear especially upper gastrointestinal tract problems [36]. In a previous study, only 8% of patients with multiple drugs were prescribed anti-ulcer drugs, which improve gastrointestinal complications induced by drugs [93]. This study gives data about the prevalence of GI complications induced by chronic drug use and which drugs are most responsible for this.

1.3 Significance of study

This study was undertaken to determine the effect of chronic drugs in patients with polypharmacy on their stomachs.. To the best of our knowledge, this study is the first of its type in Palestine. Therefore, this study will present information about the relationship between chronic drugs used in chronic disease patients and the gastrointestinal complications and their treatment. In addition, this study is important for doctors to alarm them when they prescribe multiple medications and to insure the importance of gastro-protective drugs.

1.4 Objectives

General objective

The study aims to assess gastrointestinal complications (stomach irritation, ulcers, and dyspepsia) among patients with chronic diseases and what treatment they take for this in Palestine.

Specific objectives

1. To determine the percentage of patients who use chronic drugs and suffered from gastrointestinal complications

2. To identify the most common drugs that cause these gastrointestinal complications.

3. To explore the relevant factors, including sociodemographic and clinical factors, which may be associated with increasing the risk of GI complications,

4. To find out if they take any gastro-protective agents among their prescriptions and what they are.

1.5 Literature review

The current study's research aim, design, and methodological approach have been developed after a close understanding and analysis of the existing literature. This part reviews previous research and published data that is directly relevant to the research objectives. It involves the chronic diseases in Palestine, the gastrointestinal defense mechanisms, the effect of chronic drugs on these mechanisms, and the gastro-protective drugs used.

1.5.1 Chronic diseases and polypharmacy

Chronic conditions have become a huge public health problem throughout the world and are also developing rapidly in low-income countries such as Palestine as a result of changing behavior and lifestyle. Ischemic heart disease (IHD) and hypertension had the highest ratio of chronic diseases in both genders in Gaza and the West Bank. After that, cancer took place, including lung cancer in males and breast cancer in females, followed by respiratory tract disorders [94].

According to a study conducted in 2013 and 2014 in the West Bank and Jerusalem among older people > 60 years, 84% were nonsmokers, and 78% had a low income (less than 2500 NIS), 40 chronic conditions were reported, with cardiovascular, endocrine, and musculoskeletal conditions accounting for 66%, 40%, and 32%, respectively. This means the patient may have had more than one chronic disease, so multiple drugs were prescribed for the patients, with a mean of four medications [4].

Furthermore, between 1999 and 2003, chronic diseases were the leading cause of death in the Palestinian territories, accounting for 45% of all deaths. Acute myocardial infarction and cerebrovascular disease were the leading causes of death in men, while circulatory disease and diabetes mellitus were the leading causes of death in women [95].

According to the Palestinian Central Bureau of Statistics, Palestinians in Gaza were 21%, 35%, and 48% less likely to have diabetes, hypertension, and CVD than Palestinians in the West Bank, respectively; there is no data for Palestinians in Israel. In other words, living in Gaza was a protective factor. However, being a refugee or being married, engaged, divorced, or separated was a risk factor for diabetes and CVD. In addition, females were 60% more likely than males to have hypertension. Age also contributed to a significant risk factor for chronic disease (36 to 434 times greater in those aged 40–65 years compared with those aged 0–19 years) [96].

1.5.2 Gastrointestinal defense mechanisms

There are different mechanisms in the GIT (especially the stomach) to protect itself from any harmful injury, including bicarbonate production induced by prostaglandin E synthase, mucin, growth factors, and trefoil factors, which play an important role in gastric injury healing [97].

The pineal gland produces melatonin, which can limit the gastric mucosal injury and improve healing. It can also reduce the oxidative stress via scavenging the reactive oxygen species produced by chronic use of drugs and NSAIDs, thus contributing to its anti-inflammatory effect [98].

As a result, Reactive Oxygen Species (ROS) can damage the gastric mucosa via oxidizing the nucleotide and incorporating it into genomic DNA, which enhances DNA damage and fails the repair process. As a result, abnormal cell cycle signaling happens, in addition to age-related accumulation of damaged nucleotides [99].

Furthermore, the mucosal gel layer over the epithelial cell forms the first line defense mechanism that is rich in bicarbonates and has a pH of 6 to 8. The epithelial cell forms the second defense mechanism that is involved in maintaining the mucosal integrity. The specific characteristics of the apical membrane, the strong intercellular junction and the phospholipids attached to the surface of the membrane prevent the entrance of hydrogen ions into the mucosa [100].

Dyspepsia has different symptoms between patients and varies from epigastric discomfort, bloating, fullness, and nausea. Many people suffer from dyspepsia [101]. People with dyspepsia are treated with ulcer drugs empirically. NSAIDs, CCBs,

corticosteroids, ACE inhibitors, and methylxanthines all have dyspepsia-inducing effects [102].

1.5.3 The effect of chronic medications

In spite of the stomach's ability to resist many harmful exposures due to the good physiological defense by the mucous layer and the ability to repair any damage, in 1971 they confirmed that continuous exposure to some drugs like aspirin and NSAIDs can inhibit prostaglandin synthesis, which plays an important role in all gastrointestinal defense mechanisms and, as a result, develop ulcers or prevent healing [5].

NSAIDs' toxicity is produced from their ability to inhibit the cyclo-oxygenase enzyme which converts arachidonic acid to proinflammatory prostaglandins. There are two forms of this enzyme: COX-1 and COX-2. Conventional NSAIDs can inhibit both, but the anti-inflammatory effect of these drugs results from COX-2 inhibition, and the unwanted side effects, including GIT, result from COX-1 inhibition. Thus, selective COX-2 inhibitors have a 50% reduction in gastrointestinal toxicity and are widely used in bone disorders [103].

If the patient has previously had ulcers, NSAIDs can increase the risk of these effects by fourfold. They also produce soluble molecules that can facilitate the entrance of hydrogen ions and cause ulcers, which can result in a variety of toxic outcomes such as anemia due to iron deficiency, hypoalbuminemia, and protein-losing enteropathy [104].

1.5.4 Treatment of gastrointestinal side effects

Treating the cause is the main point. If these effects are induced by NSAIDs, then stopping or lowering the dose is the solution. If gastro protective agents are not used. However, in a study in 2001, more than 20% of the prescriptions contained one or more NSAIDs among the drugs. In contrast, during the analysis of the prescriptions, there was only 17% use of selective coxib and only 8% use of gastro protective agents with their medications, which is underutilization and induced a lot of gastric side effects [93].

There is a strong recommendation for gastro-protective drugs with chronic drug use or with NSAIDs in polypharmacy patients above 65 years old. The most common gastro-protective agents were misoprostol (a synthetic prostaglandin instead of the lost natural prostaglandins [105].

Proton pump inhibitors, such as omeprazole, lansoprazole, esomeprazole, dexlansoprazole, and pantoprazole, can also be prescribed or purchased over the counter. But chronic use of PPI in high doses may increase the incidence of fractures in different bones (hip, wrist, spine) and this can be minimized by using calcium supplements [106].

Furthermore, neutralizing agents can quickly relieve stomach pain and neutralize stomach acidity. Constipation and diarrhea are the main side effects [107].

Among the gastro-protective agents, histamine (H2) blockers can reduce the released amount of the acid and improve healing. They are also prescribed or OTC, including famotidine, cimetidine, and nizatidine [108].

Chapter Two
Methodology

2.1 Study design

This study was a cross-sectional questionnaire-based (face to face interview) study to measure the prevalence of upper gastrointestinal complications in patients using chronic drugs, the type of these complications, and which treatments were usually used in these cases. It was conducted between October 2021 to May 2022.

2.2 Study setting

Palestine consists of two geographically separated zones – the Gaza Strip and the West Bank – with a total population of about five million inhabitants. Nearly 61.5% live in the West Bank and 38.5% live in the Gaza strip. This study was conducted in Jenin city in the West Bank and included patients visiting medical clinics in Ibn Sina hospital. The clinics are for patients with internal diseases, and most of them are suffering from chronic diseases. The population of this study was patients of both genders with any chronic disease from outpatient clinics.

2.3 Sample size calculation and sampling procedure

The estimated sample size was 385 patients out of the eligible patients in the clinic, so we included 400 patients. An automated software program, Raosoft sample size calculator: (http://www.raosoft.com/samplesize.html) was used to calculate the required sample size for this study. The sample size needed for our study was calculated using 50% as a response distribution to achieve a confidence level of 95% and a margin of error of 5%. Convenience sampling was used to recruit participants.

2.4 Inclusion and exclusion criteria

The inclusion criteria were as follows: males and females, confirmed diagnosis of chronic diseases and using one or more chronic medications. The exclusion criteria were as follows: patients who do not have chronic diseases or do not use chronic medications for them, patients with current cancer treatment and pregnant women.

2.5 Data collection and management

Considering the importance of data standardization for the internal validity of a study, data collection was standardized by using a Data Collection Form (Appendix A) to gather information from questionnaires. The data included sex, age, the type of chronic disease, names and numbers of drugs taken, if the patient takes NSAIDs among their drugs, gastrointestinal complications, the severity of this complication, if gastro-protective treatment is taken, the type of gastro-protective treatment. To evaluate the severity, The Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) was used, the Short-Form Leeds Dyspepsia Questionnaire is a reliable (The Pearson coefficient for test reliability was 0.93), valid and responsive (it had a sensitivity of 77% and a specificity of 75%) self-completed outcome measure for quantifying the frequency and severity of dyspepsia symptoms [109]. It includes 9 validated questions, the questionnaire score lies between (0-32), as zero represents no dyspepsia, a score between (1-8) represents mild dyspepsia, a score of (9-15) represents moderate dyspepsia and a sore of (15-32) represents severe dyspepsia [70].

2.6 Ethical approval

All aspects of the study protocol, including access to and use of patients' clinical information, were authorized by the Institutional Review Boards (IRBs) and local health authorities before the initiation of this study. In addition, a verbal consent form was obtained from each patient (Appendix B).

2.7 Pilot study

A pilot study (30 participants) was conducted to test the tool, ensure the availability of the required data, estimate the time, and modify the data collection form, as appropriate. The patients participating in the pilot study were not included in the final analysis.

2.8 Statistical analysis

The Statistical Package for Social Sciences program version 21 (SPSS) was used to enter and analyze data. Data was expressed as mean ± SD for continuous variables and as frequencies (percentages) for categorical variables. Either the Chi-square or Fisher

exact test, as appropriate, was used to test for significance between categorical variables. A univariate analysis was conducted to determine the relationship between the prevalence of dyspepsia and the patients' characteristics. The significance level was set at p-value 0.05.

Chapter Three
Results

3.1 Sociodemographic data

Our study was a cross-sectional study that was conducted on 400 patients in Ibn Sina hospital, which is located in Jenin city in Palestine, who were diagnosed with chronic diseases and were using one or more chronic medications. Table 1 shows that more than half of the patients were females (53.8%) as in figure 1.A, with age between (14-85) as in figure 1.B, and a mean of 54.7±17.5 years old. The table also shows that (56%) of them were married, and the rest were widowed (24.3%), single (9.5%) or divorced (10.3%) as in figure 2.B. Moreover, 58.5% of our patients had secondary level of education or less (19.5% secondary, 22.5% primary, 16.5% precursory), a 36.3% were under graduates and 5.3% were post graduates as in figure 2.A. With regard to employment status, 58.5% were unemployed and the rest (41.3%) were employed as in figure 3.B, 5.5%% had a monthly income that was less than 400 Dinar, 17.8% had a monthly income of between 400 and 600 Dinar and 34% between 601 and 800 Dinar, 27.5% between 801 and 1000 Dinar, and 15.3% had a monthly income of more than 1000 Dinar as in figure 3.A.

Table 1 also shows that 68.5% had health insurance as in figure 4.B. According to the locality, 46.5% of our patients were living in village, 34.8% in city, and 18.8% in camps as in figure 4.A. Finally, 70.8% of the participants were not smoking, and the rest (29.3%) were smokers as in figure 4.C.

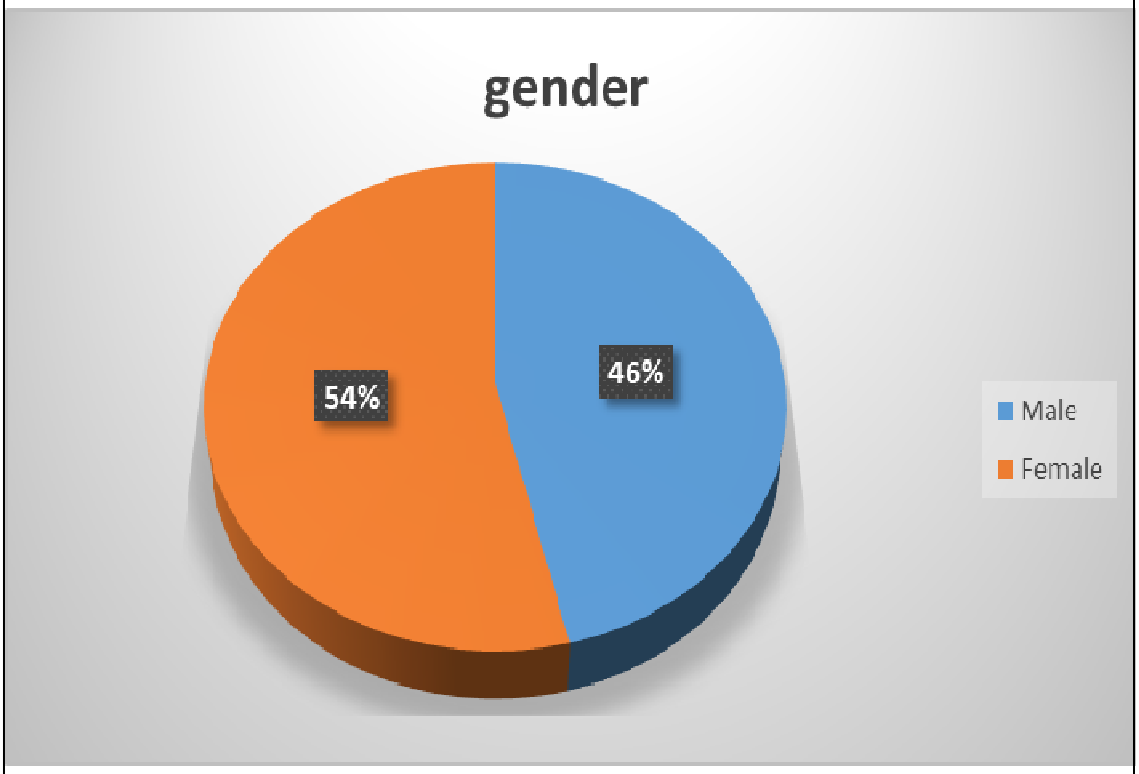
Table 1

Socio-demographic and clinical characteristics of the study sample

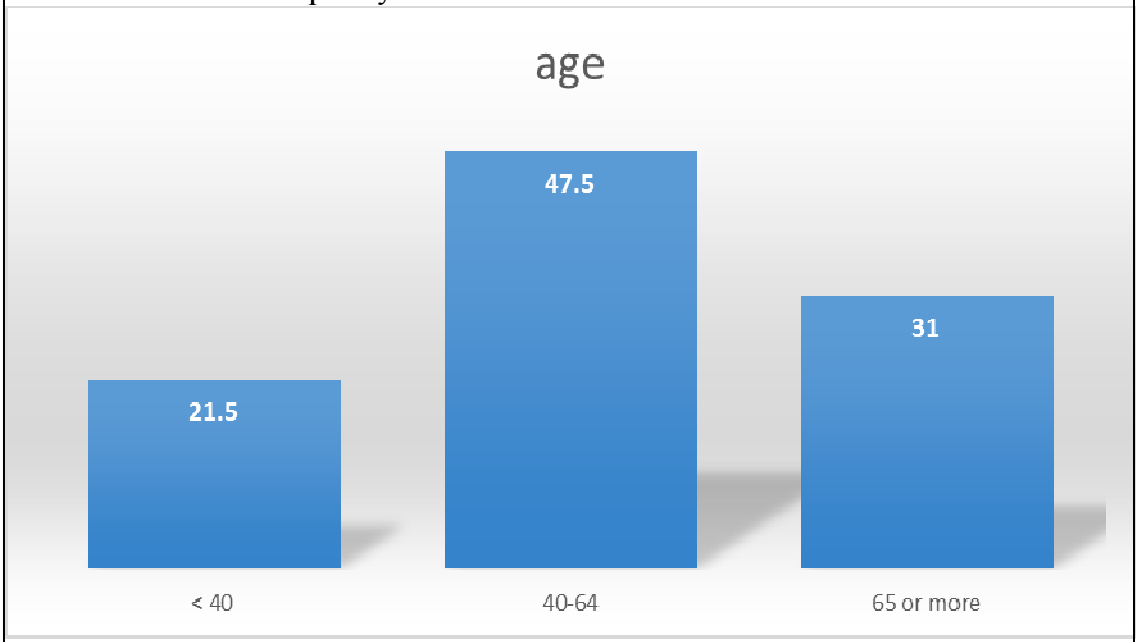
Socio-demographic Variables		**Frequency (%) N=400**
Gender	Male	185(46.2)
	Female	215(53.8)
Age	< 40	86(21.5%)
	40-64	190(47.5%)
	65 or more	124(31%)
	Mean	54.7250
	Standard deviation	17.49699
Educational status	Primary	90(22.5)
	Precursory	66(16.5)
	Secondary	78(19.5)
	Under graduated	145(36.2)
	Post graduated	21(5.3)
Social status	Single	38(9.5)
	Married	224(56.0)
	Divorced	41(10.3)
	Widower	97(24.2)
Income/month(Dinar)	less than 400	22(5.5)
	400-600	71(17.8)
	601-800	136(34.0)
	801-1000	110(27.5)
	more than 1000	61(15.2)
Employment status	Employed	165(41.4)
	Unemployed	234(58.6)
Locality	City	139(34.8)
	Village	186(46.5)
	Camp	75(18.7)
Health insurance	Don’t have insurance	126(31.5)
	Have insurance	274(68.5)
Smoking	Non smoker	283(70.8)
	Smoker	117(29.2)

Figure 1

Age disribution and gender frequency



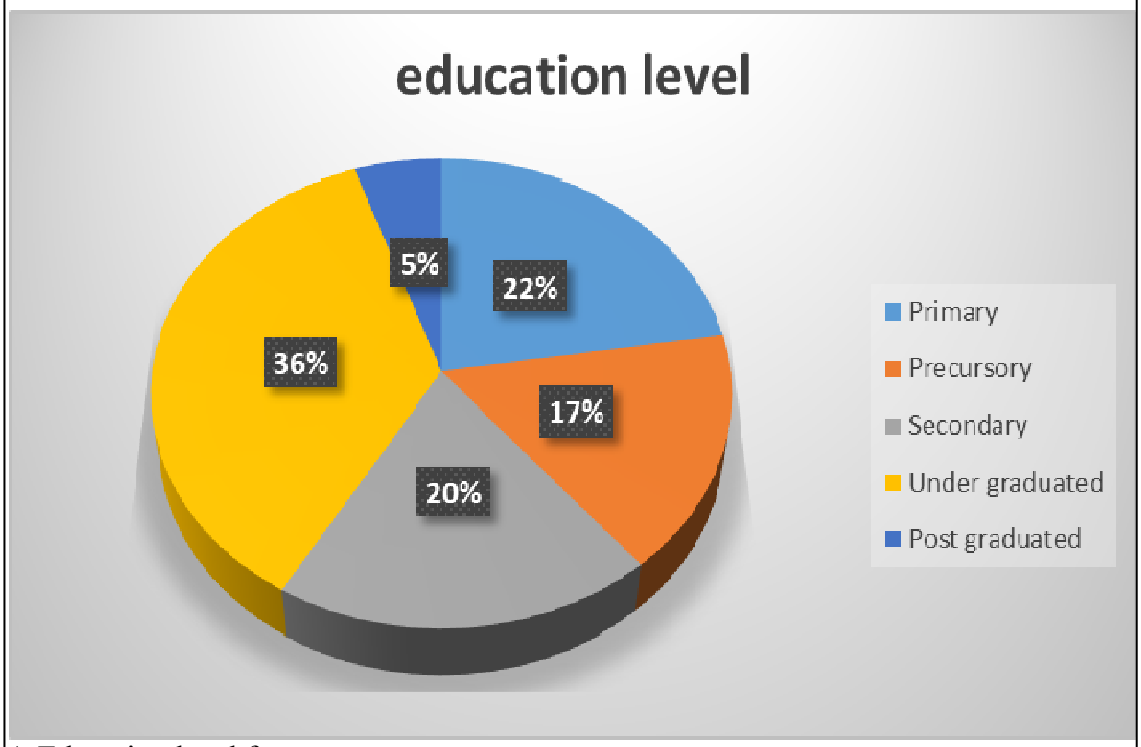
A: Male and female frequency



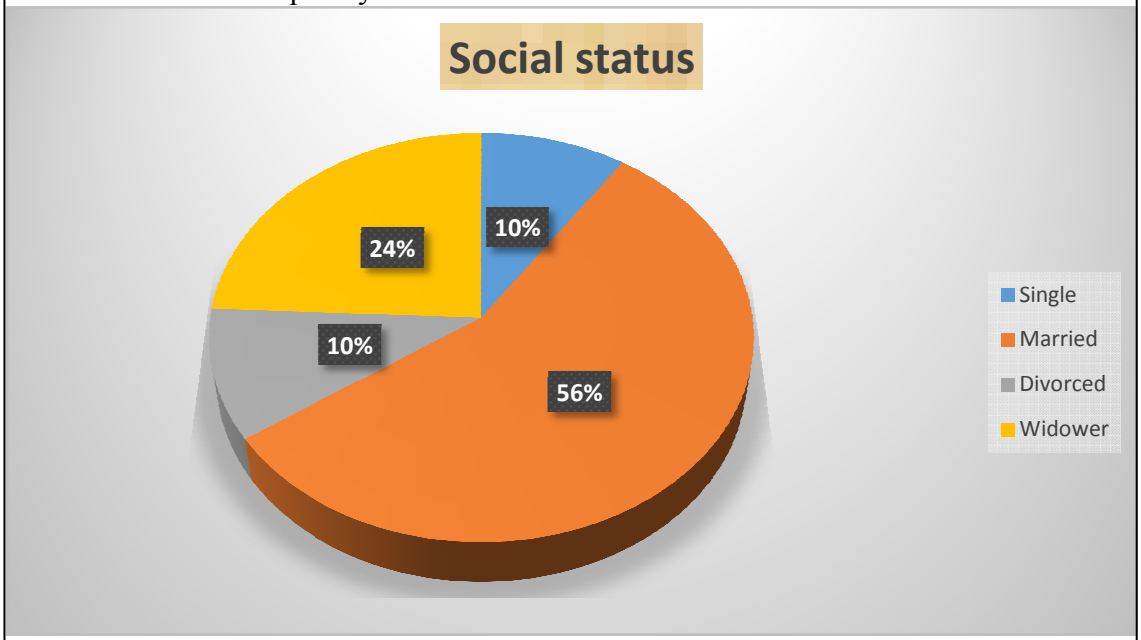
B: Age distribution

Figure 2

Education level and social status



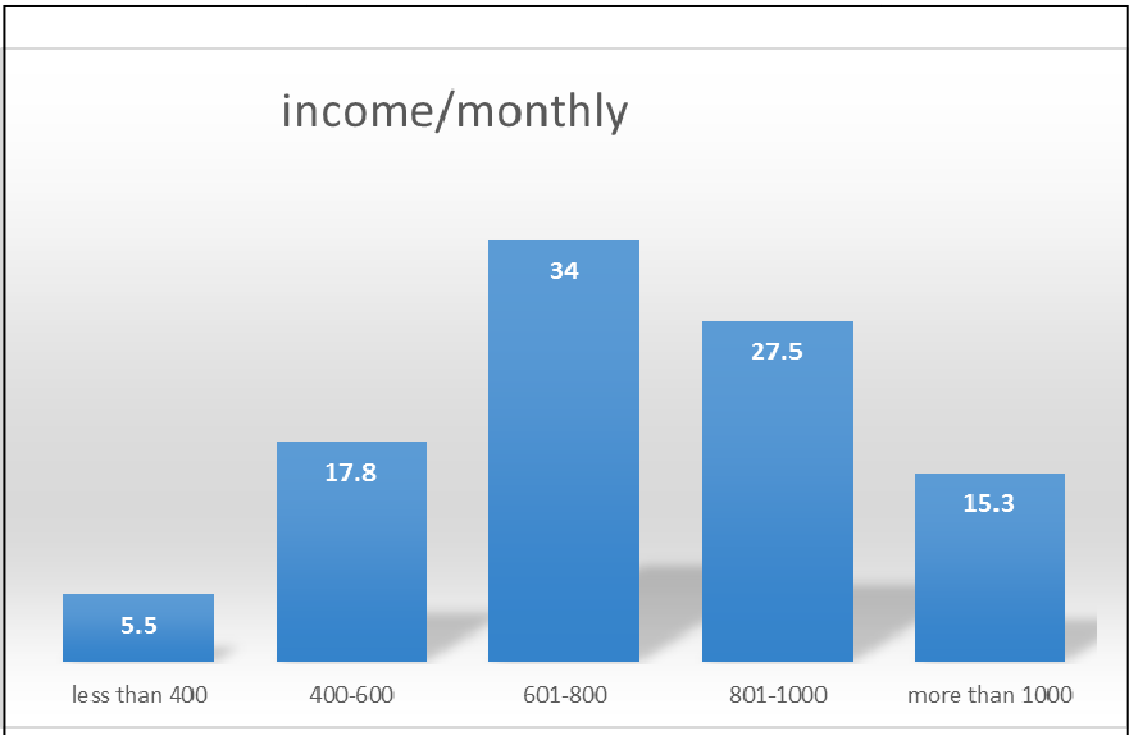
A:Education level frequency



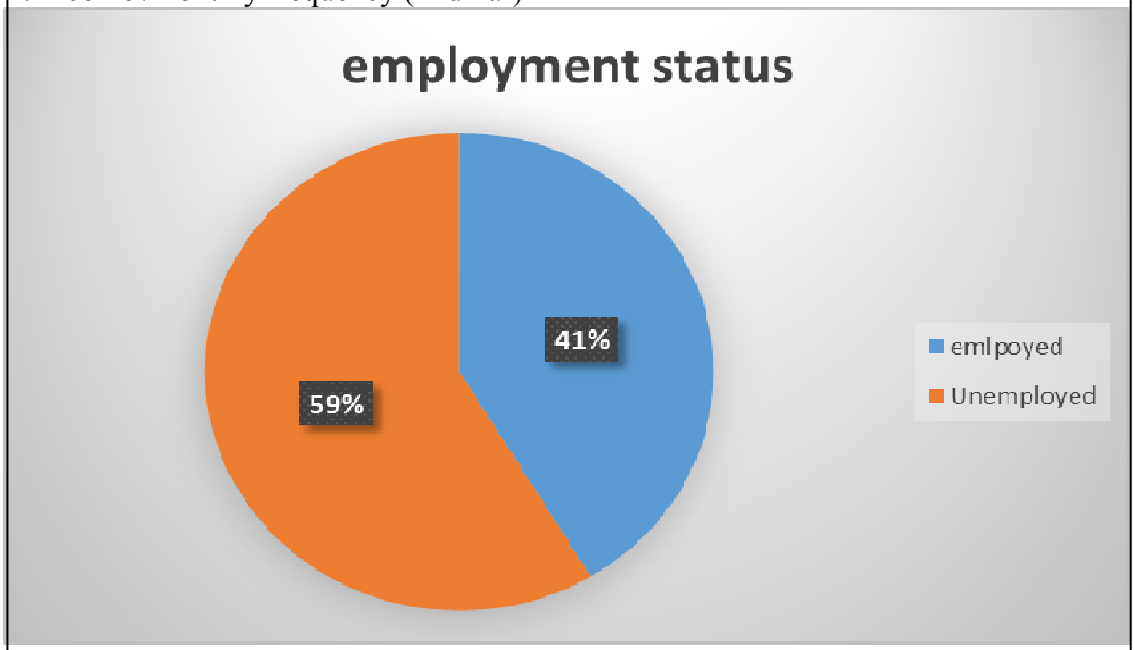
B: Social status frequency

Figure 3

Income /monthly and employment status



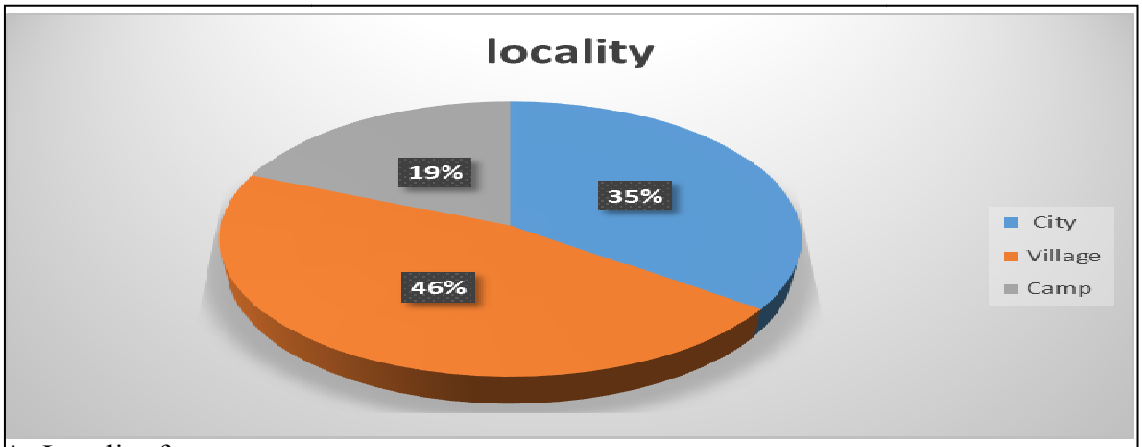
A: Income /monthly frequency (in dinar)



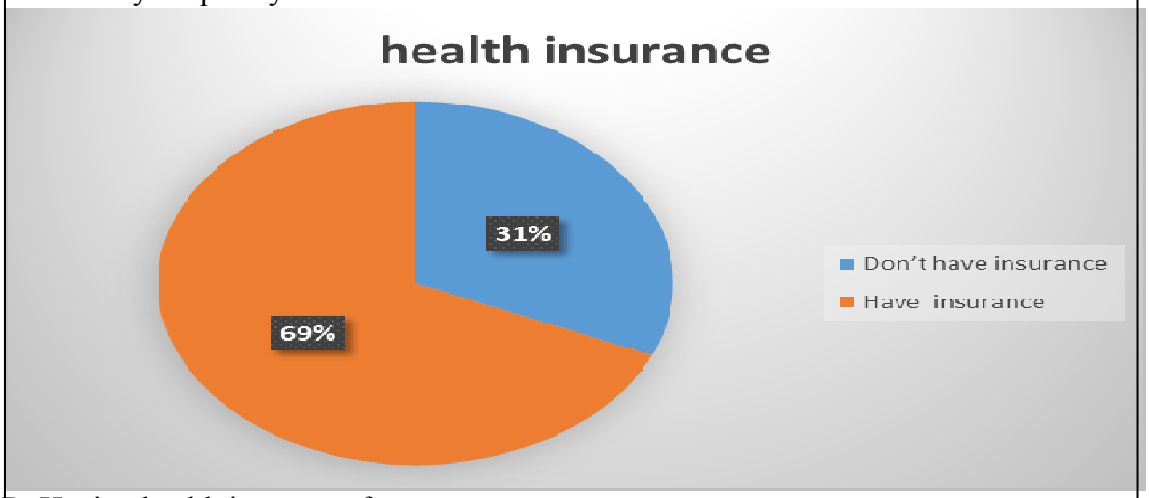
B: Employment status frequency

Figure 4

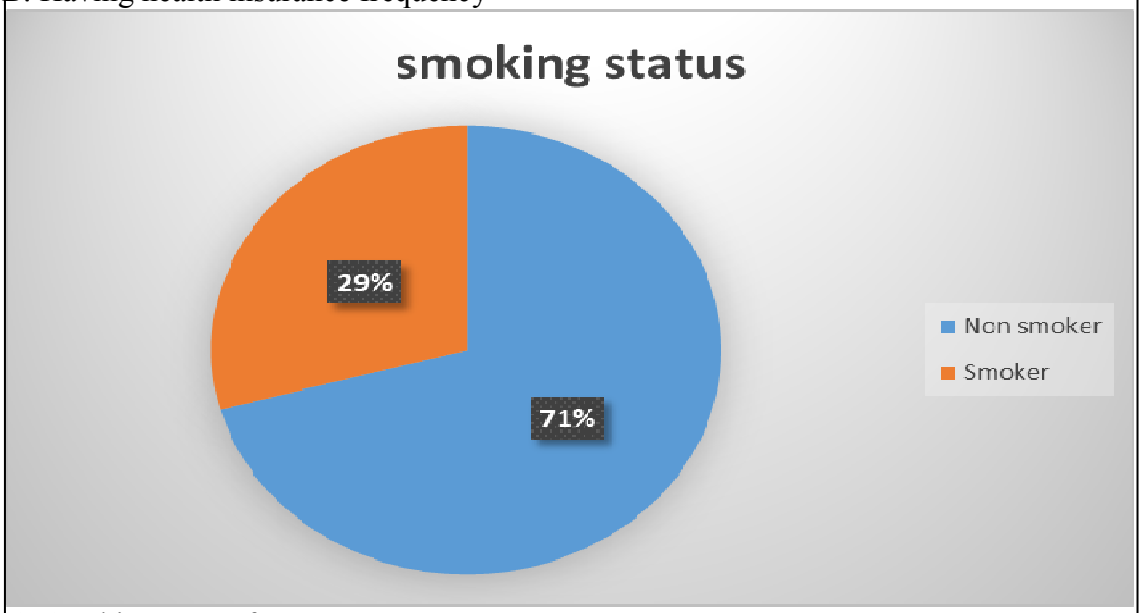
Locality, health insurance and smoking frequency



A: Locality frequency



B: Having health insurance frequency



C: Smoking status frequency

3.2 Comorbid Diseases

This study focused on patients with chronic diseases and used multiple medications. Table 2 indicates the most comorbid diseases among the patients, 44.3% had diabetes and it represented the highest percent among diseases, followed by hypertension (38%), then arthritis with a percent of (27.3%). Furthermore, there were various diseases with low percent (e.g 8.5% IHD, 6.3% cancer(were treated in the past with anticancer drugs), 7.8% lung diseases and 5.5% renal diseases as in figure 10.

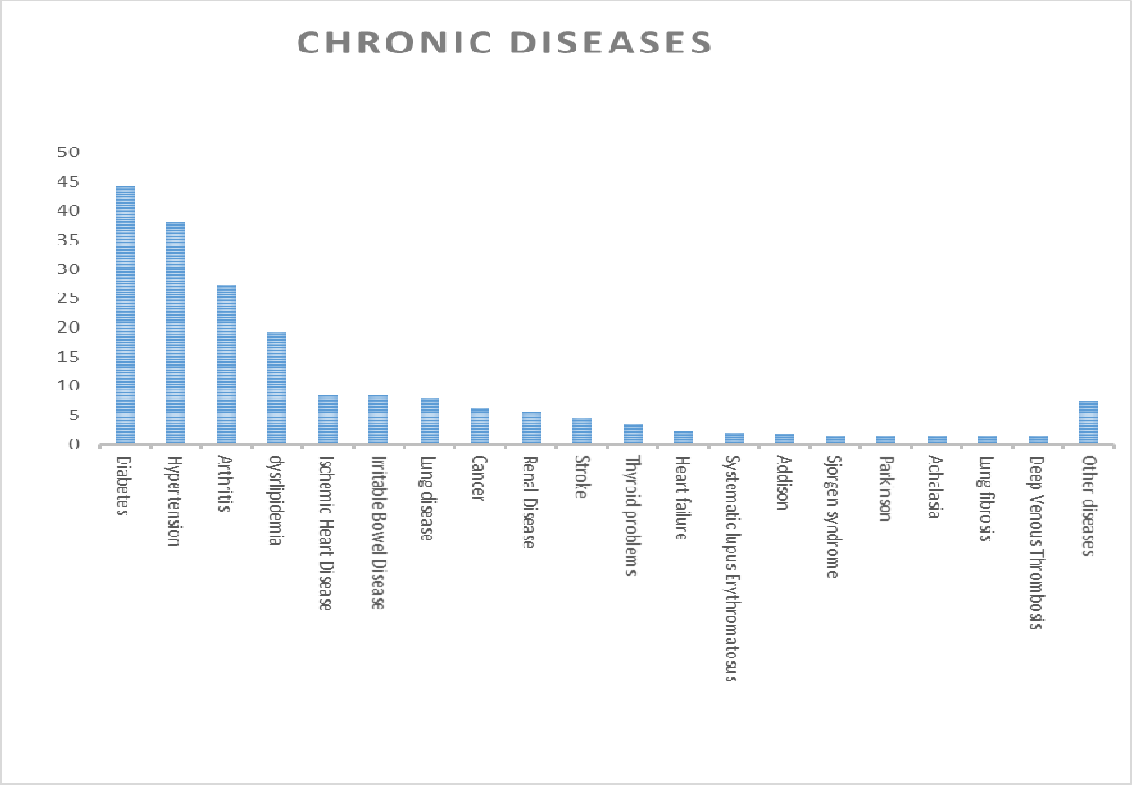
Table 2

Frequency and percentage of comorbid diseases

Comorbid disease	Frequency (%) N=400
Diabetes	177(44.3)
Hypertension	152(38.0)
Arthritis	109(27.3)
Dyslipidemia	77(19.3)
Ischemic Heart Disease	34(8.5)
Irritable Bowel Disease	34(8.5)
Lung disease	31(7.8)
Cancer	25(6.3)
Renal Disease	22(5.5)
Stroke	18(4.5)
Thyroid problems	13(3.3)
Heart failure	9(2.3)
Systematic lupus Erythromatosus	8(2)
Addison	7(1.8)
Sjorgen syndrome	6(1.5)
Parkinson	6(1.5)
Achalasia	6(1.5)
Lung fibrosis	6(1.5)
Deep Venous Thrombosis	6(1.5)
Other diseases	29 (7.3)

Figure 5

Chronic diseases frequency



3.3 Number of medications used by the patients

Table 3 indicates the number of drugs used by the patients, the mean number was 3.36 ± 1.6. Most of the patients used 3 medications (30.8%), followed by 2 medications (23.3%), then 4 medication(18.3%), then 6 medications (7.8%) as shown in figure 11.

