Elevated Urinary Pepsinogen: A Subclinical Marker of Ulcer Diathesis

M. Mujahid Ali, Ph.D., Mahboobunnisa, M.Sc., C. M. Habibullah, M.D., D.M.
Hyderabad, India

Abstract

Urinary pepsinogen levels were determind in 314 patients with peptic ulcer and in 100 healthy controls to see its possible role in pathogensis of peptic ulcer and to recognize elevated levels of urinary pepsinogen as a subclinical marker of ulcer diathesis. All patients studied were endoscopically proved to have peptic ulcer. Significantly elevated urinary pepsinogen levels were observed in patients with duodenal ulcer, pyloric ulcer and stomal ulcer, but increased level of urinary pepsinogen in gastric ulcer was not statistically significant when compared with controls. Sixteen percent of patients with duodenal ulcer had pepsinogen levels similar to the control group.

Key words: *Peptic ulcer, urinary pepsinogen*

DOI: http://dx.doi.org/10.5915/22-3-14307

A number of studies have shown that increased level of pepsinogen both in serum as well as urine are associated with duodenal ulcer,[1-3] and a few studies have also found that an elevated level is associated with an increased risk for developing this disorder.[4,5] Pepsinogen excretion in the urine is supposed to reflect the peptic activity of the stomach, and it has been recommended as a quantitative test for gastric secretory function.[6,7] It also has been applied clinically to the study of peptic ulcer, pernicious anemia and gastric cancer.[8] No correlation has been found between urinary pepsinogen and gastric acid secretion, while a positive correlation was observed between total pepsinogen, pepsinogen-I and maximal acid output.[9-11] A previous report from our center has shown a high degree of correlation between serum pepsinogen and urinary pepsinogen.[12] Group-I pepsinogen is invariably present in the urine but group-II pepsinogen is rarely found in the normal urine. This is because it exists in the circulation in a polymerized form and can not be filtered, or it is attached to a serum protein.[13,14]

This study was conducted to determine the urinary pepsinogen levels in different types of peptic ulcers, such as duodenal ulcer (DU), gastric ulcer (GU), pyloric ulcer (PU) and stomal ulcer (SU), to find out the gastric secretory function by the estimation of urinary pepsinogen, and to evaluate elevated urinary pepsinogen as a subclinical marker of ulcer diathesis.

Materials and methods

Two hundred and seventy-eight patients with DU (242 males and 36 females), ages between 15 and 69 years (mean 43 ± 16.41), and 36 male patients with GU, PU, and SU (12 in each catogory) were studied in the Department of Gastroenterology, Osmania General Hospital, Hyderabad, India. The selection of patients was based on endoscopic observations. One hundred age and sex matched healthy individuals without a history of peptic ulcer, dyspepsia or renal disease, served as controls.

Twenty-four hour urine samples were collected from patients and controls. An aliquot was used for the estimation of urinary pepsinogen. Urinary pep-

*From the Department of Gastroenterology
Osmania Medical College
Osmania General Hospital
Hyderabad, A.P., India.*

*Reprint Requests: Dr. M. Mujahid Ali
Department of Gastroenterology
Osmania General Hospital
Hyderabad, A.P., India.*

Table 1. Mean urinary pepsinogen levels in controls and patients with peptic ulcer.

Category	No.	Mean urinary pepsinogen levels (mean ± SD) in units/ml/24 hours
controls	100	1241.06 ± 330.40
duodenal ulcer	278	3440.84 ± 1478.01*
pyloric ulcer	12	3775.80 ± 1176.72*
stomal ulcer	12	3897.81 ± 1243.97*
gastric ulcer	12	1419.29 ± 562.98

*$p < 0.001$

sinogen was estimated within two days after the urine collection by the method of Mirsky et al[7] using hemoglobin as substrate.

The statistical significance of the difference in distribution of urinary pepsinogen levels in patients and controls was determined by the Student's "t" test.

Results

The mean urinary pepsinogen levels in patients and controls are given in table 1. In controls the mean urinary pepsinogen was 1241.06 ± 330.4 units/ml/24 hours (mean ± SD). A range of 600-1900 was taken as normal; any value beyond 1900 units was regarded as hyper level, any value below 600 units was considered as hypo. In DU patients the urinary pepsinogen levels in male patients was 3564.81 ± 1536.58, and in female patients it was 2738.25 ± 1346.46 units/ml/24 hours. Mean level of urinary pepsinogen both in male and female DU patients was significantly increased as compared with the mean level of controls ($p < 0.001$). Of 242 male DU patients, 34 (14%) had urinary pepsinogen within the normal range, whereas in 36 female patients, 10 (28%) had normal level of urinary pepsinogen (figure 1). The mean urinary pepsinogen in GU patients was 1419.29 ± 502.98, in PU 3775.80 ± 1176.72 and in SU it was 3897.81 ± 1243.97 units/ml/24 hours. The increased mean level of urinary pepsinogen in PU and SU was statistically significant when compared with the mean level of controls, but the increased mean level of pepsinogen in GU was not statistically significant.

Discussion

Urinary hyper-pepsinogenuria was recorded in 84% of DU patients in this study, whereas only 16% of the DU patients had pepsinogen levels in the normal range. In a previous study,[3] we classified DU patients into two groups onthe basis of total serum pepsinogen level: 1) primary DU, where hyperpepsinogenemia was associated, and 2) secondary DU, in which hyperpepsinogenemia was not associated

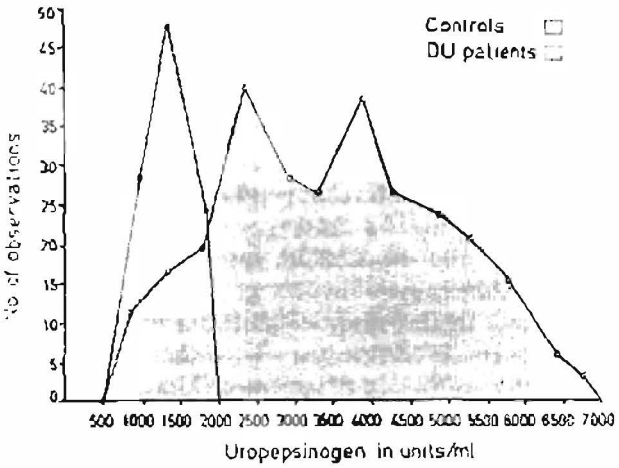

Figure. Frequency distribution of urinary pepsinogen levels in duodenal ulcer patients and in control populations. Overlap represents 16% of ulcer patients whose pepsinogen concentration fell within the control range.

with the disease. In that study 83% of patients had primary DU and 17% had secondary DU. Similar results were observed in this study when we used urinary pepsinogen as a marker. This study confirms that either serum or urine can be utilized to estimate the pepsinogen. Our previous report[12] regarding positive correlation between total serum pepsinogen and urinary pepsinogen is also confirmed by this study.

The pepsinogen present in the urine is group-I pepsinogen in serum, which plays an important role in the pathogenesis of peptic ulcer. The detection of group-I pepsinogen is difficult since it can only be detected by a radioimmunoassay method. In urine, the group-I pepsinogen can be estimated by simple colorimetric method.

The peptic secretory cell mass is influenced by sex and ABO blood gene,[13] the pepsinogen levels probably reflect the size of the gastric cell mass. This is generally smaller in females, so pepsinogen level is always lower in females. Our results are in agreement with the previous report[14] by showing lower values of pepsinogen in females.

In all the patients where hyperpepsinogenemia was recorded there will be increased acid secretion. Based on the prevailing concept that the concentration of pepsinogen in serum as well as urine reflect the capacity of the gastric mucosa to secrete hydrochloric acid. It is generally accepted that an elevated serum pepsinogen level indicates gastric acid hypersecretion, and that a low level predicts hypochlorohydria or achlorohydria.[10,11] The measurement of urinary pepsinogen can be recommended as a screening test for the detection of achlorohydria, hypochlorohydria and hyperchlorohydria, because uropepsinogen excretion closely parallels gastric acid.[11]

Significantly elevated levels of urinary pepsinogen were recorded not only in DU but also in PU and SU patients; in GU it was in the normal range except in three patients where the levels were slightly elevated. There might be increased chief cell and parietal cell mass in PU and SU as has been recorded in DU patients,[9] making the level of pepsinogen higher in both PU and DU ulcers as in Du. Sometimes pepsinogen levels are also elevated in patients with GU;[15,16] however, the cause of hyperpepsinogenemia in GU is not clear. In this disorder gastric acid output and pepsinogen levels are usually within the normal range; no association of increased chief cell mass and parietal cell mass has been noted with GU. It is generally accepted that decreased mucosal resistance secondary to gastritis is a major factor in the pathogenesis of GU.[17,18]

