Elevated Urinary Pepsinogen: A Subclinical Marker of Ulcer Diathesis

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Abstract

Urinary pepsinogen levels were determined in 314 patients with peptic ulcer and in 100 healthy controls to see its possible role in pathogenesis 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

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A number of studies have shown that increased level of pepsinogen both in serum as well as urine are associated with duodenal ulcer, and a few studies have also found that an elevated level is associated with an increased risk for developing this disorder. 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. It also has been applied clinically to the study of peptic ulcer, pernicious anemia and gastric cancer. 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. A previous report from our center has shown a high degree of correlation between serum pepsinogen and urinary pepsinogen. 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.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>Mean urinary pepsinogen levels (mean ± SD) in units/ml/24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>controls</td>
<td>100</td>
<td>1241.06 ± 330.4</td>
</tr>
<tr>
<td>duodenal ulcer</td>
<td>278</td>
<td>3440.84 ± 1478.01*</td>
</tr>
<tr>
<td>pyloric ulcer</td>
<td>12</td>
<td>3775.80 ± 1176.72*</td>
</tr>
<tr>
<td>stomal ulcer</td>
<td>12</td>
<td>3897.81 ± 1243.97*</td>
</tr>
<tr>
<td>gastric ulcer</td>
<td>12</td>
<td>1419.29 ± 562.98</td>
</tr>
</tbody>
</table>

*p < 0.001

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 considered as normal; any value below 600 units was considered hyperpepsinogenemia. In DU patients the pepsinogen level was higher than in controls. The level was 3564.81 ± 1536.58, and the increased mean level of pepsinogen was significant as compared with the mean level of controls (p < 0.001). Of 242 male DU patients, 34 (14%) had increased mean level of 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 previous studies, we classified DU patients into two groups on the basis of total serum pepsinogen level: 1) primary DU, where hyperpepsinogenemia was associated, and 2) secondary DU, in which hyperpepsinogenemia was not associated with the disease. In this 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 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, 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 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 hypochlorhydria or achlorhydria. The measurement of urinary pepsinogen can be recommended as a screening test for the detection of achlorhydria, hypochlorhydria and hyperchlorhydria, because uropepsinogen excretion closely parallels gastric acid.

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.
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, 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; 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.

It has been suggested that pepsinogen secretion has an endocrine as well as exocrine component. The high levels of serum and urinary pepsinogen results from an increased chief cell mass which is genetically determined, so that the endocrine component tends to keep the levels of pepsinogen elevated in these individuals. 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. The finding of Kollberg et al that oral PGE2 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. 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.

In secondary DU, which is supposed to be either of neuroendocrinological origin or due to a viral infection, 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 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 manifest 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
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the relationship between serum group-I pepsinogen levels and gastric acid secretion. 


Editor correction November 24, 2014.

Reference 21 should be:

Reference 22 should be: