

**PREVALENCE OF GASTRODUODENAL LESIONS IN CHRONIC
NON-STEROIDAL ANTI-INFLAMMATORY DRUG USERS
PRESENTING WITH DYSPEPSIA AT THE KENYATTA
NATIONAL HOSPITAL**

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December 2007

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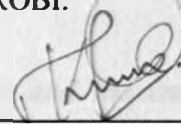
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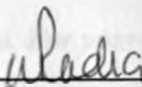
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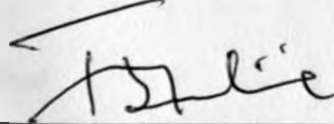
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GLOSSARY.

1. ARAMIS - Arthritis, Rheumatism and Aging Medical Information System.
2. ASTRONAUT - Acid Suppression Trial; Ranitidine versus Omeprazole for NSAID Associated Ulcer Treatment.
3. CI - Confidence interval.
4. CLASS - Celecoxib Long-term Arthritis Safety Study.
5. CLO - Campylobacter-like organism.
6. Coxibs - Selective cyclo-oxygenase 2 inhibitors.
7. GI - Gastrointestinal.
8. HELP - Helicobacter Eradication for Lesion Prevention.
9. H. pylori - Helicobacter pylori.
10. H₂-receptor - Histamine₂-receptor.
11. KNH - Kenyatta National Hospital.
12. mg - Milligram.
13. MOPC - Medical Out Patient Clinic.
14. MUCOSA - Misoprostol Ulcer Complication Outcomes Safety Assessment trial.
15. NSAID - Non-steroidal anti-inflammatory drug.
16. OMNIUM - Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management.
17. OR - Odds ratio.
18. PG - Prostaglandin.
19. PPI - Proton pump inhibitor.

- 20. PUD - Peptic ulcer disease.
- 21. SOPC - Surgical Out Patient Clinic.
- 22. TNF- α - Tumor Necrosis Factor-alpha.
- 23. UGIB - Upper gastrointestinal bleed.
- 24. UoN - University of Nairobi.
- 25. VIGOR - Vioxx Gastrointestinal Outcome Study.

ABSTRACT.

BACKGROUND.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed and used classes of drugs worldwide. It is a well known phenomenon that NSAIDs cause gastroduodenal mucosal damage resulting in outcomes ranging from non-specific dyspepsia to ulcerations, upper gastrointestinal bleeding, perforation and even death. However, no data exist to show the prevalence of these lesions in our local setting.

OBJECTIVES.

The aim of the study was to determine the prevalence of gastroduodenal lesions seen at endoscopy and histopathology in chronic NSAID users presenting with dyspepsia at the Kenyatta National Hospital.

STUDY DESIGN.

This was a hospital-based cross-sectional study.

METHODS.

72 patients aged 13 years and above, on NSAIDs for 4 weeks or more, and presenting with dyspepsia were recruited into the study. All patients and/ or guardians gave informed consent for participation in the study and for endoscopic examination. Six biopsy specimens were taken from each patient (2 from each of the following sites: - corpus, antrum and duodenum). One specimen from each of the three sites was subjected to the rapid urease test for *H. pylori* detection, while the remaining three were subjected to histopathological evaluation.

RESULTS.

47 male and 25 female patients aged between 16-77 years, with a mean age of 43.4 years were studied.

At endoscopy, only 10 (13.9%) patients had normal gastroduodenal mucosa. Gastritis was the most prevalent lesion occurring in 50% of the patients. Peptic ulcer disease had a point prevalence of 30.5% (duodenal ulcers 22.2%, and gastric ulcers 8.3%). Other lesions at endoscopy were duodenitis 16.7%, gastric erosions 5.6%, duodenal erosions 1.4% and hemorrhagic gastritis 1.4%.

At histopathology, only 5 (6.9%) patients were found to have normal gastroduodenal mucosa. Chronic active gastritis was the most prevalent lesion at 77.8%. Other lesions were chronic gastritis 12.5%, chemical gastritis 6.9%, duodenitis 41.7% and intestinal metaplasia 4.2%. Prevalence of *H. pylori* in our study population was 50%. There was no association between the gastroduodenal lesions and *H. pylori* infection.

CONCLUSIONS.

There was a high prevalence of gastroduodenal mucosal lesions both at histopathology (93.1%) and endoscopy (86.1%) in the chronic NSAID users. The point prevalence of PUD (30.5%) in our study population was much higher than that reported in dyspeptic patients from the general population at Kenyatta National Hospital in whom Lwai-Lume found a point prevalence of 23%.

Both *H. pylori* and NSAIDs were independent etiological factors in the pathogenesis of gastroduodenal lesions in chronic NSAID users.

INTRODUCTION AND LITERATURE REVIEW.

GASTRODUODENAL MUCOSAL DEFENSE.

The gastric epithelium is under a constant assault by a series of endogenous noxious substances including hydrochloric acid (HCl), pepsinogen/pepsin and bile salts, as well as exogenous substances such as medication, alcohol and bacteria. ⁽¹⁾ To combat this assault, a highly intricate biologic system is in place to protect the tissue from injury and eventual ulceration and to repair any injury that may occur. This mucosal defense system can be envisioned as a three level barrier composed of pre-epithelial, epithelial and sub-epithelial elements. ⁽¹⁾

1. PRE-EPITHELIAL ELEMENTS.

These constitute the first line of defence and comprise of a mucus-bicarbonate layer which serves as a physico-chemical barrier to multiple molecules including hydrogen ions. Mucus is secreted by the apical portions of mucus secreting gastric cells and mucus neck cells and streams out through apical defects to form the gastric mucus layer, consisting of an adherent semi-solid gel overlaid by soluble mucus. ⁽²⁾ This mucus gel functions as a non-stirred water layer impeding diffusion of ions and molecules such as pepsin. ⁽¹⁾ The mucus layer also maintains a pH gradient between the lumen and the epithelial surface. ⁽³⁾ A hydrophobic surface, comprising of phospholipids and their bound fatty acids secreted by gastric mucus cells, provides the physical barrier to repel aqueous solutions including acid. ⁽³⁾

Bicarbonate is secreted by surface epithelial cells of the gastroduodenal mucosa under and within the mucus gel, and forms a pH gradient ranging from 1 to 2 at the gastric luminal surface and approximates 6 to 7 along the epithelial cell surface. ⁽¹⁾ Stimuli of mucus and bicarbonate secretion in vivo include reflexes induced by gastric mucosal irritation, cholinergic stimuli, acid secretion and most importantly prostaglandins. ⁽²⁾

Nitric oxide and guanosine 3'5'-cyclic monophosphate (cGMP) also play an effector role in mucus release from isolated gastric cells. ⁽⁴⁾

This combination of mucus and bicarbonate secretion provides a less acidified environment near the cell surface as compared to the lumen and helps the gastroduodenal mucosa defend itself from damage.

2. EPITHELIAL ELEMENTS.

These provide the second line of defense through various mechanisms which include: - mucus production; epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production; and lastly, the maintenance of intracellular tight junctions. ⁽¹⁾

Results from the in vivo measurement of rat gastric surface cell intracellular pH (pH_i) indicate that epithelial cells have the ability to regulate pH_i, when pH in the luminal fluid is altered. ⁽⁵⁾ Besides this, epithelial cells bordering a site of injury are able to migrate and restore the damaged region independent of cell division via the process of restitution. ⁽⁶⁾ Several studies have shown that both epithelial cell regeneration and restitution are regulated by growth factors and cytokines including fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor and prostaglandins. ⁽²⁾

3. SUBEPITHELIAL ELEMENTS.

These comprise of an elaborate microvascular system within the gastric submucosal layer. Considerable evidence exists to indicate that mucosal blood flow plays an important role as a mucosal defensive factor. Tactile stimulation of the gastric mucosa leads to a prostaglandin dependent increase in mucosal blood flow, which plays a role in protecting the mucosa against contact damage with gastric contents. ⁽⁷⁾ Endogenous nitric oxide (NO) is also a defensive factor and acts by preserving mucosal blood flow in the presence of a damaging agent. ⁽⁸⁾ The architectural arrangement of the mucosal capillaries

further facilitates delivery of bicarbonate from parietal cells to surface epithelial cells during acid secretion. ⁽⁹⁾ Moreover, this microcirculatory bed provides an adequate supply of micronutrients and oxygen, while removing toxic metabolic by-products. ⁽¹¹⁾

ROLE OF PROSTAGLANDINS IN GASTRODUODENAL DEFENSE.

Prostaglandins (PGs) play a central role in gastric epithelial defense and repair. As mentioned earlier, tactile stimulation of the gastric mucosa leads to a prostaglandin-dependent increase in mucosal blood flow, which plays a role in protecting the mucosa against contact damage with gastric contents. ⁽⁷⁾ The gastric surface mucous cells also contain the apparatus that respond to prostaglandin stimulation inducing an increase in the volume of iodoplatinate reactivity of a family of lipid-containing organelles (a measure of phospholipids), which may underlie the ability of prostaglandins to increase the hydrophobic surface properties of the stomach. ⁽¹⁰⁾ In an animal model of acid-induced duodenal villous damage, 16, 16- dimethyl- prostaglandin E₂ induced an increase in basal alkaline secretion, which appeared to be a better predictor of protection against exogenous acid-induced deep villous damage. ⁽¹¹⁾

It is now clear that prostaglandins regulate mucosal blood flow; release of mucosal bicarbonate and mucus; increase mucosal hydrophobicity; inhibit parietal cell secretion and maintain epithelial cell restitution.

Prostaglandins are oxidized derivatives of the poly-unsaturated long-chain fatty acid arachidonic acid. Biosynthesis is initiated by release of arachidonic acid from membrane phospholipids by lipases (predominantly the phospholipase A₂ type), which is then oxygenated into PGG₂ and PGH₂ by the prostaglandin endoperoxide synthase enzyme better known as cyclo-oxygenase enzyme (COX). ⁽¹²⁾ The fate of PGH₂ and the distribution of prostanoids formed from it (PGD₂, PGE₂, PGF₂, prostacyclin = PGI₂ and thromboxane = T_xA₂) depends on the cell type in which it is synthesized and the tissue specific isomerases found within that cell. ⁽¹²⁾

The early 1990s led to the discovery that COX exists in two isoforms; COX-1, a wide ranging essential enzyme expressed in a constitutive manner and involved in cytoprotective and regulatory functions in the gastrointestinal mucosa, platelets and renal cells. ⁽¹³⁾ COX 2, predominantly a cytokine induced enzyme that produces prostaglandins that mediate pain and inflammation. It is expressed at low concentrations in most normal tissue but is up-regulated in inflammatory cells such as leucocytes, macrophages, fibroblasts and synoviocytes. ^(1, 12, 13)

PATHOGENESIS OF NSAID-RELATED UPPER GI TOXICITY.

NSAIDs are among the most commonly prescribed drugs worldwide. It is a well known phenomenon that they cause gastric mucosal injury ranging from non-specific dyspepsia to ulceration, upper gastrointestinal bleeding, perforation, gastric outlet obstruction and death – summarized by the term ‘NSAID gastropathy’. ⁽¹⁴⁾ They have also been shown to cause small and large intestinal injury, hepato-renal dysfunction and organ failure, as well as skin reactions. In the last decade, there has been concern that some NSAIDs, especially indomethacin, aspirin and the more potent prostaglandin synthetase inhibitors, may accelerate the process of cartilage destruction in osteoarthritis. ⁽¹⁵⁾

Despite a large number of studies on the basic mechanisms of NSAID-mediated gastrointestinal (GI) damage and the widespread clinical investigations and use of these agents, a clear picture of the mechanisms of ulcer pathogenesis has not emerged. ⁽⁶⁾ It is also not clear what separates the majority of individuals who tolerate NSAIDs well from those few who develop ulcer complications, though some risk factors like age and previous peptic ulcer disease (PUD) or upper GI bleeding (UGIB) have been identified. ⁽⁶⁾ It is noteworthy that at surveillance endoscopy in long-term NSAID users, ulceration is found with a 20-30% prevalence. ⁽¹⁶⁾ However, clinical ulcers presenting with complications occur much less frequently (0.5 - 4.0% per patient year of NSAID use). ⁽⁶⁾

The spectra of injuries that may occur in the gastric mucosa after NSAID consumption vary from acute injury to chronic injury. ^(6, 17, 18) Acutely, there may be petechiae and intramucosal gastric hemorrhages readily observed several hours after ingestion of aspirin or other NSAIDs. ^(17, 18) These may coalesce into erosions, defined as shallow breaks in the mucosal surface that are histologically distinguished as being limited only to the mucosa. ⁽¹⁸⁾ This is unlike ulcers which penetrate the submucosa and sometimes into the muscularis propria. Ulcers are described as either being acute or chronic (have scar tissue), have a lesion size usually ≥ 5 mm and a depth. ⁽¹⁸⁾ Long-term NSAID use is also associated with antral changes described as Type C gastritis. This is characterized by epithelial, endothelial and muscular hyperplasia but has no inflammatory component. ⁽¹⁷⁾

PATHOGENIC MECHANISMS FOR ACUTE MUCOSAL INJURY.

A wide range of NSAID actions that may mediate acute damage to the gastric mucosa have been identified. Whereas some factors may promote only acute damage, others may promote both acute and chronic damage. It is likely that initial mucosal injury results from the topical effects of NSAIDs. ⁽⁶⁾

1. ION TRAPPING OF WEAK NSAIDS.

A substantial increase in diffusion of luminal hydrogen ions back into the mucosal tissue has been implicated in the gastric damage induced by topically applied irritants including aspirin and salicylates, and by other anti-inflammatory agents. ⁽¹⁹⁾ Weak acids are non-ionized in the acidic gastric juice and readily permeate the apical mucosal barrier. However, once encountering the neutral environment within the gastric cells, the drug releases hydrogen ions, thereby becoming charged, trapped and concentrated within the mucosa. ⁽⁶⁾ The water-repelling hydrophobicity of the mucosa is also substantially reduced by topical application of aspirin, ⁽¹⁹⁾ which would promote hydrogen ion permeation.

2. PROSTAGLANDIN INHIBITION:-

EFFECT ON MUCOSAL BLOOD FLOW, ISCHEMIA, LEUKOCYTES AND OXYGEN FREE RADICALS.

Inhibition of prostaglandin synthesis is usually associated with long-term effects of NSAIDS. However, prostaglandin inhibition also contributes to acute mucosal injury, since several processes that protect against such injury are prostaglandin mediated. ⁽⁶⁾ Mucosal blood flow which is regulated to a large extent by prostaglandins, decreases following NSAID consumption and accompanies acute NSAID injury. ⁽⁷⁾

It has been postulated that although prostaglandins regulate blood flow, much of the decrease seen with acute injury could result from obstruction of microvessels by adherent white cells and platelets. NSAIDs induce up-regulation of cell surface adhesion molecules such as P-selectin and intercellular adhesion molecule-1 (ICAM-1) ⁽²⁰⁾ which can increase neutrophil endothelial adherence ⁽²¹⁾ and eventually lead to microvascular obstruction.