It has been suggested that pepsinogen secretion has an endocrine as well as exocrine component.[23] The high levels of serum and urinary pepsinogen results from an increased chief cell mass[10] which is genetically determined,[2] so that the endocrine component tends to keep the levels of pepsinogen elevated in these indivuduals. In the absence of overt disease this elevated level serves as a genetic as well as a subclinical marker for an ulcer diathesis. It may be assumed that in persons with the ulcer trait that resting exocrine component of pepsinogen merely gives rise to hypersecretion. This does not necessarily result in the formation of ulcer because various "cytoprotective" mechanisms become active.[24] The finding of Kollberg et al[25] that oral PGE_2 accelerates healing of the DU purely by stimulating the cytoprotective mechanism without inhibiting acid secretion lends further support to our contention. Hypersecretion remains precariously balanced against cytoprotection. Certain aggravating factors may disrupt this delicate balance by stimulating the exocrine limb causing further hypersecretion, resulting in ulceration of the mucosa. Similarly certain other factors may mediate loss of cytoprotection, tilting the balance again in favor of ulceration. Some aggravating factors may do both. Acute DU does not result in a further rise in serum and urinary pepsinogen, indicating that the endocrine component is not under stimulation.[26] Factors like ACTH may additionally stimulate the endocrine component of pepsinogen secretion so that there is a further rise in the elevated serum and urinary pepsinogen.[17]

In secondary DU, which is supposed to be either of neuroendocrinological origin or due to a viral infection,[28] the levels of serum and urinary pepsinogen are not elevated. There is no hypersecretion making the subject susceptible to DU. However, the same aggravating factors which selectively stimulate the exocrine limb of pepsinogen or cause a disruption of the cytoprotective mechanism may, under extreme conditions, give rise to peptic ulceration. There being no increased chief cell mass, nor a stimulated endocrine limb, the serum as well as the urinary pepsinogen levels remain within normal limits. Menguy et al[29] have proposed that stress ulcers (which may be included in secondary DU) are the result of mucosal energy deficits severe enough to cause cellular necrosis. Because this mechanism is unrelated to hypersecretion, such ulcers obviously do not have associated hyperpepsinogenemia and also do not menifest increased excretion of uropepsinogen.

In conclusion, a high uropepsinogen excretion is seen in patients suffering from peptic ulcer, particularly duodenal ulcer, pyloric ulcer and stomal ulcer. High levels of urinary pepsinogen may also indicate the hyper gastric secretory function, and an elevated urinary pepsinogen level may serve as a subclinical marker of ulcer diathesis.

References

1. Mirsky IA, Futherman P, Kaplan S: Blood plasma pepsinogen.II The activity of the plasma from "normal" subjects, patients with duodenal ulcer and patients with pernicious anemia. J Lab Clin Med 1952; 40:188-99.
2. Habibullah CM, Mujahid AM, Ishaq M, et al: Study of duodenal ulcer disease in 100 families using total serum pepsinogen as a genetic marker. Gut 1984;25:1380-1383.
3. Rotter I, James QS, Samloff IM, et al: Duodenal ulcer disease with elevated serum pepsinogen-I. An inherited autosomal disorder. New Engl J Med 1979;300:63-65.
4. Weiner H, Thaler M, Resiser MF, Mirsky IA; Etiology of duodenal ulcer. I. Relation of specific psychological characteristics to rate of gastric secretion (serum pepsinogen). Psychosom Med 1957;19:1-10.
5. Niederman JC, Spiro HM, Sheldon WH: Blood pepsin as a marker of susceptibility to duodenal ulcer disease. Arch Environ Health 1964;8:540-546.
6. Hirschowitz BI; Urinary Excretionof pepsinogen in gastroduodenal ulceration. Lancet 1953;1:66-69.
7. Bolt RJ, Pollard HM, and Carballo A: Determination of gastric secretory function by measurement of substances excreted by kidney. I. Uropepsin excretion in health and disease. J Lab Clin Med 1954; 43: 335-339.
8. Gray SJ, Ramsey CG, Reifenstein RM: Clinical use of the urinary uropepsin determination in medicine and surgery. N Engl J Med 1954; 251: 835-843.
9. Mujahid AM, Habibullah CM, Ishaq M, Saleem Y: Relation between gastric acid secretion and total serum pepsinogen levels in duodenal ulcer. Trop Gastroenterol 1986;7:62-64.
10. Samloff IM, Donald M, Passaro E: A study of