Table 3

Number of medications used by the patients

Number of medications	Frequency (%) N=400
1	30(7.5)
2	93(23.3)
3	123(30.8)
4	73(18.3)
5	29(7.3)
6	31(7.8)
7	10(2.5)
8	5(1.3)
9	3(.8)

3.4Medications used by the patients

Table 4 indicates the 10 most commonly used drugs by the patients in our sample, there were multiple drugs but the most drug used was aspirin (Acetylsalicylic acid) with a percent of 50%, followed by atorvastatin, bisoprolol, insulin with a percent of (29.5%, 25%, 20.3%) respectively as in figure 6.

Also some drugs had low percentages and were attached in the appendices as appendix D, Medications used with very low percentage were collected in one group as others (10%) like (isotretinoin, allopurinol, hydrochlorothiazide, lansoprazole, propranolol, escitalopram, glibenclamide, methylprednisolone, warfarin and tamoxifen).

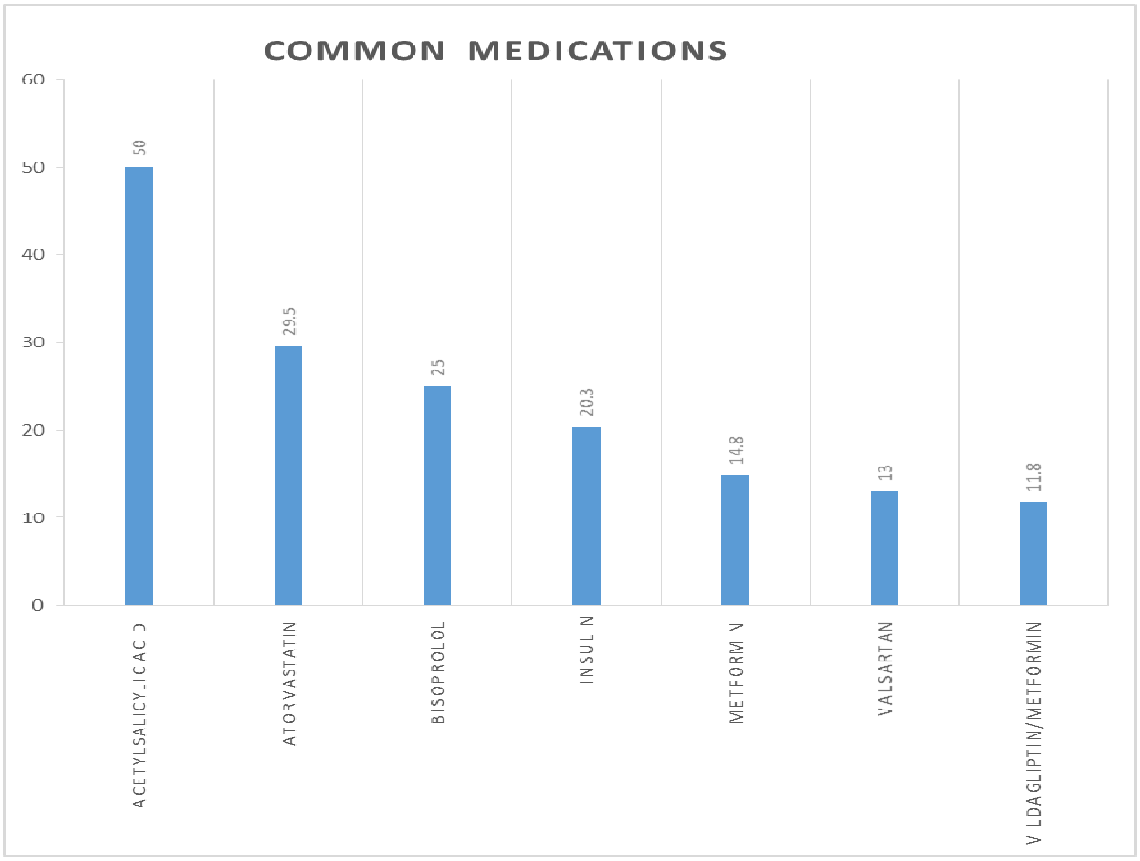
Table 4

Frequency and percentage of the 10 most prescribed medications used by the patients

Medication	**Frequency (%) N=400**
Acetylsalicylic acid	200(50)
Atorvastatin	118(29.5)
Bisoprolol	100(25)
Insulin	81(20.3)
Metformin	59(14.8)
Valsartan	52(13)
Vildagliptin/metformin	47(11.8)
Meloxicam	39(9.8)
Diclofenac	29(7.3)
Azathioprine	27(6.8)

Figure 6

The most common medications used



3.5 Upper gastrointestinal side effect among patients

Among the 400 participants who were enrolled in the study, 362 (90.5%) had some degree of dyspepsia (indigestion, regurgitation, heartburn, or nausea), as shown in Figure 7 A and B.

According to indigestion, Table 5 indicates the frequency and severity of these gastrointestinal side effects. 264 (66%) of the patients had indigestion, which occurred mainly once weekly (26%). On the other hand, 310 (77.5%) of the patients had heartburn that occurred once weekly with a percent of 33.5%. Regarding regurgitation, 209 (52.3%) of the patients had GERD that occurred once monthly with a percent of 31.1%. Also, 197(49.3%) of the patients had nausea, which occurred mainly once monthly (24%) according to figures 8 A and B.

Based on the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) scoring, of the 400 respondents, 235(58.8%), 109(27.3%) and 18(4.5%) suffered from mild, moderate and severe dyspepsia, respectively. As shown in Figure 9 .

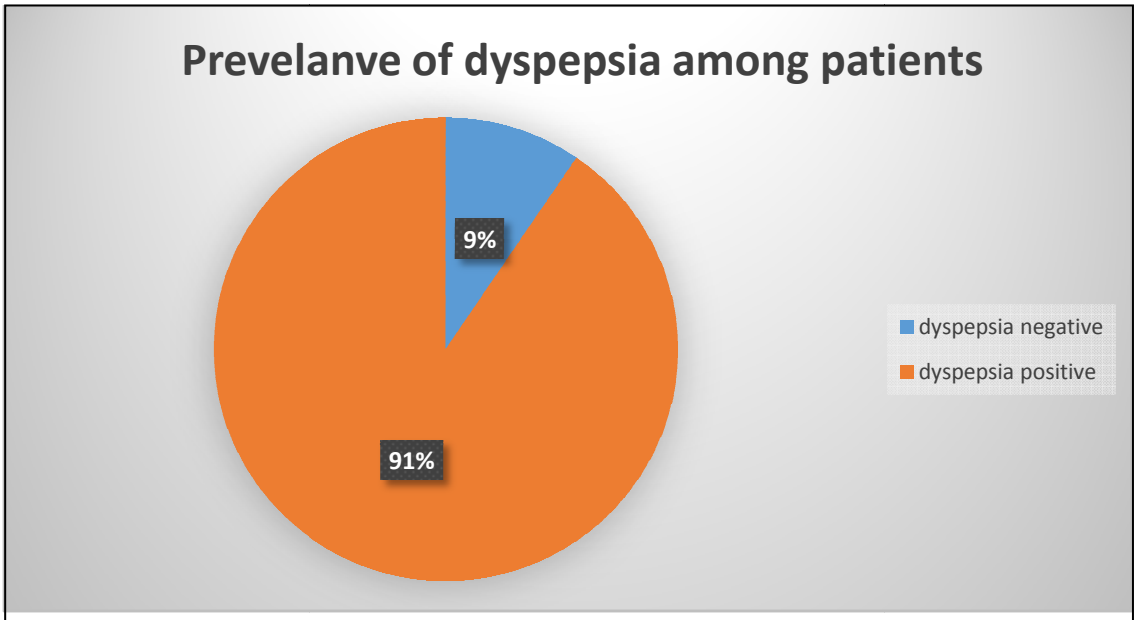
Table 5

Frequency and percentage of gastrointestinal side effects

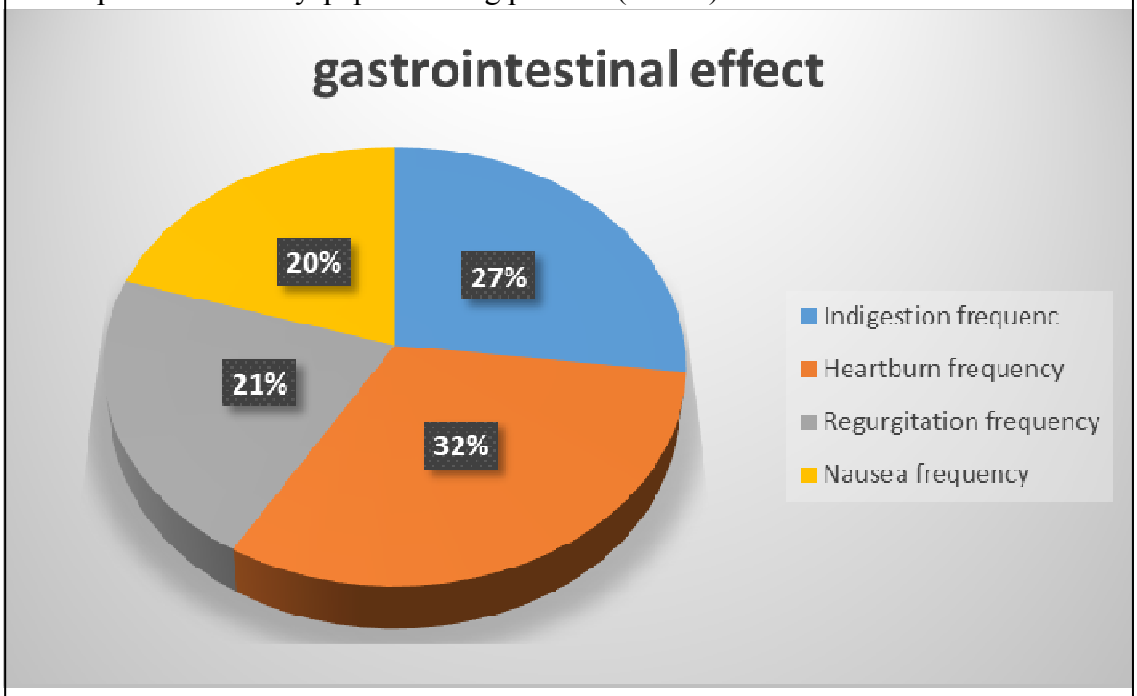
Symptoms	Percentage	Response category%				
		Not at all	Less than monthly	Between monthly and weekly	Between weekly and daily	More than daily
Indigestion frequency	264(66.0)	137(34.3)	98(24.5)	104(26.0)	51(12.8)	10(2.5)
Heartburn frequency	310(77.5)	87(21.8)	95(23.5)	134(33.5)	65(16.3)	19(4.8)
Regurgitation frequency	209(52.3)	192(48.0)	124(31.1)	43(10.8)	28(7.0)	13(3.3)
Nausea frequency	197(49.3)	205(51.3)	98(24.5)	65(16.3)	24(6.0)	8(2.0)
Indigestion severity	-	230(57.5)	112(28)	42(10.5)	15(3.8)	10(2.5)
Heartburn severity	-	177(44.3)	1(.3)	127(31.8)	72(18.1)	23(5.8)
Regurgitation severity	-	298(74.6)	68(17.0)	21(5.3)	12(3.0)	1(.3)
Nausea severity	-	280(70.0)	80(20.0)	31(7.8)	7(1.8)	2(0.5)

Figure 7

The prevalence of dyspepsia and Gastrointestinal side effect frequency



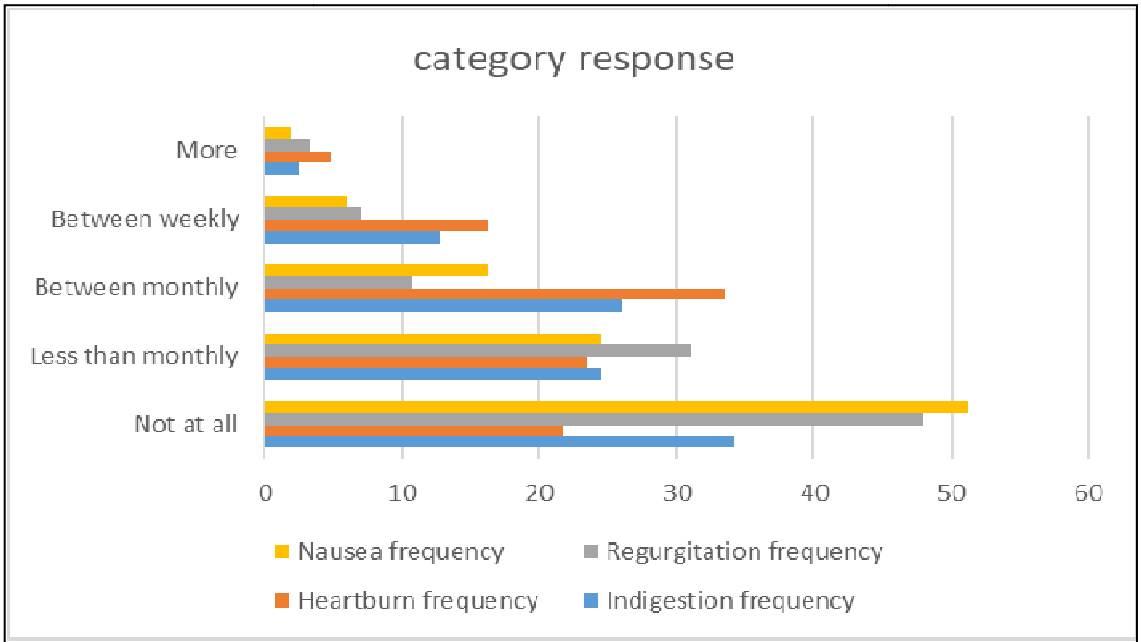
A: The prevalence of dyspepsia among patients (n=400)



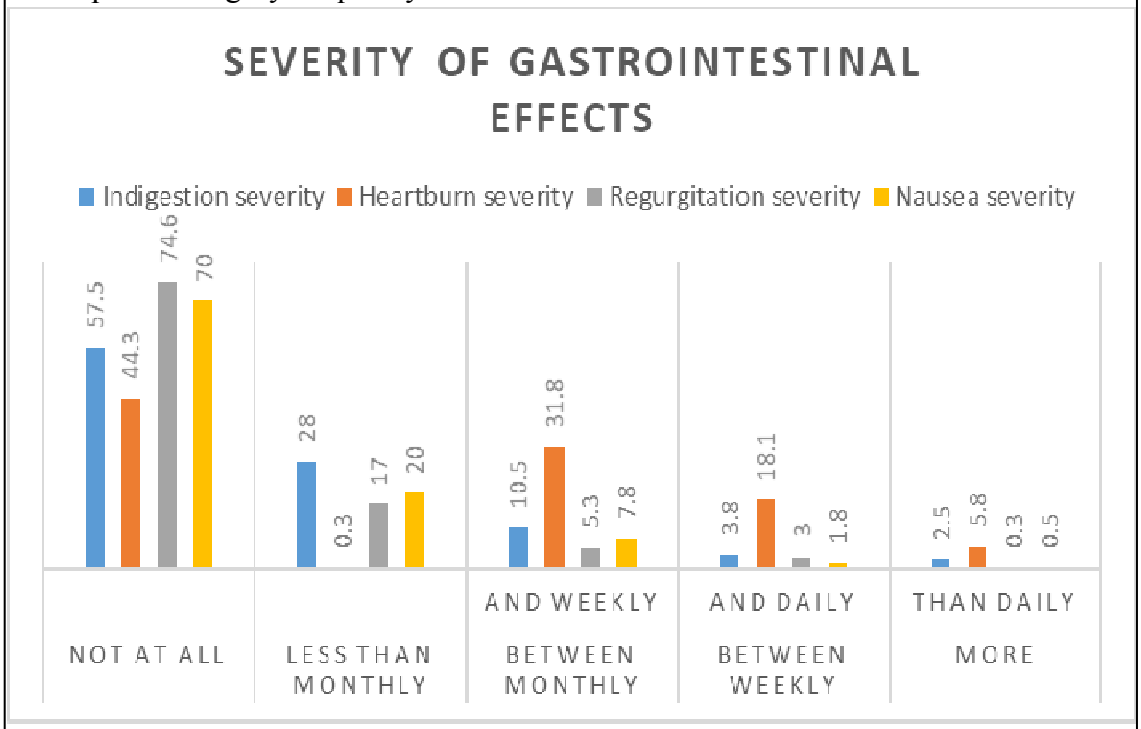
B: Gastrointestinal side effect frequency

Figure 8

Response category frequency and Gastrointestinal side effects severity



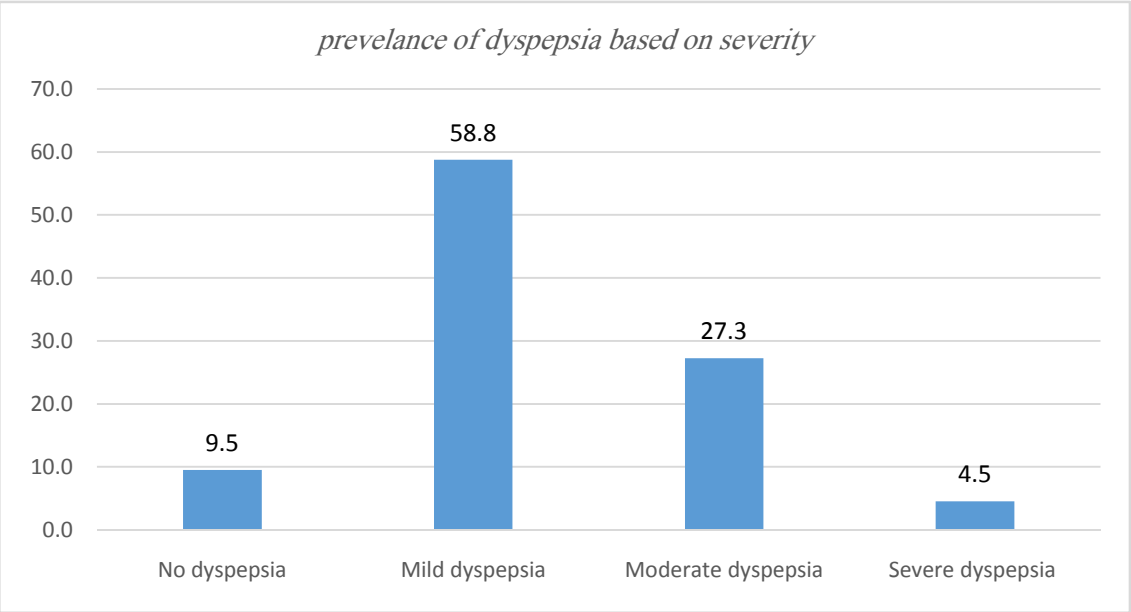
A: Response category frequency



B: Gastrointestinal side effects severity

Figure 9

Classification of participants according to the severity of dyspepsia (n=400)



3.6 factors associated with upper gastrointestinal complications

According to Table 6, there were no significant associations between dyspepsia and gender, living place, monthly income, or working status (p-values > 0.05) according to figure 10 (A, B,C,D,E and F). On the other hand, older age, being educated, not being single, having health insurance, being a smoker and using ≥ 5 medications were all associated with a higher possibility of having dyspepsia; (p-value <0.05) as shown in figures on appendix E.

Table 6

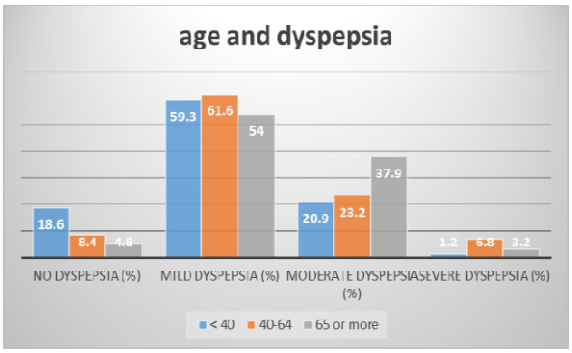
Association between dyspepsia and socio-demographic characteristics of the patients estimated by univariate analysis (n = 400).

Variables		No dyspepsia (%)	Mild dyspepsia (%)	Moderate dyspepsia (%)	Severe dyspepsia (%)	P value*
Age	< 40	16(18.6)	51(59.3)	18(20.9)	1(1.2)	0.001
	40-64	16(8.4)	117(61.6)	44(23.2)	13(6.8)	
	65 or more	6(4.8)	67(54.0)	47(37.9)	4(3.2)	
Gender	Male	16(8.6)	104(56.2)	56(30.3)	9(4.9)	0.595
	Female	22(10.2)	131(60.9)	53(24.7)	9(4.2)	
Education	Primary	3(3.3)	50(55.6)	33(36.7)	4(4.4)	0.031
	Precursory	5(7.6)	40(60.6)	20(30.3)	1(1.5)	
	Secondary	11(14.1)	55(70.5)	10(12.8)	2(2.6)	
	Under graduate	17(11.7)	80(55.2)	39(26.9)	9(6.2)	
	Post graduate	2(9.5)	10(47.6)	7(33.3)	2(9.5)	
Social status	Single	10(26.3)	21(55.3)	7(18.4)	0(0.0)	<0.001
	Married	19(8.5)	136(60.7)	62(27.7)	7(3.1)	
	Divorced	5(12.2)	27(65.9)	5(12.2)	4(9.8)	
	Widower	4(4.1)	51(52.6)	35(36.1)	7(7.2)	
Living place	City	16(11.5)	82(59.0)	35(25.2)	6(4.3)	0.849
	Village	16(8.6)	108(58.1)	55(29.6)	7(3.8)	
	Camp	6(8.0)	45(60.0)	19(25.3)	5(6.7)	
Health insurance	Yes	19(6.9)	164(59.9)	75(27.4)	16(5.8)	0.021
	No	19(15.1)	71(56.3)	34(27.0)	2(1.6)	
Monthly income	< 400	2(9.1)	14(63.6)	5(22.7)	1(4.5)	0.395
	600-400	3(4.2)	40(56.3)	25(35.2)	3(4.2)	
	800-601	15(11.0)	76(55.9)	39(28.7)	6(4.4)	
	801-1000	7(6.4)	69(62.7)	28(25.5)	6(5.5)	
	> 1000	11(18.0)	36(59.0)	12(19.7)	2(3.3)	
Employment	Yes	16(9.7)	91(55.2)	47(28.5)	11(6.7)	0.373
	No	22(9.4)	144(61.5)	62(26.1)	7(3.0)	
Smoking	Yes	8(6.8)	56(47.9)	45(38.5)	8(6.8)	0.003
	No	30(10.6)	179(63.3)	64(22.6)	10(3.5)	
Number of medications	< 5	38(11.8)	208(64.6)	73(22.7)	3(0.9)	<0.001
	5 or more	0(0.0)	27(34.6)	36(46.2)	15(19.2)	

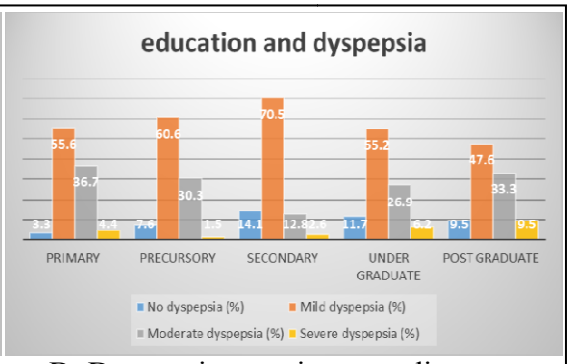
*Chi-Square test

Figure 10

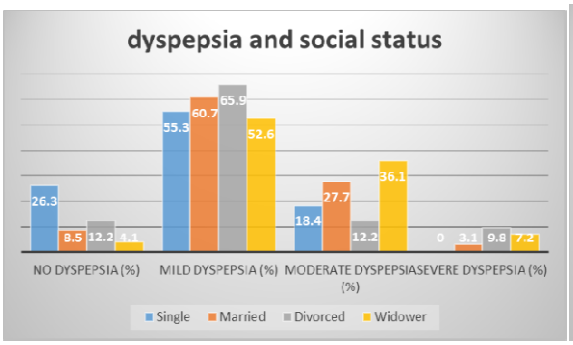
Significant associations between Dyspepsia severity according to age, education, social status, health insurance, smoking and number of medications



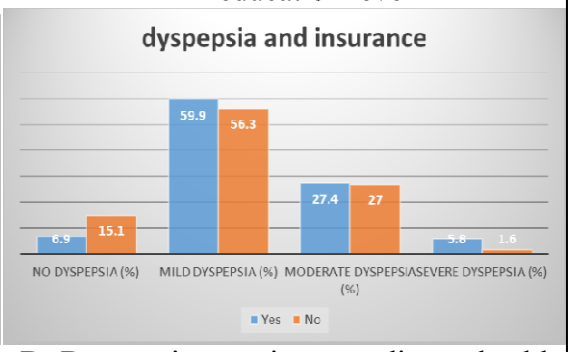
A: Dyspepsia severity according to age



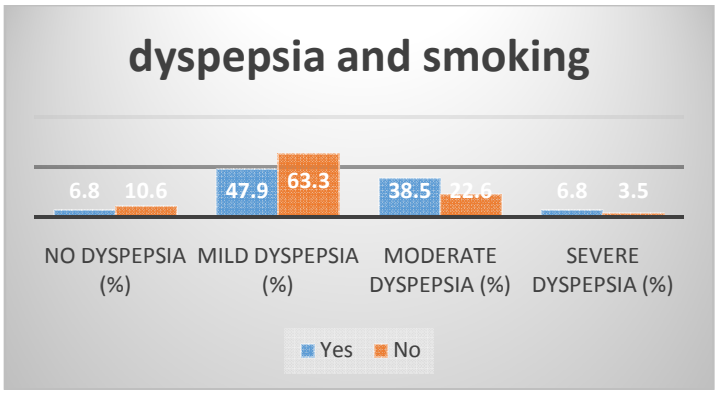
B: Dyspepsia severity according to education level



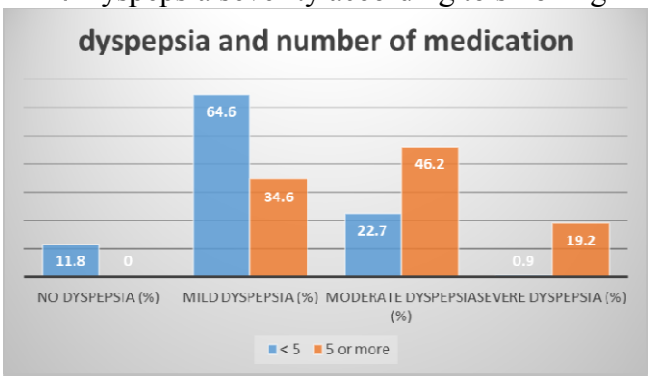
C: Dyspepsia severity according to social status



D: Dyspepsia severity according to health insurance



E: Dyspepsia severity according to smoking



F: Dyspepsia severity according to number of medication

3.7 Other gastrointestinal effects

Table 7 indicates other gastrointestinal effect like bleeding (2.8%), celiac disease (0.3%), duodenal ulcer (0.3%), endoscopy (1.3%), gastroscopy (0.3%), peptic ulcer disease (1%) and upper gastrointestinal bleeding (0.5%).

Table 7

Other gastrointestinal effect

Other gastrointestinal effect	Frequency (%) N=400
Bleeding	11(2.8)
Duodenal ulcer	1(0.3)
Need for Endoscopy	5(1.3)
Need for Gastroscopy	1(0.3)
Peptic ulcer disease	4(1)
Upper gastrointestinal bleeding	2(0.5)

3.8 Medications used to treat gastrointestinal side effects

A very high percentage 325 (81.3%) of the patients with chronic diseases used a drug that protects the stomach which was prescribed by their doctors. According to table 8 and figure 19, 52.3% of the patients used proton pump inhibitors to suppress the acid secretion from the stomach, also 10% used histamine receptor blocker (H2), 13.3% used sodium alginate/potassium bicarbonate, 3.5% used bismuth, 1% used aluminum hydroxide/magnesium hydroxide, 3.3% used famotidine/magnesium hydroxide/calcium bicarbonate. All the previous medications were used to treat acid secretion. Furthermore, 16% used mebeverine as antispasmodic, 16% used domperidone as anti-sickness, 1.8% used metoclopramide for nausea and vomiting, 4.5% used clordiazepoxide/clinidium bromide to decrease hypersecretion and hypermobility in the gastrointestinal tract, 6.5% used sulpiride for irritable bowel syndrome and duodenal ulcers as in the last figure in appendix E.

Table 8

Frequency and percentage of gastro protective drugs used by the patients

medications	**Frequency (%) N=400**
PPI	209(52.3)
Domperidone	64(16.0)
Sodium alginate/ potassium bicarbonate	53(13.3)
H2 Blockers	40(10.0)
Sulpride	26(6.5)
Chordiazepoxide/clinidium bromide	18(4.5)
Bismuth subsalicylate	14(3.5)
Famotidine/ magnesium hydroxide/calcium bicarbonate	13(3.3)
Metoclopramide	7(1.8)
Aluminum hydroxide/magnesium hydroxide	4(1.0)
Mebeverin	3(0.8)

Chapter Four
Discussion and Conclusion

4.1 Discussion

This study was one of the first in Palestine to examine whether there is any relationship between the effects of chronic drugs and the patients' gastrointestinal side effects, using a questionnaire to determine the prevalence of patients with GIT complications and their severity, and to determine the percentage of patients who used gastro-protective drugs and medications.

Most of our participants were married, middle-aged, educated, unemployed, living in a village, non-smokers, and had health insurance. Furthermore, the majority of them had multiple chronic diseases, with diabetes being the most common, followed by hypertension and arthritis, which is similar to a study conducted in Palestine that revealed that living in the West Bank was a risk factor for chronic diseases such as diabetes, hypertension, and CVD but not for cancer, and that being female, married, and being over 40 were risk factors for chronic diseases [110].

This study found that most patients took 2-4 medications daily; the mean number was 3.36 ± 1.6. This was seen in a study performed in the United States among older people where the average number of medications used daily by the patients was 4 and was increasing because of the need for cardio-protective and antidepressant medications; as a result, the gastrointestinal problems were increasing [111].

On the other hand, half of our patients used aspirin, which corresponds to a study performed in Palestine on 1192 participants; 48% were taking aspirin as one of their medications. Furthermore, a high percent of atorvastatin, bisoprolol, and insulin were used due to a widespread percent of cardiovascular diseases and endocrine diseases (mainly diabetes) among Palestinians [112].

Furthermore, 90% of our participants had upper gastrointestinal complications due to stomach irritation caused by the use of multiple drugs, especially with a high number of drugs. These findings were emphasized in a previous study which showed that continuous exposure to multiple drugs like aspirin and NSAIDs can inhibit prostaglandin synthesis, which plays an important role in all gastrointestinal defense

mechanisms like the mucosal layer, and as a result developed GIT problems [113]. Also, these results were emphasized in another study which showed that chronic drug use leads to accumulation of Reactive Oxygen Species (ROS) in the GIT and an inability to scavenge them by melatonin [114].

The prevalence of dyspepsia in this study was very high (90.5%). This differs from the prevalence of neighboring Arabian countries, as reported in Jordan by Frasakh et al (60.1%) [115],and as reported in UAE by Jaber N et al (44%) [116], while Saudi Arabia had similar dyspepsia percentage (92.4%) as reported by Alwhaibi et al, This variation in the prevalence maybe due to different confounding risk factors of dyspepsia mainly stress cause by the occupation and other factors like the common consumption of analgesics, furthermore, 58% of our participants had mild dyspepsia (1-8) score which resembles the findings of Saudi Arabian study as 41% had mild dyspepsia [70]. These mild symptoms might be explained by the wide use of gastro-protective medications which may help in decreasing the severity of symptoms.

Older age had a significant association with dyspepsia (p-value<0.05), this may be due to high probability to H pylori infection or the use of higher number of medications [117, 118]. Being a smoker also had a significant association [119]. However, high education level and being married were considered protective factors as mentioned in previous studies [120][40]. Having health insurance significantly related to dyspepsia cause it needs pharmacological treatment and diagnosis which is expensive[121, 122].

In our population, the most common and bothersome gastrointestinal side effect was heartburn; it affected the daily activities for a wide range of people. The harmful effect on the gastrointestinal tract may result from a drug's mode of action, through direct injury, by changing the mucosal integrity, or as a result of changes in colonic microbiota, and this was mentioned in a study performed in 2019 [123]. So the high number of medications used by patients may explain these bothersome frequent gastrointestinal side effects.

A very high percentage (81.3%) of the patients' prescriptions included gastro protective medication. This high percent may be due to the fact that the sample was selected from a private hospital and the doctors who prescribed medications were internists. However,

there is a low prescription for gastro protective drugs among the multiple drug users in Palestine according to a study performed in 2003 [93].

The most popular gastro-protective medications were PPIs because they are the most effective drugs in preventing acid secretion from the stomach and reducing the harmful sensation with low toxicity. However, PPIs are not appropriate for all causes of gastrointestinal problems because there are different causes than acid secretion, so some used coating agents, prostaglandin analogs, and antacids. This was shown in a study performed in 2020 [124].

4.2 Strengths and limitations

4.2.1 Strength

To the best of our knowledge, this study was one of the first to investigate the effect of chronic drug use on the gastrointestinal tract in Palestine, furthermore it investigated the main gastro protective drugs used in these patients.

4.2.2 Limitations

1. This is a cross-sectional study, so as a result, it is difficult to prove causal relationships between the questions that have been used and their associated factors.

2. This study did not explore other confounding factors like the nature of their work (stress induced GIT discomfort), adherence (so that the contributing effect of drug use), or the nature of the food they consume.

3. Because the data were gathered through a face-to-face interview, interviewer bias may have been introduced.

4. Recall bias: as the sample was mainly older people, so they may face some difficulty in remembering information.

5. Collecting samples was only performed in a private hospital in one discrete area of the West Bank.

4.3 Conclusion and Recommendations

4.3.1Conclusions

Upper gastrointestinal complications among patients with chronic diseases were very common. Fortunately, the symptoms were mild in most cases. The risk increased with age and using higher number of medications. Use of gastro-protective agents is important and Proton Pump Inhibitors were the most drugs used.

4.3.2 Recommendations

- We advise doctors to be more vigilant in this area and to prescribe appropriate gastro-protective agents based on the drug-induced effect, especially when taking multiple medications.

- We also recommend the pharmacist be in contact with patients' doctors in order to alarm them if there is a possible GIT problem resulting from a high number of medications. Also the pharmacist should advise the patients for the appropriate use of the drugs to minimize the gastrointestinal complications.

- We recommend the doctors also withdraw the gastro-protective drug if there is no need in order to prevent overuse and dependency.

- We recommend the drug manufacturer to improve the drug formulation by combining them with a gastro protective agent especially drugs used for chronic disease in order to reduce the number of medications.

- We recommend to assess the side effects of the gastro protective agents especially that 81 % of the patients are currently using them.

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Appendices

Appendix A: Data Collection form

بسم الله الرحمن الرحيم

تحية طيبة وبعد،،

في البداية نود أن نشكركم على الوقت والجهد الذي سوف تبذلونه في تعبئة هذا الاستبيان فتعاونكم بهذا الاستبيان سيساعد الباحثة على استكمال بحثها.

هذا البحث لطالبة ماجستير من جامعة النجاح الوطنية يتعلق بمدى حدوث مشاكل المعدة عند المرضى اللذين يتناولون الادوية المزمنة و ماذا يستعملون للتخفيف منها

ولذلك نرجو الموافقة على الإجابة عن هذا الاستبيان بدقة، نتائج هذه الدراسة ستستخدم لغرض الدراسة العلمية فقط ، ولن يكون بالإمكان التعرف على هوية المشاركين في تعبئة هذا الاستبيان. المشاركة في هذه الدراسة اختيارية و طوعية.

الرجاء التكرم بالإجابة على هذه الأسئلة شاكرين لكم تعاونكم...

بعد قراءة كافة المعلومات المتعلقة بالبحث:

- o أوافق على الانضمام للدراسة.
- o لا أوافق على الانضمام للدراسة.

الجزء الاول:

البيانات الشخصية:

- العمر: _____

- الجنس: ذكر انثى

- المستوى التعليمي: أمي أو ابتدائي إعدادي ثانوي بكالوريوس دراسات عليا

- الحالة الاجتماعية: اعزب متزوج مطلق ارمل

- مكان الاقامة: مدينة قرية مخيم

- هل تملك تأمين صحي: نعم لا

- ما هو معدل الدخل الشهري للعائلة بالدينار الأردني؟ أقل من 400 -601 600 -801 800 -1000 أكثر من 1000

- هل تعمل حاليا: نعم لا

- هل انت مدخن: نعم لا

الجزء الثاني:

❖ **ما الامراض المزمنة التي تعاني منها؟**

_____

❖ **كم عدد الادوية التي تتناولها يوميا؟ _____**

- **ما هي هذه الادوية؟**

_____

- هل تشعر باي من مشاكل المعدة بعد تناول الادوية؟ نعم لا

اذا كان الجواب **نعم** أي من هذه المشاكل؟

☐ **عسر الهضم (الم او عدم راحة في اعلى البطن)**

- نسبة تكرار هذا العرض خلال الشهرين الماضيين ؟

☐ لا يوجد

☐ اقل من مرة شهريا

☐ من مرة بالاسبوع الى مرة بالشهر

☐ من مرة باليوم الى مرة بالاسبوع

☐ مرة يوميا او اكثر

- نسبة تأثير المرض على النشاطات اليومية (اكل، نوم، عمل، وغيرها) خلال اخر شهرين ؟

☐ لا يوجد

☐ اقل من مرة شهريا

☐ من مرة بالاسبوع الى مرة بالشهر

□ من مرة باليوم الى مرة بالاسبوع

□ مرة يوميا او اكثر

□ **حرقة في المعدة (شعور بالحرقة في وسط الصدر)**

- نسبة تكرار هذا العرض خلال الشهرين الماضيين ؟

□ لا يوجد

□ اقل من مرة شهريا

□ من مرة بالاسبوع الى مرة بالشهر

□ من مرة باليوم الى مرة بالاسبوع

□ مرة يوميا او اكثر

- نسبة تأثير المرض على النشاطات اليومية (اكل، نوم، عمل، وغيرها) خلال اخر شهرين ؟

□ لا يوجد

□ اقل من مرة شهريا

□ من مرة بالاسبوع الى مرة بالشهر

□ من مرة باليوم الى مرة بالاسبوع

□ مرة يوميا او اكثر

□ **ارتجاع مريئي (الشعور بصعود الحمض من المعدة الى الفم)**

- نسبة تكرار هذا العرض خلال الشهرين الماضيين ؟

□ لا يوجد

□ اقل من مرة شهريا

- من مرة بالاسبوع الى مرة بالشهر
- من مرة باليوم الى مرة بالاسبوع
- مرة يوميا او اكثر

- نسبة تأثير المرض على النشاطات اليومية (اكل، نوم، عمل، وغيرها) خلال اخر شهرين ؟

- لا يوجد
- اقل من مرة شهريا
- من مرة بالاسبوع الى مرة بالشهر
- من مرة باليوم الى مرة بالاسبوع
- مرة يوميا او اكثر

- **الغثيان (الشعور بالمرض (قلبان المعدة) بدون ان تكون مريضا)**

- نسبة تكرار هذا العرض خلال الشهرين الماضيين ؟

- لا يوجد
- اقل من مرة شهريا
- من مرة بالاسبوع الى مرة بالشهر
- من مرة باليوم الى مرة بالاسبوع
- مرة يوميا او اكثر

- نسبة تأثير المرض على النشاطات اليومية (اكل، نوم، عمل، وغيرها) خلال اخر شهرين ؟

- لا يوجد
- اقل من مرة شهريا

- من مرة بالاسبوع الى مرة بالشهر
- من مرة باليوم الى مرة بالاسبوع
- مرة يوميا او اكثر

- اي من هذه الاعراض كان الاكثر ازعاج خلال الشهرين الماضيين

- عسر الهضم
- حرقة المعدة
- الغثيان
- الارتجاع مريئي

مشاكل اخرى مثل قرحة المعدة نزيف المعده او غيرها اذكرها_____

- هل تتناول شيئا لتخفيف مشاكل المعدة؟

اذا كان الجواب **نعم** ماذا تستعمل؟

شكراً جزيلاً لتعاونكم ودعمكم للبحث العلمي

Appendix B: IRB approval

An-Najah National University
Faculty of medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref : Mas. Oct. *2021/35*

IRB Approval Letter

Title of Research:

Upper Gastrointestinal Complications and Treatment among patients with Chronic Diseases : A Cross sectional Study from Palestine

Submitted by:
Deema Tumeh

Supervisor:
Rawa Al Ramahi

Approved:
31th October 2021

Your Study Title **"Upper Gastrointestinal Complications and Treatment among patients with Chronic Diseases : A Cross sectional Study from Palestine."** reviewed by An-Najah National University IRB committee and was approved on 31th October 2021

Hasan Fitian, MD

IRB Committee Chairman

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910| E-mail : hgs@najah.edu

Appendix C: form For Hospital

An-Najah
National University
Faculty of Graduate Studies

جامعة
النجـــاح الوطنية
كلية الدراسات العليا

التاريخ: 2021/11/7

حضرة الدكتور مدير مستشفى ابن سينا المحترم
جنين

تحية طيبة وبعد،،

الموضوع: تسهيل مهمة الطالبة/ ديمه محمود مصطفى طعمه، رقم تسجيل (12053106)
تخصص ماجستير علم الأدوية

الطالبة/ ديمه محمود مصطفى طعمه رقم تسجيل 12053106، تخصص ماجستير علم الأدوية في كلية الدراسات العليا، وهي بصدد اعداد الاطروحة الخاصة بها والتي عنوانها:

مضاعفات الجهاز الهضمي العلوي وعلاجها لدى مرضى الأمراض المزمنة: دراسة مقطعية من فلسطين

Upper Gastrointestinal Complications and Treatment among Patients with Chronic Diseases: A Cross Sectional Study from Palestine

يرجى من حضرتكم تسهيل مهمتها في جمع البيانات والمعلومات المتعلقة باطروحة التخرج من خلال اجراء مقابلات مع المرضى الذين يحضرون للعيادات الخارجية والاطلاع على سجلات المرضى الطبية وادويتهم من الملفات الخاصة بهم.

علماً بأن المعلومات التي يتم جمعها هي لأغراض البحث العلمي فقط، وسوف يتم الحفاظ على السرية التامة وعدم استخدام هذه المعلومات لأغراض أخرى.

شاكرين لكم حسن تعاونكم ومساعدتكم للعملية التعليمية.

مع وافر الاحترام،،

عميد كلية الدراسات العليا
أ.د وليد صويلح

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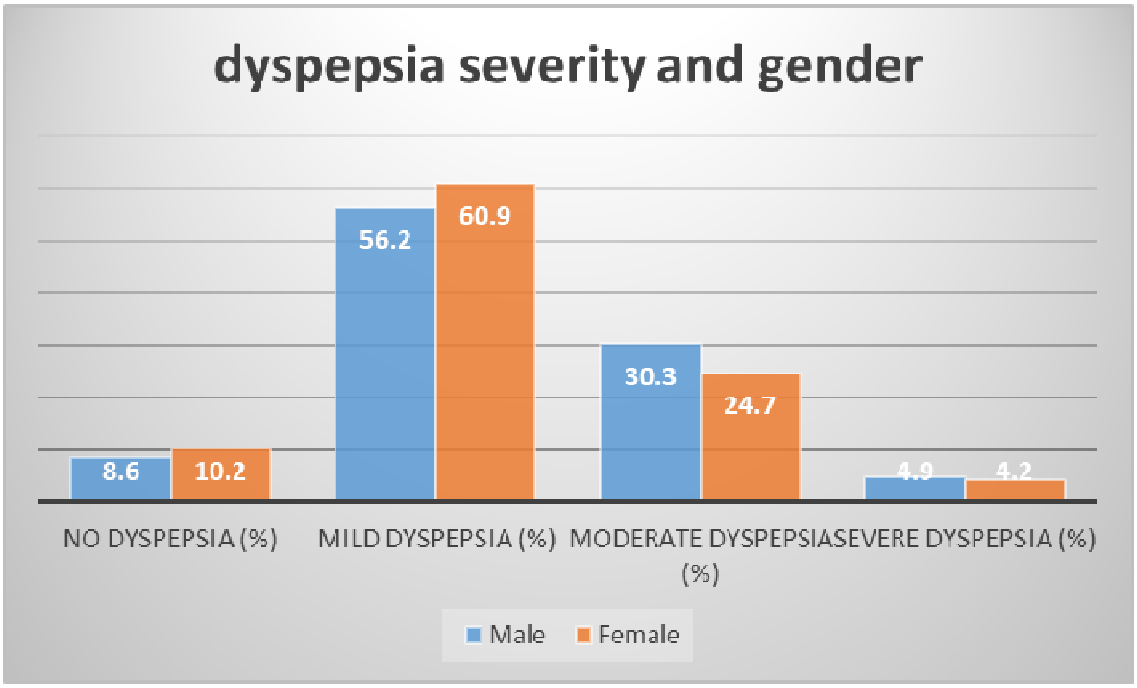
Appendix D: The rest of medications used by the patients

Medication	Frequency (%) N=400
Enalapril	26(6.5)
Piroxicam	25(6.3)
Amlodipine	24(6.0)
Dapagliflozine	24(6)
Sulfasalazine	23(5.8)
Rosuvastatin	21(5.3)
Sitagliptin	20(5)
Carvedilol	18(4.5)
Sulpiride	16(4)
Clopidogrel	14(3.5)
Atenolol	13(3.3)
Levothyroxine	13(3.3)
Leflonamide	13(3.3)
Formoterol	12(3)
Glimepiride	12(3)
Budesonide/ formoterol	12(3)
Hydroxychloroquine	12(3)
Losartan	12(3)
Esomeprazole	11(2.8)
Contraceptive pills	11(2.8)
Chlordiazepoxide/ clindium bromide	11(2.8)
Orphenadrine/ paracetamol	11(2.8)
Prednisolone	11(2.8)
Methotrexate	10(2.5)
Mycophenolate	10(2.5)
Triamcinolone	10(2.5)
Apixaban	10(2.5)
Paracetamol	10(2.5)
Furosemide	9(2.3)
Adalimumab	9(2.3)
Hydrocortisone	8(2)
Folic acid	8(2)
Budesonide	8(2)
Vitamins	7(1.8)
Gliclazide	7(1.8)
Indacaterol/ glycopyrronium	7(1.8)
Amlodipine/Valsartan	6(1.5)
Celecoxib	6(1.5)
Carbidopa-Levodopa	6(1.5)
Nintedanib	6(1.5)
Sitagliptin/metformin	5(1.3)
Cyclobenzaprine	5(1.3)
Calcium	5(1.3)
Aluminum hydroxide/magnesium	5(1.3)

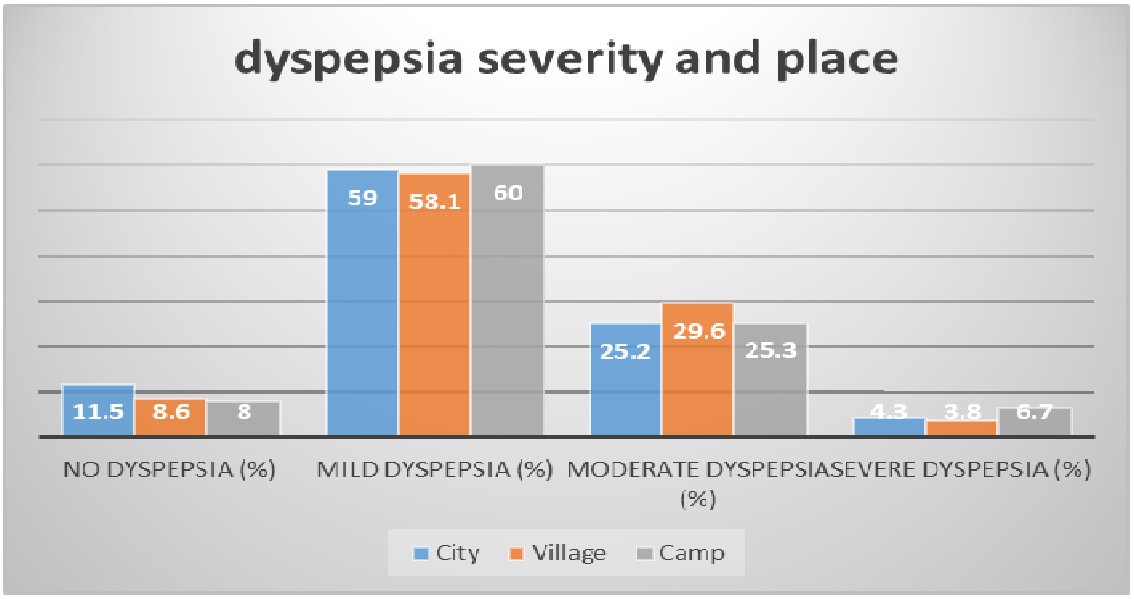
hydroxide	
Naproxen	5(1.3)
Alpha-D3	4(1)
Darbepoeten alfa	4(1)
Iron	4(1)
Pirfenidone	4(1)
Mesalazine	4(1)
Ramipril	4(1)
Candesartan	4(1)
Etanercept	3(0.8)
Others	41(10.3)