Wallace ⁽²²⁾ postulated that NSAID-induced neutrophil adherence contributes to the pathogenesis of gastric mucosal damage by occlusion of gastric microvessels by microthrombi leading to reduced gastric blood flow and ischemic cell damage, or via increased liberation of oxygen derived free radicals. Oxygen free radicals react with poly-unsaturated fatty acids of the mucosa leading to lipid peroxidation and tissue damage, and also destroys interstitial matrix following degradation of collagen and hyaluronic acids. ⁽¹⁹⁾

MECHANISMS UNDERLYING CHRONIC NSAID GASTROPATHY.

1. INHIBITION OF MUCOSAL PROSTAGLANDIN PRODUCTION.

Whereas NSAIDs can exert acute local injury on the gastric mucosa after luminal or oral administration, studies have shown that these agents can provoke extensive gastric mucosal toxicity by systemic mechanisms when given by routes that prevent local contact with the mucosa. Prodrug formulations such as sulindac, as well as the parenteral route for ketorolac, although decreasing the potential for topical mucosal injury, are still correlated with NSAID-related ulcer complications. ⁽²³⁾

The biochemical mechanisms of such systemic actions are known to involve the inhibition of COX enzymes by NSAIDs. ⁽¹⁹⁾ This leads to a reduction in the production of protective prostanoids such as PGE₂ and PGI₂ and eventually leads to gastric damage.

To further advance the fact that prostaglandins have an integral component in gastric protection, and that their reduction results in ulceration, the study by Redfern *et al.* ⁽²⁴⁾ demonstrated that antibody mediated depletion of gastric mucosal prostaglandins resulted in ulcer formation. Conversely, augmentation by the addition of exogenous prostaglandin analogs during NSAID use, resulted in protection and healing of ulcers. ⁽²⁵⁾

Currently it is known that there are two isoforms of COX enzymes; a constitutive COX-1 enzyme and an inducible COX-2 enzyme. ^(26, 27) The COX-1 isoform is present in the GI mucosa, renal system and platelets. The prostanoids synthesized by the COX-1 enzyme are involved in the control of many physiological functions including microvascular blood flow, platelet aggregation, renal tubular functions and the regulation of gastric acid production and mucosal integrity. ^(26, 27) The second isoform, COX-2, is inducible and is expressed within 4 to 24 hours in a number of cell systems including macrophages, leucocytes, synoviocytes and fibroblasts, following challenge with inflammatory mediators such as interleukin-1, lipopolysaccharide and various mitogens. ^(26, 27) This isoform is considered to be the primary source of the pro-inflammatory prostanoids

making it an appropriate target for drug development. This has led to the new drug class of anti-inflammatory agents, the COX-2 selective inhibitors or coxibs which will be alluded to later.

2. IMPAIRED MUCOSAL ADAPTATION, REPAIR AND HEALING.

Acute gastric injury caused by oral NSAIDs resolves despite continued administration of the NSAID by a process known as adaptation.⁽²⁸⁾ Though the mechanisms involved in adaptation have not been defined, it is thought that failure of these adaptive mechanisms in a small subset of individuals may contribute to chronic NSAID gastropathy.

The gastrointestinal mucosa responds to epithelial loss within minutes by epithelial migration, which restores epithelial continuity, in the process of restitution.⁽²⁹⁾ This process requires a scaffold of basal lamina constituents, particularly laminin.⁽²⁹⁾

Restitution is stimulated by a range of cytokines and growth factors including transforming growth factor (TGF β), epidermal growth factor (EGF) receptor ligands, basal fibroblast growth factor (bFGF), human growth factor, interleukin-1 β , interleukin-2, interferon gamma (IFN γ), adenosine and trefoil peptides.⁽³⁰⁾ PGE₂ and PGI₂ have been reported to enhance barrier function.⁽³⁰⁾ When this repair fails, wounds (erosions) develop that disrupt the basement membrane, forming persistent ulcers which then become candidates for producing clinically relevant events.⁽¹⁵⁾

Healing of chronic lesions like ulcers involves formation of granulation tissue, re-epithelialization, scarring and contraction of the ulcer base.⁽²⁹⁾ NSAIDs have been demonstrated to impair cell replication which contributes to delayed healing.⁽³¹⁾

Ulceration is associated prominently with COX-2 induction,⁽³²⁾ which appears to be important for the process of ulcer healing and may be inhibited by selective COX-2 inhibitors as well as by non-selective NSAIDs. COX-2 has also been shown to be important for the angiogenic response that is prominent in healing ulcers.⁽³³⁾

PREVALENCE AND RISK OF NSAID ASSOCIATED TOXICITY.

NSAIDs are among the most widely prescribed and used classes of drugs, with consumption by more than 30 million people in the USA alone. ⁽³⁴⁾ Worldwide sales amount to more than 6 billion US dollars annually and account for a large portion of the global pharmaceutical market. ⁽³⁴⁾ The relationship between NSAIDs and gastroduodenal injury and its complications is now well established. Based upon an analysis of patients in the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS), it is estimated that approximately 107,000 patients are hospitalized each year for NSAID-related GI complications, and at least 16,500 NSAID-related deaths occur annually among arthritis patients alone in the USA. ⁽³⁵⁾ The estimated annual costs of direct and indirect NSAID-related adverse effects exceed 7 billion dollars in the USA. ⁽¹⁴⁾ This places a considerable economic burden on the healthcare systems.

According to *Larkai et al.* about two-thirds of long-term NSAID users have gastric lesions identified at endoscopy. ⁽³⁶⁾ Many of these abnormalities are trivial, most being small mucosal hemorrhages or erosions that are scattered throughout the fundus and body of the stomach. The overall prevalence of peptic ulcers is 25%, with the risk of gastric ulcers being slightly higher than that of duodenal ulcers, ⁽³⁶⁾ that is, 15% versus 10% respectively.

Complications of ulcer disease, that is, hemorrhage and perforation, occur far more often in patients taking NSAIDs than in comparable control groups. ⁽³⁷⁾ The overall risk for serious adverse GI events in patients taking NSAIDs is about 3 times greater than that of controls. ⁽³⁷⁾ Clinical ulcers in NSAID users presenting with complications occur 0.5 – 4.0% per patient-year of NSAID use. ⁽⁶⁾

NSAIDs pose a risk for the development of ulcers that may bleed, than for causing bleeding from non-ulcer sources. ⁽³⁴⁾ This is attributed to the fact that non-aspirin NSAIDs bind reversibly to the cyclo-oxygenase enzyme, and therefore, thromboxane inhibition is dependent on other factors such as plasma levels and half-lives of the

drug. ⁽³⁴⁾ The risk of bleeding is low when using ibuprofen, and is high when using drugs with long plasma half-lives such as piroxicam. ⁽³⁸⁾ Aspirin on the other hand, causes irreversible acetylation of platelets and significantly affects the incidence of bleeding, even with regular low dose and occasional use. ⁽³⁹⁾

Though the incidence of GI perforation is less than that of GI bleeding, GI perforation is strongly correlated with NSAID use; the relative risk of perforation is 6 to 7 times, twice as great as that for bleeding, which is 3 to 4 times. ⁽³⁷⁾

Dyspepsia is the most common reason for discontinuation of NSAIDs. ⁽⁴⁰⁾ However, studies have shown a poor correlation between symptoms, endoscopic findings and complications. As an example, in the study by Larkai *et al.* dyspepsia was observed in <10% of patients on NSAIDs who had abnormal endoscopic results. ⁽³⁶⁾ Some studies have, however, shown that persistent symptoms beyond four weeks after the initiation of therapy may be more predictive of gastroduodenal events.

RISK FACTORS.

Published studies have proposed additional confounding factors that may increase the risk of NSAID-associated adverse events. These include: age; past history of peptic ulcer disease or upper GI bleeding; concomitant use of corticosteroids or anticoagulants; high dose NSAID therapy; concomitant use of ≥ 2 NSAIDs and the regular use of aspirin and NSAIDs. ^(37, 38, 39, 41, 42, 43) It is controversial whether the indication for NSAID use, sex of the patient, smoking or alcohol history, *Helicobacter pylori* (*H. pylori*) infection status or the use of selective serotonin re-uptake inhibitors are risk modifiers. ^(38, 42, 44, 45, 47)

1. AGE.

Older patients are more likely to develop ulcers and their complications irrespective of NSAID use. ^(38, 41) In the study by Luis *et al.* ⁽³⁸⁾ the relative risk for UGIB was 2.8 (2.5 to

3.3) in people under 60 years exposed to NSAIDs, 3.7 (2.6 to 5.4) in those of 60 years and older not exposed to NSAIDs, and 13.2 (10.1 to 17.1) in those 60 years and older exposed to NSAIDs.

One study has shown that gastric mucosal prostaglandin synthesis declines with age, and that there are impairments of mucosal blood flow, bicarbonate secretion and mucus synthesis in response to injurious challenge.⁽⁴⁸⁾ As a result, acid back-diffusion increases and the mucosa is more vulnerable with injurious stimuli.⁽⁴⁸⁾ In the same study, elderly patients were noted to have had higher basal acid output than did the younger group. These events may partly explain the increased background risk for ulceration seen in elderly patients.

2. PAST HISTORY.

Past upper GI history magnifies the risk of NSAID associated gastroduodenal complications.^(38,41) In the study by Luis *et al.* previous bleeding or perforation of the upper GI tract was the single most important predictor of UGIB with a relative risk of 13.5 (10.3 to 17.7).

However, how past history increases risk is unclear, although it has been postulated that local mucosal changes at the site of ulceration may play a role. This is due to observations that there is a strong tendency for lesions to relapse in the same location and to be of the same type as those seen initially.⁽⁴³⁾

3. NSAID DOSE AND COMBINATIONS.

Studies show a progressive linear increase in the risk of ulcer complications with increasing dose. This has been consistent across studies, even though a variety of dose ranges has been considered. The relative risk of UGIB increases from 2.1 (range 1.1 to 4.1) for patients on ibuprofen ≤ 1500 milligrams (mg) per day to 6.6 (2.6 to 16.4) for patients on >1500 mg per day, whereas that for indomethacin increases from 1.4 (0.3 to 5.8) for daily doses ≤ 75 mg to 14.4 (5.7 to 36.4) for daily doses >75 mg.⁽³⁸⁾ In the same

study, the relative risk of UGIB was significantly higher for current multiple users of NSAIDs than for single users. ⁽³⁸⁾

4. INDIVIDUAL NSAIDS.

There are important differences in the risk associated with an individual NSAID.

Azapropazone and piroxicam had relative risks greater than 10, whereas ibuprofen had the smallest risk at 2.9 in the study by Luis *et al.* ⁽³⁸⁾ However, this safety advantage was not observed in patients taking higher doses of ibuprofen.

5. DURATION OF NSAID USE.

Several studies give different results as pertains to the relative risk of gastroduodenal events and the duration of therapy. In the meta-analysis by Gabriel *et al.* ⁽³⁷⁾ an odds ratio of 8.0 (95% confidence interval (CI), range 6.4 to 18.1) for NSAID use <1 month as compared with 3.3 (95% CI, range 2.3 to 4.8) for 1 to 3 months of use and 1.9 (95% CI, 1.2 to 3.1) for more than 3 months use determined that the rate of GI complications is highest in the first month of NSAID use. However, subsequent studies have given conflicting results. In the study by Luis *et al.* ⁽³⁸⁾ with respect to duration, the relative risk after the first prescription (4.0, range 2.6 to 6.1) was no greater than the overall risk, and the risk increased slightly with long-term therapy. In a recent study by Laine *et al.* ⁽⁴¹⁾ there was no evidence of a higher event rate in the first 1 to 3 months seen among NSAID naive patients.

6. LOW DOSE ASPIRIN AND OTHER ANTICOAGULANTS.

Although the inhibition of mucosal prostaglandin synthesis is important as a predictor of aspirin ulcer formation, some of its complications, particularly UGIB, result from the inhibition of platelet thromboxane production. Lanos *et al.* ⁽⁴⁹⁾ found an exaggerated increase in bleeding time response after aspirin use in patients with aspirin related GI bleeding compared with matched controls.

The recent study by Henrik *et al.* ⁽³⁹⁾ on patients using low dose aspirin (100 to 150mg once daily) for cardiovascular prophylaxis, showed an increased risk of UGIB with an incidence rate ratio of 2.6 (95% CI, 2.2 to 2.9), and an even higher risk when aspirin was combined with other NSAIDs, with an incidence rate ratio of 5.6 (95% CI, 4.4 to 7.0). In this study, enteric coating did not seem to reduce the risk.

Similarly, in the Celecoxib Long-term Arthritis Safety Study (CLASS), ⁽⁵⁰⁾ the observed incidences of symptomatic ulcers and/or ulcer complications were not significantly different in patients taking celecoxib concomitantly with low-dose aspirin versus those taking conventional NSAIDs. There is no evidence that other anti-coagulants increase the risk of NSAID ulcers, though they are associated with a substantial increase in the risk of ulcer hemorrhage due to their anti-hemostatic properties. This risk is even higher in patients combining NSAIDs and anticoagulants. ⁽⁵¹⁾

7. CORTICOSTEROIDS.

These also seem to magnify the risk of ulcer hemorrhage. ^(41, 52) In the study by Piper *et al.* ⁽⁵²⁾ the risk of hemorrhage increased from 4.4 in NSAID users who were not on corticosteroids to 14.6 in those who were. These effects were observed in patients on prednisolone ≥ 10 mg per day.

8. ALCOHOL AND SMOKING.

Studies are inconsistent whether smoking and alcohol increase the risk of NSAID ulcer complications. Smoking is a risk factor for the initiation and recurrence of gastric and duodenal ulcers and inhibits ulcer healing; nicotine decreases gastric prostaglandin production and decreases the acid-buffering capacity of the duodenum. ⁽¹⁷⁾ Smoking has also been shown to impair mucosal adaptation to NSAID use and hence increases risk for gastroduodenal lesions. ⁽²⁸⁾ In the study by Luis *et al.* ⁽³⁸⁾ smoking increased the risk of UGIB by 40%. Studies with alcohol have been conflicting with some showing

consumption of >5 drinks per day, and alcohol-related diagnosis' such as cirrhosis or pancreatitis (i.e. long-term heavy drinking) increase risk of UGIB, while others are equivocal. ⁽¹⁷⁾

9. SEX AND COMORBIDITIES.

The male sex has been shown to be an independent risk factor for UGIB in various studies. ^(38, 41) This is probably due to the fact that males are predisposed to duodenal ulcers independent of *H.pylori* status. ⁽⁵³⁾

Severity of disability and duration of rheumatoid arthritis have been found to be independent risk factors in the Laine study, ⁽⁴¹⁾ and in the multivariate analyses of the Misoprostol Ulcer Complication Outcomes Safety Assessment trial (MUCOSA), and the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) data bank. ^(25, 35, 41) Use of medications presumably acting as surrogates for upper GI symptoms, particularly histamine-2 - receptor antagonists (H₂-receptor antagonists), modestly increase the risk of upper GI clinical events. ^(25, 35, 41)

10. *HELICOBACTER PYLORI* INFECTION

The relationship between NSAIDs and *Helicobacter pylori* (*H.pylori*) infection is controversial. Epidemiologic, ^(16, 41, 54) therapeutic, ^(44, 45, 46, 47, 55, 56) endoscopic, ⁽¹⁶⁾ and histopathologic studies ⁽⁵⁷⁾ all give discrepant results pertaining to the risks of gastroduodenal events, with some showing increased risks and others reduced risks, in NSAID users who are infected with *H.pylori*, compared with controls.

