Research Article

Prevalence of gastroduodenal lesions in chronic non-steroidal anti-inflammatory drug users presenting with dyspepsia at the Kenyatta National Hospital

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Abstract

Background: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely prescribed and used classes of drugs worldwide. They are known to cause gastroduodenal mucosal damage and can result in ulcerations, upper gastrointestinal bleeding, perforation and even death. However, no local data exist to show the prevalence.

Objectives: The main objective 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.

Design: This was a hospital-based cross-sectional study.

Methods: Seventy patients aged 13 years and above, on NSAIDs for 4 weeks or more, and presenting with dyspepsia were recruited and done for endoscopies. Six biopsy specimens were taken from each patient (2 from each of the following sites: - corpus, antrum and duodenum). One specimen from each site was subjected to the rapid urease test for *H. pylori* detection. The remaining three were subjected to histopathological evaluation.

Results: Forty 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 had 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.

Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used drugs and can cause gastroduodenal mucosal damage, from non-specific dyspepsia, ulcerations, upper gastrointestinal bleeding, perforation, to death[1]. No data exists to show the prevalence of these lesions in our local setting.

The main objective was to determine prevalence of gastroduodenal lesions in chronic NSAID users with dyspepsia, in Kenyatta National Hospital, Nairobi, Kenya. The other objectives included describing the lesions seen at endoscopy and the histopathological characteristics. The study also sort to find out the relationship between duration of NSAID use, previous peptic ulcers and UGI bleed (UGIB) and the gastroduodenal lesions. Finally the study sort 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

This was a cross-sectional, descriptive study done at KNH endoscopy unit. Patients aged over 13 years, with musculoskeletal disorders requiring chronic NSAID therapy with or without acute upper GI events (UGI bleed and / or perforation) were eligible. Those excluded were patients who had been treated for *H. pylori* infection, antibiotic use in the preceeding month, patients on gastroprotective drugs (PPIs, H_2-antagonists, misoprostol), for more than two weeks preceeding endoscopy, use of selective COX-2 inhibitors and patients

of Asian and Caucasian descent. Eighty two patients on chronic NSAID use were found eligible. Seventy five of these gave informed and written consent, and 72 of them had a successful upper GI endoscopy.

Results

Demographic and clinical details of the study patients: The mean age of the patients was 43.4 years, youngest being 16 and the oldest 77 years. Most patients were aged 21–40 years representing 51.4% of the total population. (Table 1) m: f 1.88: 1.

Table 1: Clinical details of the patients (n=72)

Characteristic	Frequency	(%)
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

Mean age of males was 42.5 years (SD ± 16.5), females was 45.1(SD ± 15.7). Ten (13.9%) of those on gastroprotective drugs used PPIs while eight (11.1%) used H_2-receptor antagonists. Of these, five had previous UGIB, three had previous PUD. Four of those with previous UGIB and one of those with previous PUD were on PPIs. Three of those over 60 were on gastro-protective drugs. NSAIDs commonly used were diclofenac (52%) and ibuprofen (26%). Forty one (61.1%) had used only one NSAID, 16 (22.2%) had switched from one type to another, while 12 (16.7%) were on more than one type.

Prevalence of gastroduodenal lesions at endoscopy: Figure 1 shows gastroduodenal lesions at endoscopy. Four patients had three lesions at endoscopy while thirteen had two. Six of the patients with duodenitis also had gastritis, whereas eight of those with peptic ulcers, had gastritis. Gastritis was the most prevalent lesion (36 cases) (Figure 2).