the relationship between serum group-I pepsinogen levels and gastric acid secretion. Gastroenterology 1975;69:1196-1200.
11. Plebani M, Dimario F, Vianello F, et al: Pepsinogen group-I radioimmunoassay and total serum pepsinogen colorimetric determination: A comparative study in normal subjects and in peptic ulcer patients. Clin Biochem 1983;16:20-22.
12. Habibullah CM, Mujahid AM, Ishaq M. Quadri GSA, Saleem Y: Relationship of urinary pepsinogen with serum pepsinogen in duodenal ulcer. Trop Gastroenterol 1985;6:26-29.
13. Seijffers MJ, Segal HL, Miller LI: Separation of pepsinogen II and pepsinogen III from human urine. Am J physiol 1964;206:1106-1110.
14. Samloff IM, Townes PL: Electrophoretic heterogeneity and relationships of pepsinogens in human urine, serum and gastric mucosa. Gastroenterology 1970;58:462-469.
15. Hirschowitz BI: Pepsinogen in the blood. J Lab Clin Med 1955;46:568-579.
16. Hoar CS, Browning JR: Plasma pepsinogen in peptic ulcer disease and other gastric disorders. A clinical and laboratory investigation. N Engl J Med 1956;255:153-58.
17. Ippoliti A, Walsh J: Newer concepts in the pathogenesis of peptic ulcer disease. Surg Clin North Am 1976;56:1479-1490.
18. Rhodes J: Etiology of gastric ulcer. Gastroenterology 1972;63:171-82.
19. Hanley WB: Hereditary aspects of duodenal ulceration. Br Med J 1964;1:936-940.
20. Chin AB: Studies on blood serum proteolytic enzyme with particular reference to gastric secretory function. Gastroenterology 1953;25:14-23.
21. Fischermann K, Strande KS, Peterson PH: Pepsinogen determination as a possible means for evaluation of gastric acid secretion. Gastroenterology 1975;69:196-200.
22. Cubberly DA, Dagradi AE, Carnelto G, Stemplix SI: Uropepsinogen excretion in gastroduodenal diseases. Gastroenterology 1955;28:80-87.
23. Samloff IM: Pepsinogen, pepsins and pepsin inhibitors. Progress in Gastroenterology 1971;60:586-604.
24. Guth PH: Pathogenesis of gastric mucosal injury. Ann Rev Med 1982;33:183-196.
25. Kollberg B, Johanson C, Stezak P: Duodenal ulcer healing with prostaglandin E_2. Gastroenterology 1981;80:1195-1200.
26. Spiro HM, Ryan AE, Jones CM: The utility of the blood pepsin assay in clinical medicine. N Engl J Med 1955;253:261-266.
27. Spiro HM, Reifenstein RW, Gray SJ: Effect of adrenocorticotropic hormone upon uropepsin excretion. J Lab Clin Med 1950;35:899-910.
28. Habibullah CM, Mujahid AM, Nayana J, Abideen KZ: Cytomegalovirus and Herpes simplex virus in duodenal ulcers. Med Sci Res 1988;16:923.
29. Menguy R, Desbaillets L, Masters YF: Mechanism of stress ulcer. Influence of hypovolemic shock on energy metabolism in the gastric mucosa. Gastroenterology 1974;66:46-55.

Editor correction November 24, 2014.

Reference 21 should be:

Fischermann K, Strande CS, Petersen PH. Pepsinogen determinations as a possible means for evaluation of gastric acid secretion. Am J Gastroenterol. 1971 Nov;56(5):447-52.

Reference 22 should be:

Cubberley DA, Dagradi AE, Carne HO, Stempien SJ. Uropepsin excretion in gastroduodenal disease; a correlative clinical study. Gastroenterology. 1955;28:80-87.