This variability in results has been attributed to the differences in study designs and methodology, (including the definition of a NSAID user; the age of patients; the types, doses, duration and indications for NSAID use; the study endpoints; definition of dyspepsia and regimens used for the eradication of *H.pylori*, ⁽⁵⁸⁾ the heterogeneous patient

populations and conflict with pharmaceutical interests,⁽⁵⁹⁾ as well as the different strains of *H.pylori* causing infection.⁽⁶⁰⁾

INTERACTION BETWEEN PATHOGENIC MECHANISMS OF *H.PYLORI* AND NSAIDs.

Both NSAIDs and *H.pylori* have a role in the pathogenesis of gastroduodenal injury. *H.pylori* is able to facilitate gastric residence, induce mucosal injury and avoid host defense.⁽¹⁾ In its causation of mucosal injury, studies have shown that basal gastrin-releasing peptide and pentagastrin-stimulated peak acid outputs are higher in *H.pylori* positive patients than in *H.pylori* negative controls.⁽⁶⁰⁾ *H.pylori* exhibits further toxic mucosal effects through toxin production and alteration in blood flow at the site of injury.⁽⁶⁰⁾ Strains with *vacA* and *cagA* genes are associated with increased interleukin-8 production which is responsible for increased production of gastrin from antral G cells.⁽⁶¹⁾

Studies have also shown that the incubation of gastric mucus with a culture supernatant of *H.pylori* reduces the viscosity of the mucus gel.⁽⁵⁹⁾ In addition, *H.pylori* infection has been shown to impair gastric adaptation to repeated administration of aspirin.⁽²⁸⁾

H.pylori is chemotactic to human neutrophils and macrophages and increases the secretion of neutrophil chemotactic cytokines, interleukin-8 and tumor necrosis factor alpha (TNF α).^(1, 60) *H.pylori* and NSAIDs thus act synergistically with respect to their effect on the gastric polymorphonuclear cells.^(1, 60)

H.pylori infection has been shown to result in increased gastric mucosal prostaglandin production. Expression of COX-2 has been observed by immunocytochemistry in the gastric mucosa of infected patients, confirming that *H.pylori* up-regulates COX-2 messenger ribonucleic acid (mRNA) expression and hence gastric mucosal prostaglandin synthesis.⁽⁶²⁾ However, in vitro studies suggest that *H.pylori* may exert an additive effect

on NSAID suppression of prostaglandin E₂ synthesis, thereby increasing the tendency for gastroduodenal injury. ⁽⁶³⁾

CLINICAL IMPLICATIONS OF *H. PYLORI* INFECTION.

➤ GASTRODUODENAL LESIONS AND ACID SUPPRESSION.

A number of trials have investigated the effect of anti-secretory drugs on ulcers associated with NSAID use. The 'Acid Suppression Trial; Ranitidine versus Omeprazole for NSAID Associated Ulcer Treatment' (ASTRONAUT) ⁽⁶⁴⁾ demonstrated that proton pump inhibitors (omeprazole 20mg or 40mg daily) were superior to H₂-receptor antagonists (ranitidine 150mg twice daily) in the healing and prevention of NSAID-associated gastropathy. The presence of *H.pylori* was associated with a significantly greater likelihood of ulcer healing and maintenance of remission. ⁽⁶⁴⁾

The 'Omeprazole versus Misoprostal for NSAID Induced Ulcer Management' trial (OMNIUM) ⁽⁴³⁾ which compared omeprazole (20mg and 40mg daily) versus misoprostol (200 micrograms (ug) four times daily) in the healing and maintenance phase showed similar results. ⁽⁴³⁾

Plausible explanations for the significantly better prognosis associated with a positive test for *H.pylori* were put forward: first, *H.pylori* stimulates the synthesis of mucosal prostaglandins in NSAID users, which could enhance healing and reduce relapse. ⁽⁴³⁾

Second, intragastric pH is higher during omeprazole therapy in *H.pylori* positive patients than in *H.pylori* negative patients ⁽⁵⁶⁾ and third, NSAID associated ulcers might be of two kinds; true primary ulcers caused by NSAID use and *H.pylori* associated ulcers exacerbated by NSAID use. ⁽⁴³⁾

➤ *H. PYLORI* ERADICATION.

Controversy exists as to whether *H.pylori* infection should be eradicated in *H.pylori* positive individuals on long-term NSAID therapy. An array of conflicting studies has

eradication group versus 28% in the control group ($p < 0.01$). This also suggested that *H.pylori* eradication before NSAID therapy reduces the risk of gastroduodenal ulceration.

➤ COMPLICATIONS.

The effects of *H.pylori* infection on the risks for gastroduodenal complications in NSAID users is also controversial. To investigate the role of *H.pylori* as a cause of bleeding peptic ulcers among NSAID users, Aalykke *et al.*⁽⁵⁴⁾ studied current users of NSAIDs admitted because of bleeding peptic ulcers (n 132). Controls were NSAID users without gastrointestinal complications (n 136). Results yielded 58 (44%) case subjects with a bleeding gastric ulcer, 54 (41%) with a bleeding duodenal ulcer, 12 (9%) with both gastric and duodenal ulcers and 8 (6%) with hemorrhagic gastritis. *H.pylori* was present in 75 (57%) cases compared with 59 (43%) controls. The adjusted odds ratio of bleeding peptic ulcer among NSAID users associated with *H.pylori* infection was 1.81 (95% CI, 1.02 – 3.21). *H.pylori* accounted for approximately 24% of bleeding peptic ulcers among the elderly. Their conclusion was that NSAID users infected with *H.pylori* have an almost two-fold increased risk of bleeding peptic ulcers compared with NSAID users without *H.pylori*.

In a meta-analysis by Huang *et al.*⁽¹⁶⁾ addressing the relationship between *H.pylori* infection and use of NSAIDs in the pathogenesis of peptic ulcer disease, they found that *H.pylori* infection increased the risk of peptic ulcer disease in NSAID takers 3.53-fold. *H.pylori* infection and NSAID use increased the risk of ulcer bleeding 1.79-fold and 4.85-fold, respectively. However, the risk of ulcer bleeding increased to 6.13-fold when both factors were present. However, in a different study by Okan *et al.*⁽⁶⁷⁾ the frequency of *H.pylori* infection was significantly lower in patients with bleeding ulcers than in controls.

➤ *H. PYLORI* AND ASPIRIN.

There is now wide agreement that *H.pylori* infection increases mucosal damage and the risk of upper GI bleeding in low-dose aspirin users. ⁽⁵⁸⁾ Among patients with *H.pylori* infection and a history of UGIB who are taking low dose aspirin, the eradication of *H.pylori* is equivalent to treatment with omeprazole in preventing recurrent bleeding. However, omeprazole is superior to eradication of *H.pylori* in preventing recurrent bleeding in patients who are taking other NSAIDs such as naproxen. ⁽⁵⁵⁾ This was the conclusion in the study by Chan *et al.* ⁽⁵⁵⁾ evaluating whether eradication of *H.pylori* infection or omeprazole treatment was more effective in preventing recurrent bleeding in chronic NSAID users on naproxen 500mg once daily, and patients on low dose aspirin, 80mg once daily.

MANAGEMENT OF NSAID GASTROPATHY.

General attention to good and parsimonious prescribing: i.e. NSAIDs being used only in patients who do not respond to other analgesics; the lowest possible doses being used; and the least toxic NSAIDs being selected; almost certainly reduces risks associated with NSAID use. ⁽¹⁷⁾ However, for high risk patients (patients with past history of PUD or UGIB, elderly patients >60 years, high dose NSAIDs use, and concurrent use of anticoagulants or corticosteroids) co-therapy with gastroprotective drugs or use of selective COX-2 inhibitors ^(14, 17) has become the mainstay of management.

GASTROPROTECTIVE DRUGS.

1. MISOPROSTOL.

Misoprostol is a prostaglandin analog used to locally replace prostaglandins the formation of which is inhibited by NSAIDs. ⁽¹⁴⁾ According to a meta-analysis by Koch *et al.* ⁽⁶⁸⁾ misoprostol prevents NSAID-induced GI damage: gastric ulceration was found to

be significantly reduced in both acute and chronic NSAID treatment, whereas duodenal ulceration was significantly reduced in chronic treatment.

The adverse effects of misoprostol are dose dependent. They include diarrhea and abdominal pain, which can be disabling and require dose reduction or discontinuation so that a compromise between efficacy and intolerance is often needed. ⁽¹⁷⁾

2. INHIBITORS OF ACID SECRETION.

Acid enhances NSAID induced mucosal damage and might activate proteolytic pepsin and increase gastric absorption of acidic NSAID leading to ion trapping. ^(19, 69) Studies have shown that H₂-receptor antagonists and PPIs protect the gastric mucosa not only by inhibiting acid secretion, but also by scavenging free radicals. ⁽²³⁾ In a recent study by Biswas *et al.* ⁽⁷⁰⁾ omeprazole was shown to be gastroprotective by having both antioxidant and antiapoptotic properties besides its role in acid secretion. Omeprazole (20mg once a day) has been demonstrated to be significantly more effective in the prevention of gastroduodenal ulcers than ranitidine (150mg twice daily) – ASTRONAUT study, ⁽⁶⁴⁾ or misoprostol (200ug twice daily) – OMNIUM study. ⁽⁴³⁾ More recently, esomeprazole, the s-isomer of omeprazole that has been shown to possess a higher systemic bioavailability and also provide significantly more effective and more sustained gastric acid control compared with other PPIs, has been shown to relieve upper GI symptoms significantly in patients continuing to take NSAIDs or selective COX-2 inhibitors. ^(71, 72) Currently, PPIs present the co-medication of choice in preventing NSAID-induced gastropathy.

SELECTIVE COX-2 INHIBITORS.

The benefit of selective COX-2 inhibitors for the protection of the GI tract has been shown in several studies. ^(50, 73, 74, 75) In the ‘Vioxx Gastrointestinal Outcome Study, (VIGOR) study, ⁽⁷³⁾ rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastro-intestinal events per 100 patient years occurred with rofecoxib as compared with 4.5 per 100

patient years with naproxen (relative risk (RR) 0.5, 95% CI, range 0.3 to 0.6; $p < 0.001$). The respective rates of complicated confirmed events (perforation, obstruction and severe upper gastro-intestinal bleeding) were 0.6 per 100 patient years and 1.4 per 100 patient-years (RR 0.4; 95% CI; range 0.2-0.8; $p = 0.005$) respectively.

In the CLASS study, ⁽⁵⁰⁾ celecoxib at dosages greater than those indicated clinically (400 mg twice daily) was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, compared with the conventional NSAIDs (ibuprofen 800mg thrice daily, or diclofenac 75mg twice daily) at standard dosages. This decrease in upper GI toxicity was strongest among patients not taking low-dose aspirin concomitantly. Since COX-2 is involved in several physiological processes, its inhibition by coxibs may lead to some apparent side effects. In the VIGOR study, ⁽⁷³⁾ the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent versus 0.4 percent; RR 0.2; 95% CI; range 0.1 – 0.7). The rate of myocardial infarction was four-fold, the rate of cardiovascular thrombotic events two-fold higher in the rofecoxib group compared with naproxen.

From the foregoing, it can be concluded that use of selective COX-2 inhibitors is associated with reduced GI toxicity especially in patients not concurrently on low-dose aspirin, even in supra-therapeutic doses. However, there is need for further studies to clarify the risk - benefit profile of these drugs.

JUSTIFICATION.

Non-steroidal anti-inflammatory drugs are among the most widely prescribed and used classes of drugs worldwide, being used for both painful and inflammatory conditions. Their use traverses all age groups.

It is well known that NSAIDs cause gastrointestinal mucosal damage resulting in non-specific dyspepsia, peptic ulceration, upper gastrointestinal bleeding, perforation and even death. These complications have been shown to have a higher occurrence in high-risk patients including elderly patients more than 60 years; patients with previous history of peptic ulcers or upper gastrointestinal bleeding; patients on high doses and combinations of NSAIDs; and patients with concomitant use of anticoagulants and corticosteroids. Use of gastroprotective medicines especially proton pump inhibitors, and the use of COX-2 selective inhibitors have been shown to reduce these gastrointestinal complications.

In our local set-up, no studies have been done to confirm the above findings. As such, no recommendations exist to guide clinicians on how to prevent or manage these lesions should they occur. Therefore, there is need for us to establish the type of lesions, their prevalence rates, the patients at high risk, and the duration it takes to develop these lesions in our setting. With this knowledge we can then develop our own local recommendations and guidelines on the use of these highly efficacious and useful drugs.

OBJECTIVES.

BROAD OBJECTIVE.

To determine the prevalence of gastroduodenal lesions in chronic NSAID users presenting with dyspepsia, in KNH.

SPECIFIC OBJECTIVES.

1. To describe the gastroduodenal lesions seen at endoscopy in chronic NSAID users.
2. To describe the histologic changes seen at histopathology in the gastroduodenal mucosal biopsies of chronic NSAID users.
3. To find out the relationship between duration of NSAID use and the gastroduodenal lesions.
4. To find out the relationship between the patients' demographic and clinical characteristics (age, sex, smoking habits, previous history of peptic ulcers and UGIB) and the gastroduodenal lesions.
5. To find out any differences in the gastroduodenal lesions seen at endoscopy and histopathology in chronic NSAID users with and without *H. pylori* infection.

MATERIALS AND METHODS.

STUDY DESIGN.

This was a cross-sectional, descriptive study.

STUDY AREA.

KNH endoscopy unit.

This is a specialized unit of the hospital that is run by qualified gastroenterologists assisted by qualified theatre nurses. The unit is charged with the responsibility of performing all upper GI endoscopies and colonoscopies for the hospital.

Patients are referred to the unit by doctors from the out-patient clinics and the wards.

STUDY POPULATION.

Patients aged 13 years and above, presenting with musculoskeletal disorders requiring chronic NSAID therapy (**Appendix I**), and dyspepsia (**Appendix I**), with or without acute upper GI events (UGIB and / or perforation) were eligible.

They were recruited from the medical outpatient clinics (MOPC); the surgical outpatient clinics (SOPC), especially the orthopedic clinics; and both general medical and surgical wards. Those admitted were interviewed by the principal investigator on the post-admission day.

SAMPLING TECHNIQUE.

Consecutive chronic NSAID users presenting with dyspepsia, seen in the MOPC and SOPC willing to participate in the study were enrolled. Patients admitted in the general medical and surgical wards with chronic NSAID use and dyspepsia, with or without acute upper GI events (UGIB and/or perforation) and willing to participate in the study were also enrolled consecutively.

SAMPLE SIZE CALCULATION.

The minimum sample size estimated using the formula for the calculation of sample size in a prevalence study was 72, as shown below.

$$n = \frac{Z_{(1-\alpha/2)}^2 \times p(1-p)}{d^2}$$

Where :- n = sample size.

Z = standard normal deviate.

p = estimated prevalence of the characteristic.

d = degree of precision or accuracy.

α = level of significance.

For this study, the prevalence of peptic ulceration in chronic NSAID users was taken as 25% based on previous studies⁽³⁶⁾. The confidence level was taken as 95%, and the error margin as 10%.

PATIENT SELECTION.

INCLUSION CRITERIA.

1. Chronic NSAID users with dyspepsia, who consent to undergo upper GI endoscopy.
2. Patients aged 13 years and above.
3. Written, informed consent by the patient.

EXCLUSION CRITERIA.

1. Previous attempt to eradicate *H. pylori* infection or use of antibiotics in the month before enrollment.
2. Use of gastroprotective drugs (PPIs, H₂-antagonists, misoprostol), for more than two weeks prior to endoscopy.
3. Use of selective COX-2 inhibitors.
4. Patients of Asian and Caucasian descent.

PROCEDURES.

All patients completed a questionnaire under the principal investigator's supervision, detailing their demographic features, including their age, sex, inpatient / outpatient status, as well as smoking habits. **(Appendix II)**

A thorough medical history detailing previous PUD/UGIB, coexisting comorbid conditions and drug history was taken. The drug history encompassing: the NSAID currently on use, the dosage, the duration of use, whether being used singly or in combination with other NSAIDs, as well as other medications being used concurrently, was also taken. **(Appendix II)**

History of dyspepsia, defined as chronic or recurrent upper abdominal pain or discomfort that was not relieved by bowel actions or passage of flatus, was specifically sought for from all the patients by the principal investigator. **(Appendix I)**

Verification of NSAID use was achieved by inspection of an authentic doctor's prescription, patient's file, medication packs or the remaining tablets. Verification of the patient's comorbid conditions was also done by reading through the patient's file.

Those enrolled were assigned a study number and requested to sign a consent form for participation in the study and for upper GI endoscopy. For those below 18 years, this was done by their parents/guardians. (**Appendix IV and V**) The patients were then given the earliest appointment for endoscopy, where possible within 72 hours of recruitment, and advised to starve for 6-8 hours prior to the procedure.

UPPER GI ENDOSCOPY.

The patients underwent upper GI endoscopy performed by a consultant gastroenterologist in the presence of the principal investigator. This was done using a forward viewing fiberoptic instrument. (Olympus fiberoptic scope model Q20, Q40 or XQ20)

The procedure was performed in the standard manner after initial local pharyngeal anaesthesia. Once the endoscope was safely introduced into the stomach, the gastroenterologist evaluated the gastroduodenal tract and reported on the gross macroscopic features as outlined in the study definitions. (**Appendix I and II**) 6 biopsy specimens were then obtained from the gastroduodenal mucosa, two from each of the following sites: corpus, antrum, and the first part of the duodenum. Additional biopsy specimens were taken from any suspicious looking lesions.

One biopsy specimen from each site was placed in the campylobacter-like organism (CLO) test well for the rapid urease test. The remaining biopsy specimens were fixed in 10% buffered formalin in separate labeled bottles for histological investigations.

All endoscopes and biopsy forceps were washed and sterilized in 2% glutaraldehyde solution for 10 minutes prior to each examination.

DETECTION OF *H. PYLORI*.

Possible *H. pylori* infection was evaluated by histological examination and the rapid urease test.

Biopsy specimens for histology were fixed in 10% buffered formalin before transportation to the Pathcare laboratory, where they were processed after a minimum 6 hours. In the laboratory, they were embedded in paraffin and sectioned at 5µm. These sections were then stained with haematoxylin-eosin and modified Giemsa stain for the histological detection of *H. pylori*.⁽⁵⁷⁾

The other biopsy specimens, from similar sites as those taken for histopathology, were placed in a CLO test well for the rapid urease test. (Esokit ® Hp test. Cambridge Life Sciences Limited.) This test is a marker of the presence of viable *H. pylori* organisms and detects the conversion of urea to ammonia by the bacterial urease. In performing this test, the lid of the CLO test kit was opened to expose the fluid in which the biopsy specimens were then completely immersed. Thereafter, the CLO test kit was re-sealed, and the patient's name, date and time of immersion were recorded. The CLO test kit was then transported to the laboratory where it was kept at room temperature at 20-25°C. Results were read at 3 and 22 hours after immersion. A positive test constituted a color change from yellow to red.

H. pylori infection was deemed positive when either of the two tests, histology or rapid urease test, revealed a positive result.

HISTOLOGICAL ANALYSIS OF THE GASTRIC MUCOSA.

Biopsy specimens for histology, already fixed in 10% buffered formalin, were transported to the Pathcare laboratory where they were processed after a minimum of 6 hours in the formalin. They were embedded in paraffin and sectioned at 5µm. These processed sections were then stained by haematoxylin and eosin, according to the method of May-Grunwald-Giemsa.⁽⁵⁷⁾ They were assessed independently and blindly by a consultant pathologist trained in gastrointestinal pathology. A second pathologist was consulted in the event of any doubtful situation.

All processed biopsy specimens were evaluated for chronic gastritis according to the updated Sydney system for classifying and grading gastritis,⁽⁷⁶⁾ as well as for chemical gastritis according to the modified version of Dixon's system for grading chemical gastritis.⁽⁷⁷⁾ Any other abnormal histological findings found were also reported on.

(Appendix II)

Using the updated Sydney system⁽⁷⁶⁾; chronic inflammation, *H. pylori* density, polymorphonuclear neutrophil activity, glandular atrophy, and intestinal metaplasia, were reported on. To improve comparability of parameters, specimens were scored for *H. pylori* density, intestinal metaplasia, and glandular atrophy as positive (1) or negative (0). Chronic inflammation and polymorphonuclear activity were graded as negative (0), mild (1), moderate (2), or marked (3).**(Appendix II)** The grading of the polymorphonuclear neutrophil activity and chronic inflammation into mild, moderate and marked was done according to the visual analogue scales provided by the updated Sydney classification. Patients scoring 4 or more were considered to have chronic active gastritis which is characterized by a high infiltration of polymorphonuclear neutrophils. **(Appendix II)** Scores of 1 to 3 were taken to as chronic non-active gastritis, simply referred to as chronic gastritis. Where a two-grade difference between the antrum and the body existed, these cases were further distinguished as antral predominant or body predominant gastritis, respectively, as specified by the Updated Sydney classification.⁽⁷⁶⁾

(Appendix II)

All biopsy specimens were also graded according to the modified version of Dixon's system⁽⁷⁷⁾ for chemical gastritis. Foveolar hyperplasia, oedema and prominent smooth muscle fibers were graded as absent (0), or present (1); loss of polymorphonuclear neutrophils and plasma cells were scored inversely from marked (0), to absent (3). **(Appendix II)** Patients scoring more than 6 were considered to have chemical gastritis.

Quality control standards were put in place in the analysis of the biopsy specimens. This was done by effecting both internal (Pathcare Laboratory-Kenya) and external quality control measures. External quality control was assured by pathologists from Pathcare Laboratory-South Africa who randomly reviewed some of the specimens already reported on. This was used as the tool for evaluating and validating the histopathology results.

DATA COLLECTION AND ANALYSIS.

DATA COLLECTION.

All patients were interviewed by the principal investigator. A structured questionnaire **(Appendix II)** and a careful review of prescriptions were used.

The questionnaire sought details of NSAIDs intake, and other relevant history including past history of gastrointestinal disease, smoking habits, and other comorbidities and drugs co-administered.

The principal investigator coded all the data at the time of the interview and all the biopsy specimens during endoscopy before transportation to the laboratory.

DATA ANALYSIS.

The data was verified, cleaned and entered into the software package for social sciences (SPSS version 12.0.1).

Descriptive analysis including proportions for categorical variables and measures of central tendency and dispersion for continuous variables were used.

The Chi-square test was used to determine the relationship between gastroduodenal lesions and the patients' demographic and clinical characteristics as well as the duration of NSAID use.

Comparison between the *H.pylori* positive and negative groups was performed using the Chi-square test or the Fisher's exact probability test. Odds ratio was used to determine the likelihood of a particular diagnosis in the presence or absence of *H. pylori* infection.

95% and its associated confidence intervals were employed in deciding the statistical significance. A p-value of less than 0.05 was considered significant.

ETHICAL CONSIDERATIONS.

Permission to carry out the study was sought from the Department of Internal Medicine, UoN; Pathcare Laboratory Ethical and Scientific Review Committee; and the Ethical and Scientific Committee, KNH.

All patients and the parents/guardians of those aged below 18 years were given a detailed explanation of the purpose and nature of the study. (**Appendix III**) The endoscopy procedure was explained to the patients and the parents/guardians. The role of upper GI endoscopy as part of the routine management of patients presenting with dyspepsia and its safety profile with very minimal risk to the patient was also explained. Patients were enrolled only after ascertaining their full understanding of these issues and after giving an informed written consent. For those below 18 years parents/guardians were required to give the consent. (**Appendix III**)

All information obtained about the patients was handled with utmost confidentiality and used only for the intended purposes. Results obtained from endoscopy, CLO test and histopathology were forwarded to the attending physicians to enhance patients' management. Failure to give consent did not in any way jeopardize the care given to the patient.

All costs accruing from the study were met by the principal investigator.

PATIENT'S CONSENT.

Eligible patients were invited to take part in the study and were given a detailed explanation as to the importance and relevance of the study. Those who gave an informed and written consent to take part in the study underwent upper GI endoscopy. Informed and written consent was sought from the parent/guardian for patients below 18 years.

(Appendix IV, V)

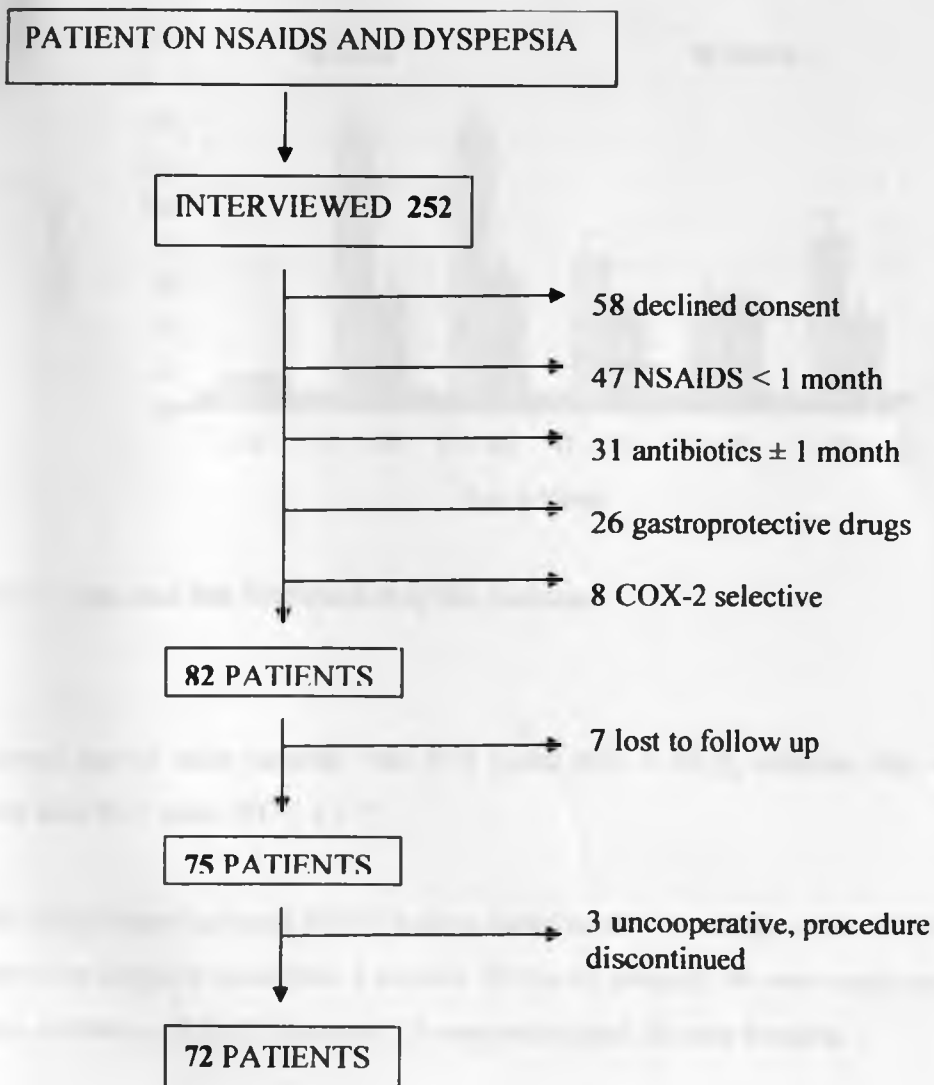
DURATION OF STUDY.

It had been estimated that the study would take three months. However, due to the breakdown of the endoscopy equipment and the subsequent closure of the unit for repairs, the study took six months instead. It was carried out between the months of February and March, and restarted again between June and August. Patient recruitment continued until the desired sample size was achieved.

RESULTS.

1. RECRUITMENT.

Recruitment into the study began in February 2007 and ended in August 2007. A total of 82 consecutive patients on chronic NSAID use and presenting with dyspepsia were found eligible for the study. 75 of these gave an informed and written consent, though only 72 of them had a successful upper GI endoscopy. This was our targeted minimum sample size. The flow chart below shows the recruitment process leading to the desired minimum sample size.



2. DEMOGRAPHIC AND CLINICAL DETAILS OF THE STUDY PATIENTS.

The mean age of the patients was 43.4 years (SD \pm 16.2), with the youngest being 16 years and the oldest 77 years (range 61 years). Most patients were aged between 21–40 years representing 51.4% of the total population.

The ratio of male to female patients was 1.88: 1. (See *Figure 1* below for the age and sex distribution of the patients.)

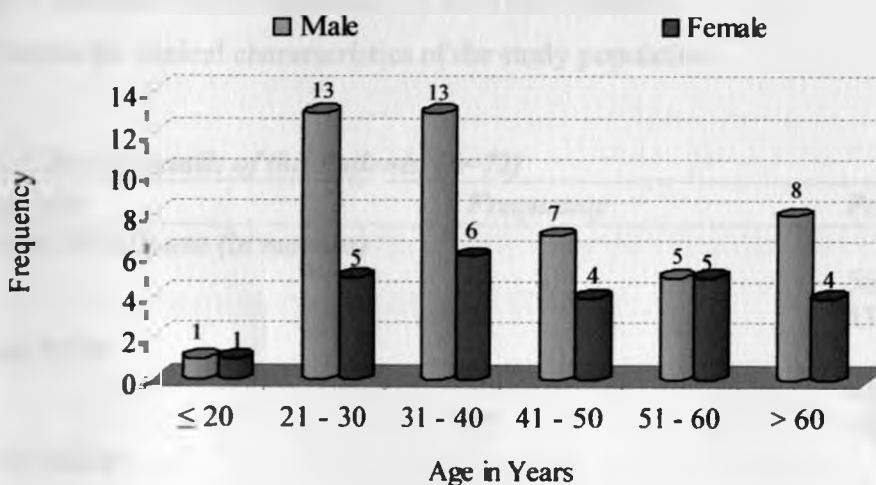


Figure 1: Age and Sex Distribution of the Patients

The mean age of male patients was 42.5 years (SD \pm 16.5), whereas that of female patients was 45.1 years (SD \pm 15.7).

41 (56.9%) patients had used NSAIDs for a duration of 1- 3 months, whereas 31 (43.1%) had used the drugs for more than 3 months. Of the 41 patients, 34 were males and 7 were females, whereas, of the 31 patients, 13 were males and 18 were females.

5 (6.9%) patients had previous history of PUD, while 8 (11.1%) had previous history of UGIB having presented with hematemesis and /or melena stools.

A total of 18 (25%) patients had been on gastro-protective drugs for less than 2 weeks prior to the upper gastrointestinal endoscopy. 10 (13.9%) were on PPIs while 8 (11.1%) were on H₂-receptor antagonists. Out of these, 5 had a previous history of UGIB while 3 had a history of PUD. Four of those with previous UGIB and one of those with previous PUD were on PPIs. Only three of the patients aged 60 years and above were on gastro-protective drugs.

15 (20.8%) patients smoked cigarettes, all were male patients.

Table 1 details the clinical characteristics of the study population.

Table 1: Clinical Details of the Patients. (n=72)

Characteristic	Frequency	Percentage
Duration of NSAID use (in months)		
1 to 3	41	56.9
> 3	31	43.1
History of PUD		
Yes	5	6.9
No	67	93.1
History of UGIB		
Yes	8	11.1
No	64	88.9
Use of Gastro-protective drugs		
Yes	18	25.0
No	54	75.0
Cigarette Smoking		
Yes	15	20.8
No	57	79.2

NSAIDs commonly prescribed to the patients were diclofenac (52 patients) and ibuprofen (26 patients). 41 (61.1%) patients had used only one type of NSAID in their course of treatment, 16 (22.2%) had switched from one type to another, while 12 (16.7%) were on more than one type of NSAID at any one time of treatment.

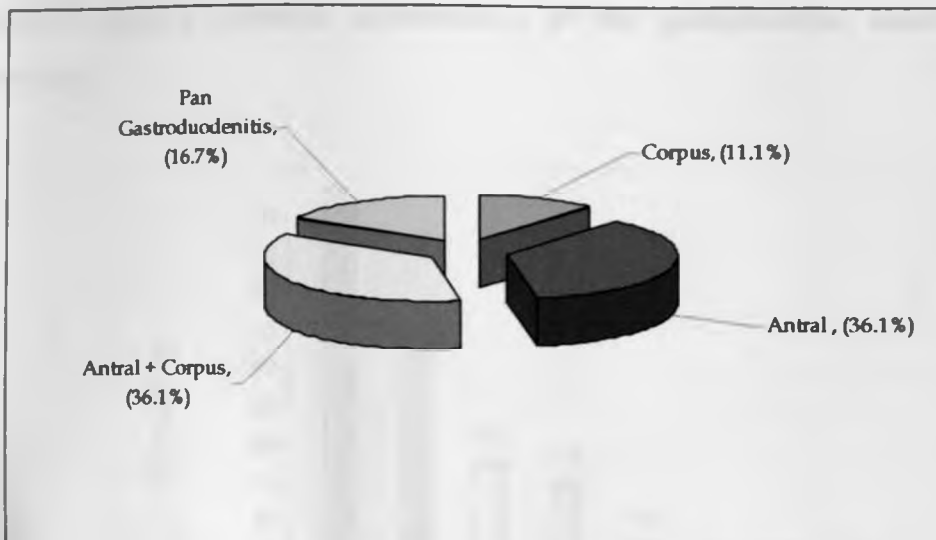


Figure 4: Distribution of Gastritis at Endoscopy.

4. RELATIONSHIP BETWEEN THE PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS, AND THE GASTRODUODENAL LESIONS SEEN AT ENDOSCOPY.

There was no significant association between the age or gender of the patients and the gastroduodenal lesions found at endoscopy. However, of the 15 patients who smoked cigarettes, 11 had gastroduodenal lesions with the relative risk of finding a lesion in a smoker being 2.3. However, none of the lesions was significantly associated with smoking. On the other hand, gastritis was a significant finding in the non-smokers.

(p-value 0.001)

Table 2 below shows this relationship.

Figure 3 shows a graphical representation of the gastroduodenal lesions seen at endoscopy.

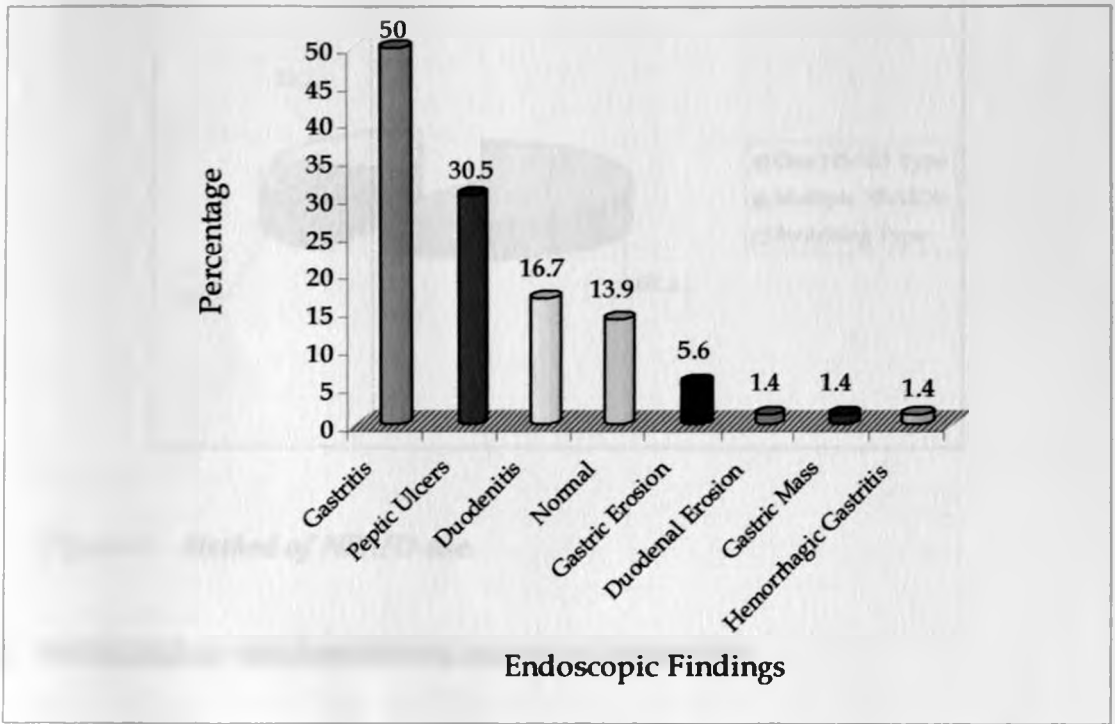


Figure 3: Prevalence of Gastroduodenal lesions at Endoscopy.

Gastritis was the most prevalent lesion at endoscopy. 4 of the 36 patients with gastritis had corpus gastritis (11.1%), 13 had antral gastritis (36.1%), 13 had both corpus and antral gastritis (36.1%), while 6 had pangastroduodenitis (gastritis in the body, fundus, antrum and duodenitis). Figure 4 below shows the distribution of gastritis at endoscopy.

Figure 2 below demonstrates the method of NSAID use.

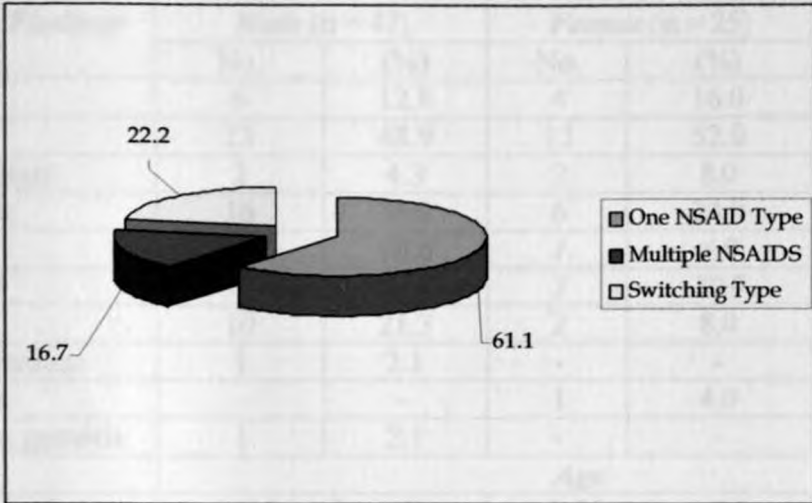


Figure 2: Method of NSAID use.

3. PREVALENCE OF GASTRODUODENAL LESIONS AT ENDOSCOPY.

The commonest endoscopic finding was gastritis in 36 (50%) patients followed by peptic ulcers in 22 (30.5%), [duodenal ulcers 16 (22.2%), antral gastric ulcers 5 (6.9%), and fundal gastric ulcer 1 (1.4%)], duodenitis in 12 (16.7%), and gastric erosions in 4 (5.6%). Other gastroduodenal lesions found at endoscopy were: - duodenal erosions in one patient, angiodysplasia with hemorrhagic gastritis in one patient, gastroduodenal bile reflux in four patients and a gastric mass in one patient. Oesophageal lesions found during the procedure were: - gastroesophageal reflux disease in 5 (6.9%) patients, oesophageal candidiasis in 6 (8.3%), and oesophageal varices in 1 (1.4%).

Of note, however, was the fact that the gastroduodenal lesions were not mutually exclusive. 4 patients had three lesions at endoscopy while 13 had two lesions. As an example, 6 of the patients with duodenitis also had gastritis, whereas 8 of those with peptic ulcers also had gastritis.

Table 2: Endoscopic Findings according to the Demographic factors of the Patients.

<i>Endoscopic Findings</i>	<i>Sex</i>				<i>p-value</i>
	<i>Male (n = 47)</i>		<i>Female (n = 25)</i>		
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>	
Normal	6	12.8	4	16.0	0.706
Gastritis	23	48.9	13	52.0	0.804
Gastric erosions	2	4.3	2	8.0	0.509
Peptic ulcers:	16	34.0	6	24.0	0.378
<i>Gastric</i>	5	10.6	1	4.0	0.332
<i>Duodenal</i>	11	23.4	5	20.0	0.741
Duodenitis	10	21.3	2	8.0	0.150
Duodenal erosions	1	2.1	-	-	-
Gastric mass	-	-	1	4.0	-
Hemorrhagic gastritis	1	2.1	-	-	-
<i>Endoscopic Findings</i>	<i>Age</i>				<i>p-value</i>
	<i>< 50yrs (n = 57)</i>		<i>≥ 50yrs (n = 15)</i>		
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>	
Normal	8	13.8	2	13.3	0.944
Gastritis	27	47.4	9	60.0	0.384
Gastric erosions	4	7.0	-	-	-
Peptic ulcers:	18	31.6	4	26.7	0.713
<i>Gastric</i>	5	8.8	1	6.7	0.793
<i>Duodenal</i>	13	22.8	3	20.0	0.816
Duodenitis	7	12.3	5	33.3	0.052
Duodenal erosions	1	1.8	-	-	-
Gastric mass	1	1.8	-	-	-
Hemorrhagic gastritis	-	-	1	6.7	-
<i>Endoscopic Findings</i>	<i>Cigarette smoking habits</i>				<i>p-value</i>
	<i>Smokers (n = 15)</i>		<i>Non-Smokers (n = 57)</i>		
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>	
Normal	1	6.7	9	15.8	0.363
Gastritis	2	13.3	34	59.6	0.001
Gastric erosions	1	6.7	3	5.3	0.833
Peptic ulcers:	6	40.0	16	28.1	0.372
<i>Gastric</i>	1	6.7	5	8.8	0.793
<i>Duodenal</i>	5	33.3	11	19.3	0.245
Duodenitis	1	6.7	11	19.3	0.243
Duodenal erosions	-	-	1	1.8	-
Gastric mass	-	-	1	1.8	-
Hemorrhagic gastritis	-	-	1	1.8	-

5 patients had a previous history of PUD in our study population. 2 of these had lesions in the oesophagus and were thus not analyzed further, while the remaining 3 had gastroduodenal lesions as shown in *table3* below. There were no significant lesions found at endoscopy in the patients with previous history of PUD or UGIB. However, the numbers were too small to make any conclusions.

Table 3: Endoscopic Findings according to Previous History of PUD and UGIB.

Endoscopic Findings	Previous History of PUD			
	Prior PUD (n = 5)		No prior PUD (n = 67)	
	No.	(%)	No.	(%)
Normal	-	-	10	14.9
Gastritis	2	40.0	34	50.7
Gastric erosions	-	-	4	6.0
Peptic ulcers:	-	-	22	32.8
<i>Gastric</i>	-	-	6	8.9
<i>Duodenal</i>	-	-	16	23.9
Duodenitis	1	20.0	11	16.4
Duodenal erosions	-	-	1	1.5
Gastric mass	-	-	1	1.5
Hemorrhagic gastritis	-	-	1	1.5
Endoscopic Findings	Previous History of UGIB			
	Prior UGIB (n = 8)		No prior UGIB (n = 64)	
	No.	(%)	No.	(%)
Normal	-	-	10	15.6
Gastritis	3	37.5	33	51.6
Gastric erosions	1	12.5	3	4.7
Peptic ulcers:	2	25.0	20	31.3
<i>Gastric</i>	-	-	6	9.4
<i>Duodenal</i>	2	25.0	14	21.9
Duodenitis	1	12.5	11	17.2
Duodenal erosions	-	-	1	1.6
Gastric mass	-	-	1	1.6
Hemorrhagic gastritis	1	12.5	-	-

PEPTIC ULCER DISEASE AT ENDOSCOPY.

A total of 22 patients had peptic ulcers – 16 in the duodenum, 5 in the antrum, and 1 in the fundus. This accounts for a point prevalence of 30.5% of PUD in chronic NSAID users presenting with dyspepsia at KNH. 16 of the ulcers were found in male patients accounting for a point prevalence of 34% in this population (12 duodenal ulcers, 3 antral ulcers and 1 fundal ulcer), while 6 were found in female patients accounting for a point prevalence of 24% (4 duodenal ulcers and 2 antral ulcers).

PUD was distributed throughout the different age categories, with the highest frequency occurring in the 41-50 years age-group. The mean age of patients with PUD was 44 years while that of patients without PUD was 42 years. There was no significant association between age and the presence of PUD. ($p=0.713$)

14 of the patients with peptic ulcers had used NSAIDs for 1-3 months, with the remaining 8 having used for more than 3 months. However, the difference in duration of NSAID use showed no significant association with the finding of PUD at endoscopy. ($p = 0.585$)

14 patients with PUD had concurrent *H. pylori* infection, while 8 did not. However, this was not statistically significant ($p = 0.125$)

5. RELATIONSHIP BETWEEN DURATION OF NSAID USE AND THE GASTRODUODENAL LESIONS AT ENDOSCOPY.

Duration of NSAID use showed no significant association with the lesions found at endoscopy. *Table 4* outlines the findings.

Table 4: Endoscopic Findings according to Duration of NSAID use.