Appendix E: The rest of figures

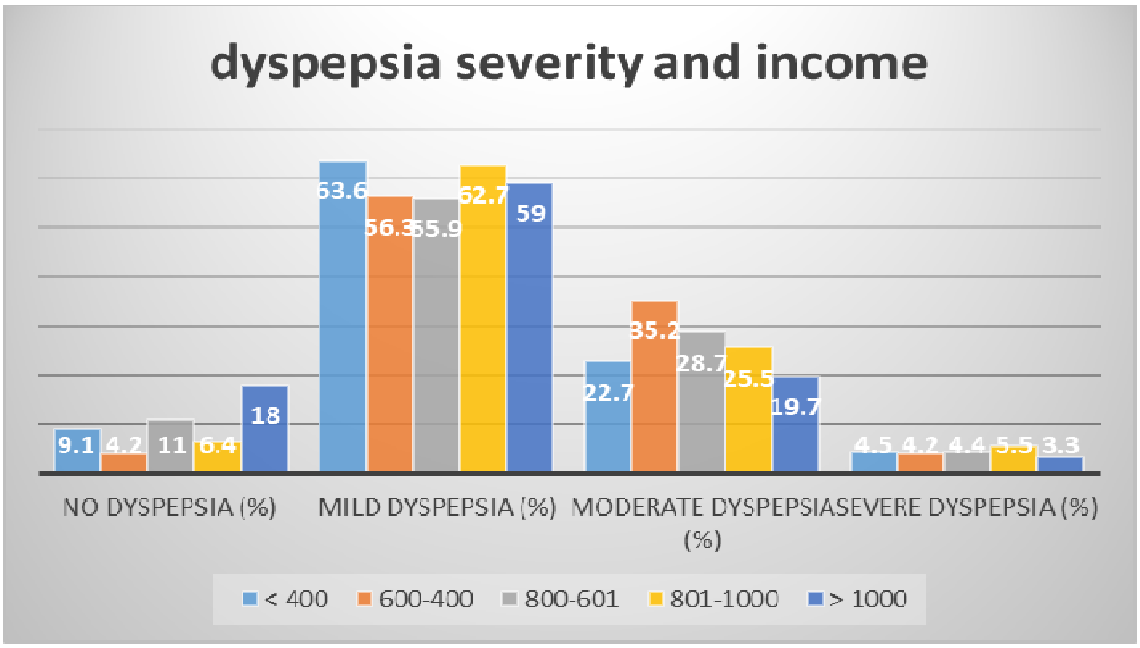
1.Dyspepsia severity according to gender (insignificant)



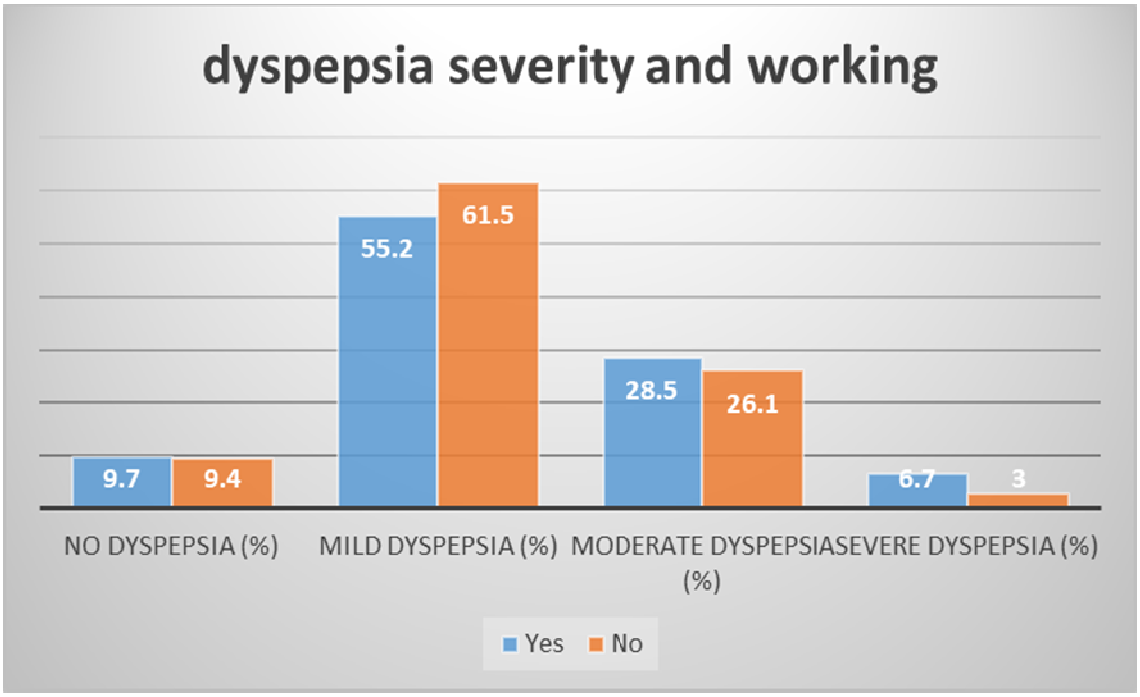
2.Dyspepsia severity according to the living place (insignificant)



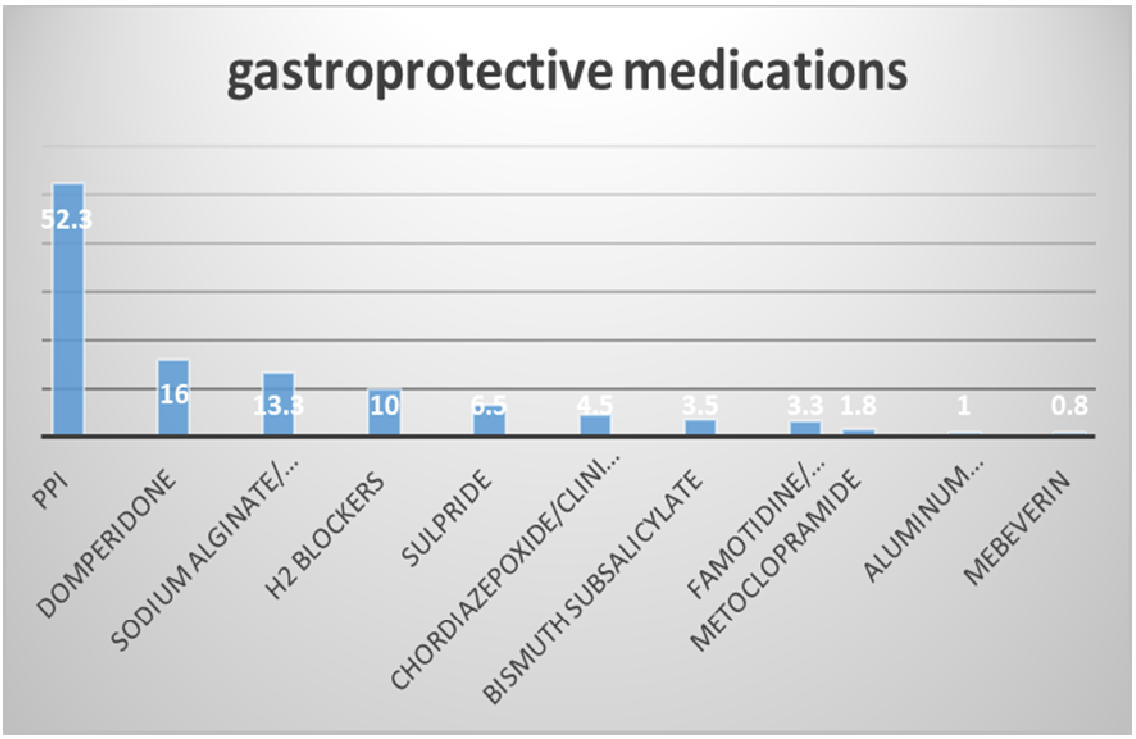
3.Dyspepsia severity according to income monthly (insignificant)



4.Dyspepsia severity according to working (insignificant)



5.The kind and frequency of gastro protective medications



جامعة النَّجاح الوطنيَّة
كليَّة الدّراسات العليا

مضاعفات الجهاز الهضمي العلوي وعلاجها لدى مرضى الأمراض المزمنة: دراسة مقطعية من فلسطين

إعداد
ديمة محمود مصطفى طعمة

إشراف
أ.د. رواء الرمحي

قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في علم الأدوية بكلية الدراسات العليا
في جامعة النجاح الوطنية في نابلس، فلسطين.
2022

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الملخص

الخلفية: يعاني معظم الأشخاص الذين تزيد أعمارهم عن 60 عامًا من مرض مزمن واحد على الأقل. نتيجة لذلك ، يجب استخدام العديد من الأدوية. تحدث مضاعفات الجهاز الهضمي بسبب الآثار الضارة لهذه الأدوية المزمنة على المعدة.

الأهداف: تهدف الدراسة إلى تقييم مدى انتشار المرضى الذين يتناولون الأدوية المزمنة والذين يعانون من مضاعفات الجهاز الهضمي العلوي ، وشدة هذه الأعراض ، وما إذا كانوا يتناولون أي أدوية واقية للجهاز الهضمي أم لا.

المنهجية: هذه دراسة مقطعية من خلال استبيانات من العيادات الخارجية في مستشفى متخصص. تم تضمين المرضى الذين يعانون من أمراض مزمنة والذين كانوا يتناولون دواء واحدًا مزمناً على الأقل في الدراسة. تم استخدام نموذج جمع البيانات لجمع المعلومات. تم استخدام استبيان ليدز قصير المدى لعسر الهضم (SF-LDQ) لتقييم شدة أعراض الجهاز الهضمي العلوي. تم إجراء التحليل الإحصائي باستخدام الحزمة الإحصائية للعلوم الاجتماعية (SPSS) الإصدار 21.

النتائج: تم تضمين ما مجموعه 400 مريض يعانون من أمراض مزمنة ويستخدمون أدوية متعددة. من بينهم 53.8٪ إناث و 56٪ متزوجين و 58.5٪ عاطلين عن العمل و 70٪ ليسوا مدخنين ومتوسط العمر 54.7 ± 17.5 سنة. أكثر الأمراض المرضية المشتركة بين المرضى كانت السكري وارتفاع

ضغط الدم والتهاب المفاصل بنسب 44.3٪ و 38٪ و 27.3٪ على التوالي. يستخدم معظم المرضى ما بين 2 و 4 أدوية يوميًا. الأكثر استخدامًا كان الأسبرين بنسبة 50٪ ، يليه أتورفاستاتين ، بيسوبرولول ، ثم الأنسولين بنسب 29.5٪ ، 25٪ ، 20.3٪ على التوالي. من بين 400 مشارك ، عانى 362 (90.5٪) من الآثار الجانبية للجهاز الهضمي العلوي مثل عسر الهضم (66٪) وحرقة المعدة (77.5٪) والغثيان (49.3٪) وارتجاع المرئ (52.3٪). بناءً على درجة SF-LDQ ، من بين 400 مستجيب ، 235 (58.8٪) ، 109 (27.3٪) و 18 (4.5٪) عانوا من عسر الهضم الخفيف والمتوسط والشديد على التوالي، بينما 9.5% من المشتركين لم يعاني من عسر الهضم. كانت مثبطات مضخة البروتون هي المجموعة الأكثر وصفًا في 209 (52.3٪) مريضًا. التقدم في السن ، وعدم العزوبية ، والتأمين الصحي ، والتدخين واستخدام 5 أدوية او اكثر كلها كانت مرتبطة باحتمال أكبر للإصابة بعسر الهضم ؛ (قيمة p <0.05).

الخلاصة: كانت مضاعفات الجهاز الهضمي العلوي بين مرضى الأمراض المزمنة شائعة جدا. لحسن الحظ ، كانت الأعراض خفيفة في معظم الحالات. يزداد الخطر مع تقدم العمر واستخدام عدد أكبر من الأدوية. من المهم استخدام عوامل حماية الجهاز الهضمي عند الحاجة لها.

كلمات مفتاحية: أمراض مزمنة، أعراض جانبية للجهاز الهضمي العلوي، تهيج المعدة، عسر الهضم، فلسطين.