Figure 1: Prevalence of gastroduodenal lesions at endoscopy

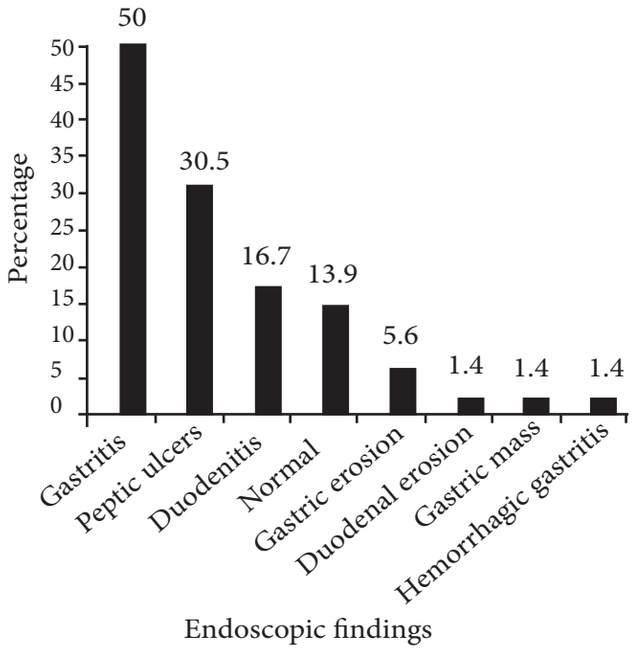


Figure 2: Distribution of gastritis

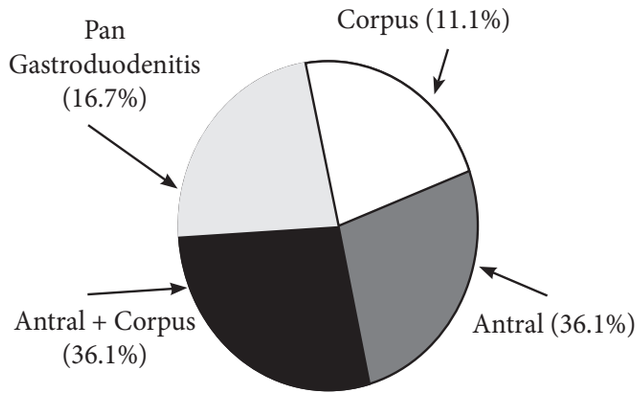


Table 2: Endoscopic findings according to previous history of PUD and UGIB

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
Gastric	-	-	6	8.9
Duodenal	-	-	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
Gastric	-	-	*6*	*9.4*
Duodenal	*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 point prevalence of 30.5% of PUD in chronic NSAID users presenting with dyspepsia. Sixteen were males (point prevalence of 34%),12 duodenal, 3 antral and 1 fundal. Six were found in females, (point prevalence of 24%) 4 duodenal, 2 antral. The highest frequency of PUD occurred in 41-50 years age-group, with a mean age of 44 while those without was 42 years. Fourteen patients with peptic ulcers had used NSAIDs for 1-3 months, with the remaining 8 using for longer period. However, there was no significant association with the finding of PUD at endoscopy (p = 0.585). Fourteen patients with PUD had *H. pylori* infection, while 8 didn't (p = 0.125). Table 3 shows relationship between duration of NSAID use and lesions found at endoscopy and Figure 3 shows the histological distribution of the lesions. Table 4 shows the distribution of lesions in those with and without *H. pylori* infection.

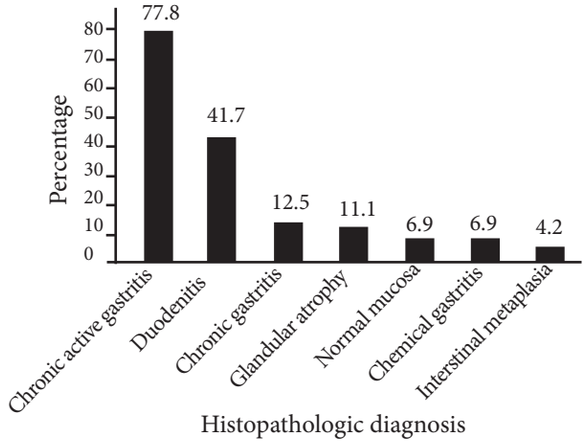
Table 3: Relationship between duration of NSAID use and the gastroduodenal lesions at endoscopy

Endoscopic findings	1-3 months (n = 41)		More than 3months (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
Gastric	4	9.7	2	6.4	0.615
Duodenal	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	-

Table 4: Differences in gastroduodenal lesions seen in patients with and without H. *pylori* infection at endoscopy

Endoscopic findings	Total	*H. pylori* +		*H. pylori* -		OR (95% CI)	P-value
		No.	(%)	No.	(%)		
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
Gastric	6	3	50.0	3	50.0	1.0 (0.10-5.3)	1.000
Duodenal	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	-	-

Figure 3: Prevalence of gastroduodenal lesions at histopathology



Unlike endoscopy where 10 (13.9%) patients were found to have normal gastroduodenal mucosa, only 5(6.9%) had normal mucosa at histopathology. Many patients had more than one histological finding. Eight patients had three mucosal lesions concurrently histologically while 28 had two mucosal lesions . Twenty three (31.9%) patients with chronic active gastritis also had duodenitis. Three (4.2%) with chronic active gastritis also had chemical gastritis, while all the 3(4.2%) patients with intestinal metaplasia had chronic active gastritis.