<i>Endoscopic Findings</i>	<i>1-3 months</i> (n = 41)		<i>More than 3 months</i> (n = 31)		p-value
	No.	(%)	No.	(%)	
Normal	4	9.8	6	19.4	0.244
Gastritis	19	46.3	17	54.8	0.475
Gastric erosions	3	7.3	1	3.2	0.453
Peptic ulcers:	14	34.1	8	25.8	0.447
<i>Gastric</i>	4	9.7	2	6.4	0.615
<i>Duodenal</i>	10	24.4	6	19.4	0.611
Duodenitis	8	19.5	4	12.9	0.456
Duodenal erosions	-	-	1	3.2	-
Gastric mass	1	2.4	-	-	-
Hemorrhagic gastritis	-	-	1	3.2	-

6. DETECTION OF *H. PYLORI* INFECTION.

The presence of *H. pylori* infection was evaluated both by histological examination and by the Rapid Urease test (CLO). Biopsy specimens from three sites: - gastric body, gastric antrum and duodenum were each subjected to the CLO test and were also stained with hematoxylin–eosin and the modified Giemsa stains for *H. pylori* detection. A patient was deemed positive for *H. pylori* when any of the three biopsy specimens yielded a positive result at histopathology and /or CLO.

36 (50%) patients were found to have *H. pylori* infection. *Table 5* details their characteristics.

Table 5: Characteristics of Patients with *H. pylori* infection.

Characteristic	Total	<i>H.pylori</i> +	Percentage	p-value
Sex				
Male	47	23	48.9	0.675
Female	25	13	52.0	
Age in years				
≤ 20	-			
21-30	18	9	50.0	0.677
31-40	19	9	47.4	
41-50	11	7	63.6	
51-60	10	6	60.0	
>60	12	5	41.7	
Cigarette smoking				
Yes	15	9	60.0	0.682
No	57	27	47.4	
Duration of NSAID use in months				
1-3	41	20	48.8	0.658
>3	31	16	51.6	
UGIB	8	1	12.5	0.024
PUD	5	1	20	0.164

H. pylori infection was found in 48.9% of the male population and 52% of the female population. There was no significant association between the sex of the patient and the presence of *H. pylori*. (p=0.675)

Though the 41-50 years age group had a high prevalence of *H. pylori*, there was no association between age and the presence of *H. pylori*. (p=0.677)

However, a previous history of UGIB was associated with the absence of *H. pylori* infection. (p-value = **0.024**)

7. DIFFERENCES IN GASTRODUODENAL LESIONS SEEN IN PATIENTS WITH AND WITHOUT *H. PYLORI* INFECTION AT ENDOSCOPY

Table 6 details the endoscopic findings in the presence and absence of *H. pylori* infection.

Table 6: Endoscopic Findings according to the presence of *H. pylori* Infection.

<i>Endoscopic findings</i>	<i>Total</i>	<i>H. pylori +</i>		<i>H. pylori -</i>		<i>OR (95% CI)</i>	<i>p-value</i>
		<i>n,</i>	<i>%</i>	<i>n,</i>	<i>%</i>		
Normal	10	2	20.0	8	80.0	0.21 (0.04-1.04)	0.041
Gastritis	36	22	61.1	14	38.9	0.4 (0.16-1.0)	0.059
Gastric erosions	4	2	50.0	2	50.0	1.0 (0.13-7.5)	1.000
Peptic ulcers:	22	14	63.6	8	36.4	0.45 (0.16-1.3)	0.125
<i>Gastric</i>	6	3	50.0	3	50.0	1.0 (0.10-5.3)	1.000
<i>Duodenal</i>	16	11	68.8	5	31.3	2.73 (0.84-8.9)	0.089
Duodenitis	12	8	66.7	4	33.3	2.3 (0.6-8.4)	0.206
Duodenal erosions	1	1	100	-	-	-	-
Gastric mass	1	-	-	1	100	-	-
Hemor. Gastritis	1	-	-	1	100	-	-

The finding of a normal gastroduodenal mucosa was significant in those patients without *H. pylori* infection (p-value 0.041, OR 0.21(0.04 – 1.04). However, no abnormal lesions were significant in the patients who had *H. pylori* infection

8. PREVALENCE OF GASTRODUODENAL LESIONS AT HISTOPATHOLOGY.

The commonest histological diagnosis was chronic active gastritis found in 56 (77.8%) patients of the study population followed by duodenitis in 30 (41.7%) patients, chronic non-active gastritis (chronic gastritis) in 9 (12.5%), chemical gastritis in 5 (6.9%), intestinal metaplasia in 3 (4.2%) and glandular atrophy in 8 (11.1%) patients. These prevalences are shown in *Figure 5* below.

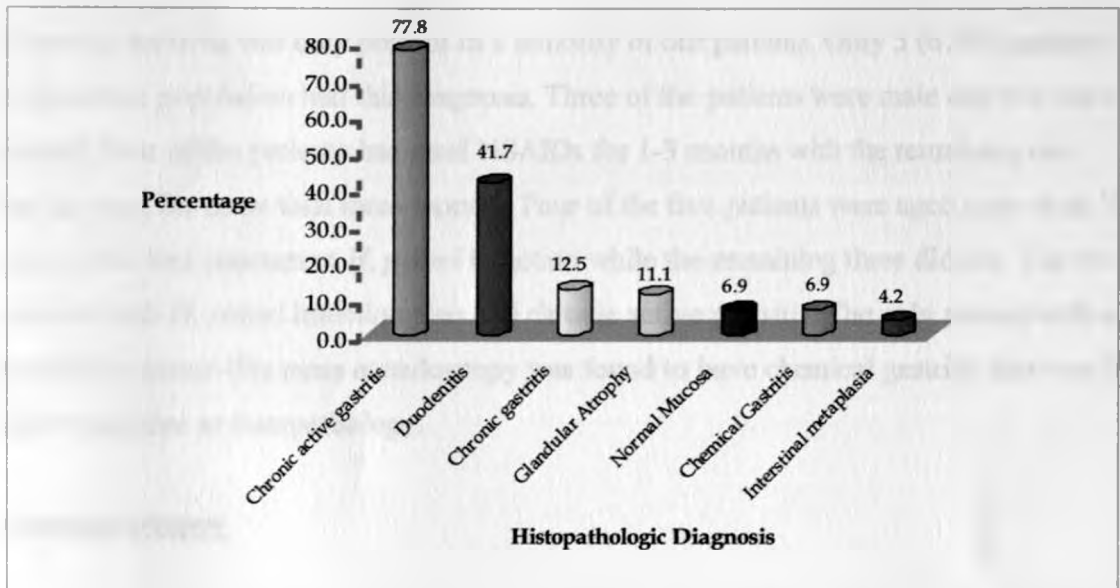


Figure 5: Prevalence of Gastroduodenal Lesions at Histopathology.

Unlike endoscopy where 10 (13.9%) patients were found to have a normal gastroduodenal mucosa, only 5 (6.9%) patients had normal mucosa at histopathology. However, similar to the endoscopic results, many patients had more than one histological finding. 8 patients were noted to have three mucosal lesions occurring concurrently at histology while 28 had two mucosal lesions occurring concurrently. As an example, 23 (31.9%) patients with chronic active gastritis also had duodenitis at the same time, 3 (4.2%) with chronic active gastritis also had chemical gastritis, while all the 3 (4.2%) patients with intestinal metaplasia also had chronic active gastritis.

CHRONIC ACTIVE GASTRITIS.

25 (44.6%) of the patients with chronic active gastritis had moderately active gastritis with 7 (12.5%) having severe active gastritis. Most patients had either antral predominant gastritis (51.8%), or a pan-gastritis (42.7%) with only 5.3% of the patients having a purely corpus gastritis.

CHEMICAL GASTRITIS.

Chemical gastritis was only present in a minority of our patients. Only 5 (6.9%) patients in the entire population had this diagnosis. Three of the patients were male and two were female. Four of the patients had used NSAIDs for 1-3 months with the remaining one having used for more than three months. Four of the five patients were aged more than 50 years. Two had concurrent *H. pylori* infection while the remaining three did not. The two patients with *H. pylori* infection also had chronic active gastritis. The only patient with a suspicious tumor-like mass at endoscopy was found to have chemical gastritis that was *H. pylori* negative at histopathology.

GLANDULAR ATROPHY.

Glandular atrophy was found in 8 (11.1%) patients of our study population. One patient with glandular atrophy also had intestinal metaplasia. Four of the patients also had *H. pylori* infection while seven of the eight patients had chronic active gastritis.

9. RELATIONSHIP BETWEEN THE PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS, AND THE GASTRODUODENAL LESIONS AT HISTOPATHOLOGY.

More patients had a diagnosis of duodenitis at histopathology (41.6%) as compared to endoscopy (16.7%), with this being a significant finding in male patients at histopathology. ($p=0.027$)

Though only 3 patients had intestinal metaplasia, 2 were aged over 50 years and this was statistically significant. ($p=0.046$) One of these patients also had *H. pylori* infection.

Glandular atrophy was significant in those aged 50 years and above. However, our numbers were too small to give a concrete conclusion.

None of the gastroduodenal lesions seen at histopathology were significantly associated with cigarette smoking, with the relative risk for any abnormal histological lesion in smokers being 0.5.

Table 7 outlines these findings.

Table 7: Histological Findings according to Demographic factors.

Histological Findings	Sex				p-value
	Male patients (n = 47)		Female patients (n = 25)		
	No.	(%)	No.	(%)	
Normal	4	8.5	1	4.0	0.472
Chronic active gastritis	36	76.6	20	80.0	0.741
Chronic gastritis	5	10.6	4	16.0	0.513
Duodenitis	24	51.1	6	24.0	0.027
Intestinal metaplasia	3	6.4	-	-	-
Chemical gastritis	3	6.4	2	8.0	0.797
Glandular atrophy	4	8.5	4	16.0	0.336
Histological Findings	Age				p-value
	Age <50 years (n = 57)		Age ≥ 50 years (n = 15)		
	No.	(%)	No.	(%)	
Normal	5	8.8	-	-	-
Chronic active gastritis	44	77.2	12	80.0	0.816
Chronic gastritis	7	12.3	2	13.3	0.913
Duodenitis	24	42.1	6	40.0	0.883
Intestinal metaplasia	1	1.8	2	13.3	0.046
Chemical gastritis	3	5.3	2	13.3	0.274
Glandular atrophy	4	7.0	4	26.7	0.031
Histological Findings	Smoking Status				p-value
	Smokers (n = 15)		Non-smokers (n = 57)		
	No.	(%)	No.	(%)	
Normal	2	13.3	3	5.3	0.274
Chronic active gastritis	11	73.3	45	78.9	0.642
Chronic gastritis	2	13.3	7	13.3	0.913
Duodenitis	7	46.7	23	40.4	0.659
Intestinal metaplasia	-	-	3	5.3	-
Chemical gastritis	-	-	5	8.8	-
Glandular atrophy	1	6.7	7	12.3	0.538

Chronic active gastritis was significantly found in patients who had no history of PUD as compared to those with a previous history of PUD. ($p = 0.035$) However, our numbers were too small to make any conclusions. *Table 8* outlines this relationship.

Chronic active gastritis was a significant finding in those patients without history of UGIB, (p -value = 0.045), whereas chronic gastritis was a significant finding in those with a previous history of UGIB ($p = 0.023$). However, the numbers were again too small to make any significant conclusions. *Table 8* outlines this relationship. The relative risk of finding any abnormal histological diagnosis for PUD and UGIB was 0.3 and 0.52 respectively.

Table 8: Histological Findings according to History of PUD and UGIB.

<i>Histological Findings</i>	<i>History of PUD</i>			
	<i>Prior PUD (n = 5)</i>		<i>No prior PUD (n = 67)</i>	
	No.	(%)	No.	(%)
Normal	1	20.0	4	6.0
Chronic active gastritis	2	40.0	54	80.6
Chronic gastritis	1	20.0	8	11.9
Duodenitis	2	40.0	28	41.8
Intestinal metaplasia	-	-	3	4.8
Chemical gastritis	-	-	5	7.5
Glandular atrophy	-	-	8	11.9
<i>Histological Findings</i>	<i>History of UGIB</i>			
	<i>Prior UGIB (n = 8)</i>		<i>No prior UGIB (n = 64)</i>	
	No.	(%)	No.	(%)
Normal	1	12.5	4	6.3
Chronic active gastritis	4	50.0	52	81.3
Chronic gastritis	3	37.5	6	9.4
Duodenitis	5	62.5	25	39.1
Intestinal metaplasia	-	-	3	4.7
Chemical gastritis	1	12.5	4	6.7
Glandular atrophy	-	-	8	12.5

10. RELATIONSHIP BETWEEN DURATION OF NSAID USE AND HISTOPATHOLOGICAL FINDINGS.

Duodenitis was significant in patients who had used NSAIDs for 1-3 months ($p=0.004$).

Other lesions showed no relationship with the duration of NSAID use. *Table 9* below details this relationship.

Table 9: Histological Findings according to Duration of NSAID use.

Histological Findings	1-3 months (n = 41)		More than 3 months (n = 31)		p-value
	No.	(%)	No.	(%)	
Normal	2	4.9	3	9.7	0.428
Chronic active gastritis	31	75.6	25	80.6	0.611
Chronic gastritis	6	14.6	3	9.7	0.529
Duodenitis	23	56.1	7	22.6	0.004
Intestinal metaplasia	-	-	3	9.7	-
Chemical gastritis	4	9.8	1	3.2	0.280
Glandular atrophy	3	7.3	5	16.1	0.239

11. HISTOLOGICAL FINDINGS VERSUS *H. PYLORI* INFECTION.

Similar to the endoscopic findings, the presence of a normal gastroduodenal mucosa was noted in those patients without *H. pylori* infection. Of the 5 patients with a histological diagnosis of normal mucosa, none had *H. pylori* infection. Similarly, the finding of chronic gastritis was significant in those without *H. pylori* infection. ($p=0.013$, OR 0.1 95%CI 0.01-0.8). *Table 10* outlines this relationship.

Table 10: Histological Findings according to *H. pylori* Infection.

Histologic findings	Total	<i>H. pylori</i> +		<i>H. pylori</i> -		OR (95% CI)	p-value
		n,	%	n,	%		
Normal	5	-	-	5	100	-	-
Chronic active gastritis	56	35	62.5	21	37.5	25.0 (3.1-203.2)	<0.001
Chronic gastritis	9	1	11.1	8	88.9	0.1 (0.01-0.8)	0.013
Duodenitis	30	16	53.3	14	46.7	1.3 (0.5-3.2)	0.633
Intestinal metaplasia	3	1	33.3	2	66.7	0.5 (0.04-5.6)	0.555
Chemical gastritis	5	2	40.0	3	60.0	0.6 (0.12-4.1)	0.643
Glandular atrophy	8	4	50.0	4	50.0	1.0 (0.23-4.3)	1.000

On the other hand, chronic active gastritis was significant in those with *H. pylori* infection. (p-value < 0.001, odds ratio = 25.0 (95% CI 3.1-203.2). However, no other lesions were significant in the presence of *H. pylori* infection.

DISCUSSION.

Non-steroidal anti-inflammatory drug-associated gastrointestinal toxicity is a broad subject encompassing symptoms as well as mild to severe gastrointestinal complications. In this cross-sectional study, we were able to determine the prevalence of gastroduodenal lesions in chronic NSAID users presenting with dyspepsia at KNH, in a purely African population. It is worth noting that almost all data available on this topic has been obtained from studies done in the West. (28, 35, 36, 37, 38, 41)

We recruited consecutive patients from the SOPC, the MOPC and the general medical and surgical wards between February and August 2007 as long as they satisfied our inclusion criteria and were willing to participate in the study. While this was our study design, various unforeseeable problems were encountered during the recruitment process. 58 patients declined to give consent after interrogation. 42 of these were out-patients and the rest were in-patients. Most patients cited their main concern as being their primary illness – osteoarthritis, rheumatoid arthritis, trauma, malignancies – and thus ignored the dyspepsia. For the outpatients, time off from their schedules, the long distance to and from KNH and the discomfort of using public transport or traveling long distances for those with deformities or severe pain hindered their participation. This left us with mainly in-patients to recruit from, thereby introducing a selection bias in the recruitment process. This can be appreciated from the younger age group of our patients as will be discussed below. However, since the minimum sample size estimated for the study was achieved and since all the patients fulfilled the inclusion criteria, the high number of patients declining to participate did not affect our results.

The mean age of patients in our study population was 43.4 ± 16 years. Studies have shown that the use of NSAIDs increases with age, with the point prevalence of prescription NSAID use being 10-15% in persons older than 65 years. (40) In the study by Frezza *et al.* (57) the mean age of the patients was 66.5 years. In fact, in most studies done so far, the mean age of the patients has been > 60 years. Our study population, however, tended to have relatively younger patients. This was attributed to the fact that most of our

patients had been hospitalized with complicated traumatic conditions. This was unlike in other studies where most patients enrolled have been on treatment for osteoarthritis or rheumatoid arthritis. We also had a male preponderance with a male to female ratio of 1.88: 1. This again was a reflection of the male to female patients admitted with traumatic and other orthopedic conditions at KNH surgical wards, at the time of recruitment.

Despite all patients having presented with dyspeptic symptoms, only 18 (25%) of them had used gastroprotective drugs for at least two weeks prior to the upper gastrointestinal endoscopy. Of note, however, was the fact that most patients with previous history of PUD and UGIB were on gastroprotective drugs. 5 of the 8 patients with a history of UGIB and 3 of those with a history of PUD were on gastroprotective drugs. According to the American College of Gastroenterology guidelines, use of gastroprotective drugs, preferably PPIs or alternatively H₂-receptor antagonists are recommended especially in patients at high risk for NSAID-related gastrointestinal complications. ⁽⁷⁸⁾ These include patients with prior history of gastroduodenal events (PUD, UGIB), age > 60 years, high dosage of NSAIDs, and concurrent use of corticosteroids or anticoagulants. ⁽⁷⁸⁾

At endoscopy, the most prevalent lesion was gastritis seen in 36 (50%) of the study population (4 corpus gastritis, 13 antral gastritis, 19 both antral and corpus gastritis). The prevalence of duodenitis was 16.7%, PUD 30.5% (duodenal ulcers 22.2%, antral ulcers 6.9%, fundal ulcers 1.4%), whereas mucosal erosions were found in only 6.9% of the study population (corpus erosions 1.4%, antral erosions 4.2%, duodenal erosions 1.4%). Only 10 (13.9%) patients had a normal looking gastroduodenal mucosa. Our results contrast sharply those of Larkai *et al.* ⁽³⁶⁾ where they evaluated the endoscopic appearance of the gastroduodenal mucosa in 65 patients on NSAIDs for at least 6 weeks. In their study, 21 (32%) patients had an endoscopically normal stomach and duodenum, and 44 (68%) had evidence of injury (mucosal hemorrhage 44.6%, erosions 53.8%, both mucosal hemorrhage and erosions 34%). Only 10 patients in their series had ulcers detected (7 gastric, 2 pyloric channel and 1 duodenal bulb) for a point prevalence of 15.4%. On the other hand, in the study by Frezza *et al.* where 118 patients on chronic

NSAID use were evaluated, the point prevalence of PUD was 32.2% (21 duodenal ulcers, 15 gastric ulcers, 2 gastric and duodenal ulcers).⁽⁵⁷⁾

The difference in results may have been occasioned by a lack of standard definitions of injury, so that valid comparisons may not be made. While endoscopy studies provide valuable information, endoscopic endpoints are to some extent subjective and need to be appropriate to the type of study (i.e. acute versus chronic). As an example, acute injury typically presents with petechiae and intramucosal gastric hemorrhages which are readily observed several hours after ingestion of aspirin and other NSAIDs, as well as erosions which are defined as shallow breaks in the mucosal surface.⁽¹⁸⁾ Ulcers, on the other hand, may either be acute or chronic, with acute ulcers being 3-5mm, and chronic ulcers > 5mm with scar tissue.⁽¹⁸⁾ Our study was designed with the intention of studying the chronic endpoints. It is not surprising, therefore, that we had very few patients with the acute lesions – mucosal erosions (6.9%), and no acute hemorrhages – but more with the chronic lesions especially gastritis and peptic ulcer disease.

All published studies have proposed additional confounding factors that may increase the risk of NSAID associated adverse gastrointestinal events.^(17, 28, 37, 41, 48, 51, 52) However, contributions of these individual factors to the overall risk, as well as their mechanism of action are subject to ongoing research and debate. These factors include:- history of previous PUD,^(37, 41) history of previous UGIB,^(37, 41) age > 60 years,^(41, 48) alcohol and cigarette smoking,⁽²⁸⁾ duration of NSAID use,⁽³⁸⁾ the concomitant use of ≥ 2 NSAIDs,⁽³⁷⁾ high NSAID dose,⁽³⁷⁾ and the concomitant use of corticosteroids and anticoagulants.^(51, 52)

When we analyzed our results for these confounding risk factors: the patients' age; previous history of PUD and UGIB; duration of NSAID use; and the patients' gender; all showed no significant association with the gastroduodenal lesions seen at endoscopy. ($p > 0.05$) However, gastritis was a significant finding in the non-smokers. ($p = 0.001$) This was surprising because Baumeister *et al.*⁽⁷⁹⁾ showed that nicotine decreases gastric prostaglandin production and also decreases the acid buffering capacity of the duodenum. Yeomans *et al.*⁽⁸⁰⁾ had reported an increase in the risk of NSAID associated gastrointestinal toxicity in NSAID users who were cigarette smokers. This conflicting

result and the lack of association in the former confounding factors may be attributed to the fact that our study was not powered to look for any associations between these risk factors and the gastroduodenal lesions. It is therefore not surprising that we had very few patients with these particular attributes and thus cannot make any conclusions based on these results.

The first papers published studying the relationship between chronic NSAID use and the mucosal colonization by *H. pylori* had reported a lower prevalence of *H. pylori* in the gastric mucosa of patients receiving chronic NSAID treatment.^(83, 84) It was thought that the gastric environment created by the use of anti-inflammatory medication might be unfavorable to *H. pylori* implantation,⁽⁸⁴⁾ a view confirmed by the fact that NSAIDs can block the growth of the bacterium in vitro.⁽⁸⁵⁾ However, other studies reported an equal prevalence of *H. pylori* in chronic NSAID users and control groups.⁽⁵⁷⁾ The prevalence of *H. pylori* in our study population was 50%. This is much lower than in studies conducted locally in dyspeptic patients drawn from the general population. Lwai-Lume *et al.*⁽⁸⁶⁾ reported a prevalence of 69% in a population where only two patients were on NSAIDs. It may, therefore, be possible that anti-inflammatory drugs impair the implantation and growth of *H. pylori* in the gastroduodenal mucosa, and hence the low prevalence of *H. pylori* in our study population of chronic NSAID users, vis-à-vis the prevalence in the general population.

The relation between *H. pylori* infection and use of NSAIDs in the pathogenesis of gastroduodenal lesions has been controversial. In the meta-analysis by Huang *et al.*⁽¹⁶⁾ both *H. pylori* infection and NSAIDs were independently and significantly found to increase the risk of peptic ulcers and ulcer bleeding. Several studies have however shown that *H. pylori* infection does not influence the endoscopic grade of gastroduodenal mucosal lesions in long-term NSAID users.^(57, 87, 88) In our series of patients, the finding of a normal gastroduodenal mucosa was significant in those patients without *H. pylori* infection. ($p=0.041$, OR 0.21 95% CI 0.04-1.04) However, none of the gastroduodenal lesions were significant in the presence of *H. pylori* infection. Similar results were reported by Ishikawa *et al.*⁽⁸⁸⁾ In their study, the prevalence of gastroduodenal lesions

(other than reflux oesophagitis which was significantly higher in the *H. pylori* negative group) did not depend upon the presence of *H. pylori*. It does seem likely that *H. pylori* does not contribute significantly to the pathogenesis of the gastroduodenal lesions in patients under medication with NSAIDs.

NSAIDs have been associated with a high prevalence of gastroduodenal ulcers. NSAID-related ulcers may originate by two possible mechanisms: - the concomitant presence of *H. pylori* infection and / or the mucosal damage now thought to show up as chemical gastritis. ⁽⁷⁶⁾ Laine *et al.* showed that gastric ulcers associated with the use of NSAIDs are an important sub-group of ulcers that do not require the presence of *H. pylori* infection for their formation. ⁽⁸¹⁾ The point prevalence of PUD in our study patients was 30.5%. *H. pylori* infection was present in 14 of the 22 patients with peptic ulcers at endoscopy. Two patients had chemical gastritis, but in 6 patients neither of these factors could explain the presence of the peptic ulcers. While the group of patients positive for *H. pylori* had a greater number of ulcers than those without *H. pylori* or chemical gastritis, this was not significant. ($p=0.125$) Lwai-Lume *et al.* ⁽⁸⁶⁾ reported a point prevalence of PUD of 23% (19% duodenal ulcers, 4% gastric ulcers) in dyspeptic patients recruited from the general population at KNH. In her study, duodenal ulcers were significantly associated with *H. pylori* infection whereas gastric ulcers were not. We may argue for a synergistic effect between NSAIDs and *H. pylori* in causing gastroduodenal damage, but it does seem that in some cases, NSAIDs may have been responsible for producing the lesions via different pathways than those mentioned above. NSAIDs may damage the mucosa via inhibition of the synthesis of prostaglandins ⁽⁶⁾ and functional impairment of the mucosal barrier. ⁽⁸²⁾ These may underlie those ulcers found in the *H. pylori* negative cases.

At histopathology, 77.8% of our study population had chronic active gastritis, 12.5% had chronic gastritis, 6.9% had chemical gastritis, 41.7% had duodenitis, 11.1% had glandular atrophy and 4.2% had intestinal metaplasia. Most patients had more than one histological finding.

According to the Updated Sydney System, a diagnosis of chemical or reactive gastritis is indicated by the finding of: - foveolar hyperplasia; edema and smooth-muscle proliferation in the lamina propria; together with normal numbers or a minor increase in chronic inflammatory cells. ⁽⁷⁶⁾ This histological picture suggests an etiological role for some chemical irritant or drug, ⁽⁷⁶⁾ with the main causative agents being bile reflux, NSAIDs and sometimes alcohol abuse. Only a minority of our patients (6.9%) had chemical gastritis. The prevalence of chemical gastritis in chronic NSAID users described by different authors has been variable. In the study by Frezza *et al.* ⁽⁵⁷⁾ the prevalence of chemical gastritis was 10%, while in that by Taha *et al.* ⁽⁸⁴⁾ the prevalence was 26%. According to El-Zimaity and colleagues, ⁽⁸⁹⁾ this may be accounted for by a variety of reasons, including the facts that of all the patients regularly taking NSAIDs, only a few (those with greater sensitivity) develop chemical gastritis, and mucosal damage may be patchy.

A much debated topic is whether the presence of *H. pylori* modifies the histological picture associated with NSAID-induced mucosal damage. In our series of patients, the finding of a normal gastroduodenal mucosa was significant in patients without *H. pylori* infection. Chronic gastritis was also significant in patients without *H. pylori* infection. ($p=0.013$) On the other hand, the finding of chronic active gastritis was significant in those patients with *H. pylori* infection. ($p < 0.001$, OR 25 95% CI 3.1-203.2) Of the 56 patients diagnosed as having chronic active gastritis, 35 had *H. pylori* infection. However, no other lesions were noted to be significant in the presence of *H. pylori*. In the study by Frezza *et al.* ⁽⁵⁷⁾ of the 53 *H. pylori* positive patients who were chronic users of NSAIDs, a third had a score consistent with chronic active gastritis. The Updated Sydney System describes chronic active gastritis as being characterized by the simultaneous presence of a mononuclear cell infiltrate and a high infiltration of polymorphonuclear neutrophils which are attracted to the tissue by the presence of *H. pylori*. ⁽⁷⁶⁾ From the foregoing, we may conclude that, the absence of *H. pylori* is significantly associated with the finding of a normal gastroduodenal mucosa at histology and endoscopy in dyspeptic patients on chronic NSAID use. Its presence, however, does not significantly affect the gastroduodenal lesions except for the finding of chronic active

gastritis which is usually associated with its colonization. Therefore, both *H. pylori* and NSAIDs seem to act independently in causing gastroduodenal lesions in chronic NSAID users.

Three of the patients in our study population with chemical gastritis also had chronic active gastritis. Two of these patients also had *H. pylori* infection. The Updated Sydney System stresses that an individual patient may have histopathological evidence of more than one type of gastritis as a result of being exposed to more than one etiological agent. ⁽⁷⁶⁾ In our patients, there was simultaneous presence of gastritis due to chronic ingestion of NSAIDs (chemical gastritis) and chronic active gastritis associated with *H. pylori* infection.

Though only 3 patients had intestinal metaplasia in our study population, two were aged above 50 years. ($p=0.046$) All the three patients had used NSAIDs for > 3 months. One had concurrent *H. pylori* infection, and none was on gastroprotective drugs. Intestinal metaplasia is common in chronic gastritis of all causes and increases in prevalence with disease duration. ⁽⁷⁶⁾ It is generally regarded as a condition that predisposes to malignancy, more so for those lesions with large intestinal characteristics (Type III metaplasia). ⁽⁷⁶⁾ This was an important observation, which may be construed to mean that for elderly patients who have been on NSAIDs for a long duration the risk of intestinal metaplasia is higher.

Duodenitis was a significant histological finding in male patients in our study. ($p=0.027$) At endoscopy, more male patients (10 out of 12 patients with duodenitis) had a diagnosis of duodenitis, though this was not significant. ($p=0.150$) Hawkey and colleagues ⁽⁵³⁾ had reported that males are more predisposed to duodenal ulcers, independent of *H. pylori* status as compared to women. Though this was an interesting observation, our study was not powered to detect associations of the lesions in the two sexes, and thus we cannot comment much on this finding.

Past history of upper gastrointestinal events (PUD or UGIB) has been shown to magnify the risk of NSAID associated gastroduodenal complications. ^(37, 38, 41) Our study did not evaluate for the recurrence of upper gastroduodenal events, but looked at the gastroduodenal lesions at histopathology. Contrary to our expectations, those patients in our study who had previous history of upper gastrointestinal events tended to have less chronic active gastritis and chronic gastritis as compared to those patients without history of the same. Refer Tables 19 and 20. Despite the numbers being small, this was indeed an interesting observation, since the recurrence of upper gastrointestinal events have been postulated to be from mucosal changes from previous ulcer sites, with a strong tendency for lesions to relapse in the same location and to be of the same type as those seen initially. ⁽⁴³⁾ It is worth noting that most of our patients (62.5% with previous UGIB and 60% with previous PUD) were on gastroprotective drugs at the time of evaluation. Further, only one patient with previous UGIB and one with previous PUD had *H. pylori* infection. Given the past history of upper gastrointestinal events in them, it is very possible that they had already received *H. pylori* eradication therapy and hence the low rates of chronic active gastritis witnessed. However, our numbers were too small for any conclusions to have been made.

Intestinal metaplasia was significant in patients who had used NSAIDs for > 3 months whereas duodenitis was significant in patients who had used NSAIDs for 1-3 months. (p=0.042 and 0.004 respectively) The finding of duodenitis in patients using NSAIDs for short durations has not been reported in other studies. There is therefore need for other studies to evaluate this finding further. Intestinal metaplasia has, however, been shown to increase in prevalence with disease duration. ⁽⁷⁶⁾

Our study showed a poor correlation between the histopathologic and endoscopic findings of gastritis and duodenitis. Whereas gastritis was present in 91.7% of the histopathology specimens, only 50% was reported at endoscopy. Similarly, duodenitis was reported in 41.7% of the histopathology specimens but was noted in only 16.7% of the patients at endoscopy. These results are in keeping with previous studies which have shown a poor correlation between endoscopic and histopathologic findings. ^(91, 92)

CONCLUSIONS.

1. We have a high prevalence of gastroduodenal lesions in chronic NSAID users presenting with dyspepsia (81.6% at endoscopy, 93.1% at histopathology), with the prevalence of PUD (30.5%) being much higher than that in dyspeptic patients drawn from the general population (23%), at the Kenyatta National Hospital.
2. Both *H. pylori* infection and NSAIDs act as independent etiological factors in the pathogenesis of the gastroduodenal lesions found in chronic NSAID users.
3. A previous history of UGIB and PUD is not associated with a worse grade of gastroduodenal lesions both at endoscopy and histopathology.

STUDY LIMITATIONS.

1. Only chronic NSAID users presenting with dyspepsia were enrolled. We may have missed out many patients with gastroduodenal lesions who were not dyspeptic.
2. Patients on gastroprotective drugs for less than two weeks were included in the study. These drugs are used in the treatment of NSAID-induced gastroduodenal lesions. Studies that have evaluated their efficacy in NSAID gastropathy have run for more than four weeks. We cannot tell what effects these drugs may have had on the mucosa of those patients who had used them.
3. We neither controlled for nor evaluated for other factors that may have led to the development of gastroduodenal lesions on their own, or worsened the NSAID-induced lesions such as alcohol and gastroduodenal bile reflux.
4. Our study had three gastroenterologists reporting on the gross macroscopic findings of the gastroduodenal mucosa. Whereas study definitions of the lesions they may have seen were clearly set out, there was no way of validating their findings.

RECOMMENDATIONS.

1. Due to the high prevalence of gastroduodenal lesions seen in chronic NSAID users in our setting, it would be wise to give prophylactic gastroprotective drugs to these patients.
2. Larger studies powered to evaluate the specific variables (age, gender, past history of UGIB and PUD, *H. pylori*) and their associations with the gastroduodenal lesions seen in chronic NSAID users with dyspepsia are recommended.

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APPENDIX I – STUDY DEFINITIONS.

Chronic NSAID use Daily use of NSAIDs for a duration of one month and above. ⁽³⁸⁾

Chronic NSAID users were either on;

Single use – one type of NSAID only.

Switching use – one NSAID type for sometime followed by another NSAID type some other time during the same treatment duration.

Multiple use - on two or more NSAIDs at the same time.

Dyspepsia Chronic or recurrent upper abdominal pain or discomfort (not relieved by bowel actions or passage of flatus).

Discomfort was defined as a subjective negative feeling that was non-painful, and may have incorporated a variety of symptoms including early satiety, upper abdominal fullness or nausea. ⁽⁴⁰⁾

Peptic ulcer..... A circumscribed mucosal break 5mm or more in diameter, in the gastric or duodenal mucosa , with a well-defined ulcer crater or definite depth, measured by standard Olympus biopsy forceps. ⁽¹⁸⁾

Gastric/duodenal erosion..... Shallow mucosal break less than 5mm in diameter, or superficial mucosal breaks without depth, in the gastroduodenal mucosa. ⁽¹⁸⁾

Gastritis/duodenitis Mucosal erythema without any mucosal breaks appearing in the gastroduodenal mucosa as seen using the endoscope.

Gastric/duodenal bleed..... referred to either active bleeding, or the endoscopy finding of a platelet plug seen protruding from a vessel wall in the base of an ulcer (also called sentinel clot or visible vessel), or a large adherent clot covering the ulcer base. ⁽¹⁾

Gastric outlet obstruction referred to either relative obstruction secondary to ulcer-related inflammation and edema in the peripyloric region, or a fixed mechanical obstruction secondary to scar formation with stenosis in the peripyloric. ⁽¹⁾

Perforation..... a break through the mucosa extending to the serosa, with leakage of the gastric or duodenal contents into the peritoneal cavity. ⁽¹⁾

Low dose aspirin Daily aspirin dose below 150mg. ⁽³⁹⁾

Non-aspirin anti-platelet drug .. This referred to either clopidogrel or ticlopidine.

Corticosteroid use Referred to doses of prednisolone greater than 10mgs per day. ⁽⁵²⁾

APPENDIX II - QUESTIONNAIRE

1. DEMOGRAPHICS.

Name _____

Age _____

Sex F M

Race _____

Outpatient number _____

Inpatient number _____

Study number _____

2. NSAID HISTORY.

a) Currently on NSAIDs (Yes = 1, No = 2)

b) Duration of use (Actual period used)

Less than 1 month = 1

1 to 3 months = 2

More than 3 months = 3

No use for ≥ 1 mnth = 4

c) NSAID used.

Aceclofenac = 1

Diclofenac = 2

Diflunisal (Dolobid) = 3

Indomethacin = 4

Ibuprofen = 5

Ketoprofen (Oruvail) = 6

- Mefenamic acid = 7
- Meloxicam = 8
- Naproxen = 9
- Nimesulide = 10
- Piroxicam = 11
- Other (Specify) = 12

d) Required daily doses. (Low dose = 1)

(High dose = 2)

- | | | | |
|------------------------------------|--------------------------|----------|--------------------------|
| 1) Aceclofenac $\leq 100\text{mg}$ | <input type="checkbox"/> | > 100mg | <input type="checkbox"/> |
| 2) Diclofenac $\leq 100\text{mg}$ | <input type="checkbox"/> | > 100mg | <input type="checkbox"/> |
| 3) Difunisal $\leq 750\text{mg}$ | <input type="checkbox"/> | > 750mg | <input type="checkbox"/> |
| 4) Ibuprofen $\leq 1500\text{mg}$ | <input type="checkbox"/> | > 1500mg | <input type="checkbox"/> |
| 5) Indomethacin $\leq 75\text{mg}$ | <input type="checkbox"/> | > 75mg | <input type="checkbox"/> |
| 6) Ketoprofen $\leq 150\text{mg}$ | <input type="checkbox"/> | > 150mg | <input type="checkbox"/> |
| 7) Mefenamic $\leq 1250\text{mg}$ | <input type="checkbox"/> | > 1250mg | <input type="checkbox"/> |
| 8) Meloxicam $\leq 10\text{mg}$ | <input type="checkbox"/> | > 10mg | <input type="checkbox"/> |
| 9) Naproxen $\leq 750\text{mg}$ | <input type="checkbox"/> | > 750mg | <input type="checkbox"/> |
| 10) Nimesulide $\leq 150\text{mg}$ | <input type="checkbox"/> | > 150mg | <input type="checkbox"/> |
| 11) Piroxicam $\leq 15\text{mg}$ | <input type="checkbox"/> | > 15mg | <input type="checkbox"/> |
| 12) Other (Specify) | <input type="checkbox"/> | | <input type="checkbox"/> |

e) Method of NSAID use (Appendix I)

- Single use = 1
- Switching use = 2
- Multiple use = 3

3. DYSPEPSIA HISTORY.

- a) Chronic or recurrent upper abdominal pain (Yes = 1, No = 2)
- b) Chronic or recurrent upper abdominal discomfort (Yes = 1, No = 2)

4. i) UPPER GI HISTORY.

- a) History of PUD (Yes = 1, No = 2)
- b) History of hematemesis (Yes = 1, No = 2)
- c) History of melena stools. (Yes = 1, No = 2)

(Description of melena stool as tarry black stool while patient is on NSAIDs shall be explored.)

4. ii) ATTEMPT AT ERADICATION OF *H. PYLORI*.

- a) Use of any antibiotic in the last 4 weeks. (Yes = 1, No = 2)

5. USE OF GASTROPROTECTIVE DRUGS.

- Less than 2 weeks = 1
- More than 2 weeks = 2
- No use = 3

6. CORMORBID STATES.

- Hypertension = 1
- Diabetes = 2
- Rheumatoid arthritis = 3
- Osteoarthritis = 4
- Systemic lupus = 5
- Fibromyalgia = 6

Carcinoma/sarcoma = 7

Others (Specify) = 8

7. OTHER CO-PRESCRIBED MEDICATIONS.

Low dose aspirin = 1

Corticosteroids = 2

Other antiplatelets = 3

Anti-coagulants = 4

Antihypertensives = 5

Oral hypoglycemics = 6

Disease modifying anti-rheumatic drugs = 7

Others (Specify) = 8

None co-prescribed = 9

8. CIGARETTE SMOKING. (Yes = 1, No = 2)

9. ENDOSCOPIC FINDINGS.

Normal = 1

Gastritis Body = 2a

Antrum = 2b

Gastric erosions Body = 3a

Antrum = 3b

Gastric ulcer Body = 4a

Antrum = 4b

- Gastric bleed
 - Body = 5a
 - Antrum = 5b
- Gastric perforation = 6
- Duodenitis = 7
- Duodenal erosions = 8
- Duodenal ulcers = 9
- Duodenal bleed = 10
- Duodenal perforation = 11
- Gastric outlet obstruction = 12
- Tumors = 13
- Others (Specify) = 14

10. RAPID UREASE TEST. (Positive = 1, Negative = 2)

- 10a) Body
- 10b) Antrum
- 10c) Duodenum

11. HISTOPATHOLOGICAL FINDINGS.

a) The Sydney system for grading chronic gastritis. (score >4)

Variable	Positive=1	Negative=0			Tally
<i>H. pylori</i> density					
Intestinal metaplasia					
Glandular atrophy					
	Negative=0	Mild=1	Moderate=2	Marked=3	
Chronic inflammation					
Polymorphonuclear activity					

b) The modified Dixon's system for chemical gastritis. (score >6)

Variable	Positive=1	Negative=0			Tally
Foveolar hyperplasia					
Oedema					
Prominent smooth muscle fibers					
	Marked=0	Moderate=1	Few=2	Absent=3	
Polymorphonuclear neutrophils					
Plasma cells					

c) THE HISTOPATHOLOGIC DIAGNOSIS.

- No lesions = 1
- Chronic active gastritis = 2
- Chronic gastritis = 3
- Chemical gastritis = 4
- H. pylori* present = 5
- H. pylori* absent = 6
- Adenocarcinoma = 7
- Lymphoma = 8
- Gastric atrophy = 9
- Duodenitis = 10
- Intestinal metaplasia = 11

d) THE HISTOLOGICAL SUBCLASSIFICATION.

- Mild active gastritis = 1
- Moderate active gastritis = 2
- Severe active gastritis = 3

12. SUB-CLASSIFICATIONS.

1. ANTRAL GASTRITIS.

Variable	Positive=1	Negative=0			Tally
<i>H. pylori</i> density					
Intestinal metaplasia					
Glandular atrophy					
	Negative=0	Mild=1	Moderate=2	Marked=3	
Chronic inflammation					
Polymorphonuclear activity					

2. CORPUS GASTRITIS.

Variable	Positive=1	Negative=0			Tally
<i>H. pylori</i> density					
Intestinal metaplasia					
Glandular atrophy					
	Negative=0	Mild=1	Moderate=2	Marked=3	
Chronic inflammation					
Polymorphonuclear activity					

3. CONCLUSION.

- a) Antral predominant gastritis = 1
- b) Corpus predominant gastritis = 2
- c) Pan-gastritis = 3

APPENDIX III – CONSENT EXPLANATION.

1. Dr Wangechi Wanjohi, would like to inform you that I am conducting a study on our patients here at KNH, aged 13 years and above, who have been on NSAIDs for a period of one month and above. The study seeks to find out the adverse gastroduodenal effects of these drugs including peptic ulcers, erosions, bleeding and perforations.

1. The study is in part fulfillment of the requirement for my degree of Master of Medicine in Internal Medicine, UoN.
2. The study has been approved by the KNH Scientific and Ethical Committee and the Department of Internal Medicine, UoN.
3. You as the patient has the right to choose to participate or withdraw from participation in the study, and such withdrawal shall not in any way affect your management here at KNH.
4. The study entails your having an upper gastrointestinal endoscopy examination. This involves the use of a flexible fiberoptic tube that is passed through the mouth into the esophagus, stomach and duodenum, without any effort on your part. This is done by a consultant gastroenterologist who shall anaesthetize your pharynx using an anaesthetic spray to minimize gagging. If you are too anxious to have the procedure, the gastroenterologist shall give you some intravenous midazolam so that you are sedated and at ease during the procedure.
5. The gastroenterologist shall get multiple biopsy specimens from the stomach and the duodenum which shall be analyzed by a pathologist. The multiple specimens shall be taken since the gastroduodenal lesions following chronic NSAID use may have a patchy distribution.

6. There are minimal risks associated with the procedure. A perforation of the esophagus or the stomach is possible with a risk less than 1 case per 1000 procedures done. There is also a low risk of significant bleeding in 0.3 cases per 1000 procedures following endoscopy. Rarely, some patients experience cardiac arrhythmias, aspiration pneumonitis, transient bacteremia, sore throat, respiratory depression and allergic reactions associated with the sedation.
7. The endoscopy and histopathology findings shall be communicated to your primary physician to enhance your management.
8. The findings of this research may be used in future to guide treatment for those using chronic NSAIDs.

If you have fully understood the above information and are still willing to participate in the study, you shall be required to sign a consent form expressing your willingness to participate in the study and to have an upper gastrointestinal endoscopy. For those patients below 18 years the parent/guardian shall be required to give the written consent.

Thank you.

For any further enquiries feel free to call me on the following number;

Wangechi Wanjohi,

0721 78 78 98.

APPENDIX IV- CONSENT FORM (OVER 18 YEARS).

This is to confirm that I _____ ,
having been explained to and fully understood the nature of this study, do hereby consent
to have an upper gastrointestinal endoscopy. The nature and effects of this procedure
have been explained to me.

I am aware that a tissue biopsy shall be taken for research purposes, and that the findings
shall be forwarded to my primary doctor to enhance my management.

I am also aware that my withdrawal from this study shall not in any way hamper my
management.

Date _____

Patient's signature _____

Investigator's signature _____