Table 5: Histological findings according to history of PUD or UGIB

Histological findings	History of PUD			
	Prior PUD (n = 5)		No prior PUD (n = 67)	
	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
	History of UGIB			
Histological findings	Prior UGIB (n = 8)		No prior UGIB (n = 64)	
	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

Table 5 further breaks down the histological findings in those who had a history of PUD and UGIB. Chronic active gastritis was significant in patients with no history of PUD compared to those with previous PUD (p = 0.035). However, our numbers were too small to make any conclusions. It was also a significant finding in those without previous 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. The relative risk of finding any abnormal histological diagnosis for PUD and UGIB was 0.3 and 0.52 respectively.

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). *Histological findings versus H. pylori infection:* Normal gastroduodenal mucosa was noted in those without *H. pylori* infection. Of the five patients with a histological diagnosis of normal mucosa, none had *H. pylori* infection. Finding of chronic gastritis was significant in those without *H. pylori* infection. (p=0.013, OR 0.1 95%CI 0.01-0.8). Chronic active gastritis was significant in those with *H. pylori* infection. (p-value < 0.001, OR = 25.0 (95% CI 3.1-203.2). However, no other lesions were significant in the presence of *H. pylori.*

Discussion

NSAID associated gastrointestinal toxicity encompasses symptoms from mild to severe complications. Most data on this topic has been obtained from studies done in the West[2-4].

The mean age of our patients was 43.4 ± 16 years. Use of NSAIDs increases with age, with the point prevalence of NSAID use being 10-15% in those over 65 years[5]. Frezza *et al*[6] found the mean age of patients was 66.5 years. Our population had relatively younger patients because most had complicated traumatic conditions. In other studies, most patients had arthritis. We also had a male:female ratio of 1.88:1. This reflected the patients admitted with traumatic and other orthopaedic conditions at KNH surgical wards during recruitment.

Despite all patients having dyspeptic symptoms, only 18(25%) of them had used gastroprotective drugs for at least two weeks prior to endoscopy. Most patients with previous PUD and UGIB were on gastroprotective drugs. Five of the eight patients with previous UGIB and three of those with previous PUD were on gastroprotective drugs. American College of Gastroenterology recommends use of gastroprotective drugs especially in patients at high risk for NSAID-related gastrointestinal complications[7].

At endoscopy, the most prevalent lesion was gastritis 3(50%) (Figure 1). Our results contrast sharply with those of Larkai *et al*[4] who evaluated endoscopic appearance of the gastroduodenal mucosa in 65 patients on NSAIDs for at least 6 weeks. Twenty one (32%) had an endoscopically normal stomach and duodenum, and 44(68%) had evidence of injury. Only 10 patients in their series had ulcers detected (7 gastric, 2 pyloric channel and 1 duodenal bulb), point prevalence of 15.4%.

These differences may be due to a lack of standard definitions of injury. While endoscopy studies provide valuable information, endoscopic endpoints are subjective and need to be appropriate to the type of study[8].

Our study was designed to study the chronic endpoints. All published studies have proposed confounders that may increase the risk of NSAID associated adverse gastrointestinal events[2,9]. These include:- previous PUD, previous UGIB[10,11] above 60 years[11], alcohol and cigarette smoking,[2] duration of NSAID use,[12] use of ≥ 2 NSAIDs, high doses,[10] and use of corticosteroids and anticoagulants[13].

Previous PUD and UGIB and duration of NSAID use, showed no significant association with the lesions at endoscopy ($p > 0.05$). Other studies published show the relationship between chronic NSAID use and mucosal colonization by *H. pylori* reported a lower prevalence of H. *pylori* in the gastric mucosa of chronic NSAID users[14,15]. It's thought the gastric environment created by NSAIDs might be unfavorable to *H. pylori* implantation, confirmed by the fact that NSAIDs can block the growth of bacterium *in vitro*[16]. However, other studies reported an equal prevalence of *H. pylori* in chronic users and control groups[17]. Our prevalence of *H. pylori* was 50%, lower than in studies conducted locally in dyspeptic patients in the general population. Lwai-Lume *et al*[18] reported a prevalence of 69% in a population where only two patients were on NSAIDs. It may be possible that NSAIDs impair implantation and growth of H. *pylori* in the gastroduodenal mucosa, hence the lower prevalence in our population.

The relation between *H. pylori* and NSAIDs use in pathogenesis of gastroduodenal lesions is controversial. Both *H. pylori* infection and NSAIDs were independently and significantly found to increase the risk of peptic ulcers and ulcer bleeding[19]. Several studies have shown that *H. pylori* doesn't influence the endoscopic grade of mucosal lesions in long-term users[6]. In our patients, the finding of a normal gastroduodenal mucosa was significant in those without *H. pylori* infection (p=0.041, OR 0.21 95% CI 0.04-1.04). However, no lesions were significant in the presence of *H. pylori*.

NSAIDs have been associated with a high prevalence of gastroduodenal ulcers, either by the presence of *H. pylori* and/or the mucosal damage now thought to present as chemical gastritis[20]. The point prevalence of PUD in our patients was 30.5%. *H. pylori* infection was present in 14 of the 22 patients with peptic ulcers at endoscopy. While those with *H. pylori* had more ulcers than those without it or chemical gastritis, this wasn't significant (p=0.125). Lwai-Lume *et al*[18] reported a point prevalence of PUD of 23% (19% duodenal, 4% gastric) from the general population. These duodenal ulcers were significantly associated with *H. pylori* infection whereas gastric ulcers weren't. There may be a synergistic effect between NSAIDs and *H. pylori* in causing gastroduodenal damage, but it seems that in some cases, NSAIDs may have been responsible for producing the lesions via different pathways. NSAIDs may damage the mucosa via inhibition of prostaglandins synthesis[21] and functional impairment of the mucosal barrier[22]. These may explain those ulcers found in the *H. pylori* negative cases.

Using the Updated Sydney System[23], Only 6.9% of our patients had chemical gastritis. The prevalence of chemical gastritis in chronic NSAID users is variable. El-Zimaity *et al*[24] proposed various reasons, considering that of all those regularly taking NSAIDs, few (with greater sensitivity) develop chemical gastritis, and mucosal damage may be patchy.

In our patients, the finding of a normal gastroduodenal mucosa and chronic gastritis (p=0.013) was significant in patients without *H. pylori*. Chronic active gastritis was also significant in those with *H. pylori* ($p < 0.001$, OR 25 95% CI 3.1-203.2). Thirty five of the 56 with chronic active gastritis had *H. pylori*. *H. pylori* and NSAIDs seem to act independently in causing gastroduodenal lesions in chronic NSAID users.

Three patients with chemical gastritis also had chronic active gastritis. Two also had *H. pylori* infection. The Updated Sydney System stresses that a patient may have histopathological evidence of more than one type of gastritis due to exposure to more than one aetiological agent. Our patients had gastritis due to chronic NSAIDs ingestion (chemical gastritis) and chronic active gastritis associated with *H. pylori* infection.

Though only three patients had intestinal metaplasia, only two were above 50 years (p=0.046). All three patients had used NSAIDs for > 3 months. One had concurrent *H. pylori* infection, none was on gastroprotective drugs. Intestinal metaplasia is common in chronic gastritis and it predisposes to malignancy, especially for lesions with large intestinal characteristics (Type III metaplasia). Elderly patients on chronic NSAIDs use, may have higher risk of intestinal metaplasia.

Previous PUD or UGIB has been shown to magnify the risk of NSAID associated gastroduodenal complications[25]. Those with previous upper gastrointestinal events, had less chronic active and chronic gastritis than those without. This was 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 of the same type[26].

Intestinal metaplasia was significant in patients who had used NSAIDs for > 3 months (p=0.042) whereas duodenitis was significant in patients who had used NSAIDs for 1-3 months (p= 0.004). The finding of duodenitis in patients using NSAIDs for short durations hasn't been reported in other studies and therefore needs further evaluation.

The study found a poor correlation between histopathologic and endoscopic findings of gastritis and duodenitis. Gastritis was in 91.7% of histopathology specimens, yet only 50% was reported at endoscopy. Duodenitis was reported in 41.7% of histopathology specimens only 16.7% at endoscopy. These results are in keeping with previous studies[27,28].

Conclusions

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. Both *H. pylori*

infection and NSAIDs act as independent aetiological factors in the pathogenesis of the gastroduodenal lesions found in chronic NSAID users. A previous history of UGIB and PUD is not associated with a worse grade of gastroduodenal lesions both at endoscopy and histopathology.

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