Non-Functional P2X<sub>7</sub> Receptor; A New Biomarker for Colorectal Cancer

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Abstract

P2X<sub>7</sub> is an apoptotic APT receptor that is non-functional on cancer cells. It has been shown to be a reliable marker for identification of malignancy in the epithelial cancers of the prostate, breast, skin and uterine cervix. In the prostate, the receptor locates strongly to the apical membrane of malignant cells and also similarly locates in adjacent “normal” glands (a field effect). In this study, we tested the applicability of P2X<sub>7</sub> as a biomarker in colorectal carcinogenesis.

Methods: We examined 330 endoscopic and surgical specimens from 158 consecutive patients. Cytoplasmic staining judged simply as positive or negative provided the best sensitivity and specificity.

Results: Staining in colonic neoplastic tissue was dominantly in the cytoplasm, although there was translocation to the nucleus in some patients. Sensitivity for cancer was 100% and for adenomas 82%. Specificity was 100% (negative in normal biopsies). There was no correlation of staining with Dukes staging judged simply as positive or negative provided the best sensitivity and specificity.

Conclusions: There was a clear discrimination between malignant neoplasm and normal cells. Correlation of cytoplasmic and nuclear staining with molecular stages of the adenoma-carcinoma sequence is planned.

Key Words: biomarker, colorectal cancer, P2X receptor

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Analysis of Postgastrectomy Serum Amylase

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Abstract

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Introduction

Hypermagnesemia may be observed when secreted amylase enters into the blood stream at increased rate. Also, if metabolic clearance of serum amylase is lowered than its usual metabolic rate, hyperamylasemia can be seen. The pancreas and salivary glands account for almost all of the serum amylase activity. Two different types, pancreatic type II-type vs. salivary type II-type, of isomylase can be distinguished by laboratory techniques currently available. It is common to observe hyperamylasemia in the presence of pancreatic insufficiency, for which the II-type of isomylase is responsible. However, various insults in the bowel, such as bowel ischemia, infarction or...
perforation, have shown to increase the serum level of pancreatic isoenzyme. Increased absorption of amylase from the intestinal lumen may be one possible explanation. S-type hyperamylasemia is usually noted in diseases or conditions involving the salivary glands. Nevertheless, conditions in which there is no clinical evidence of salivary gland disease may exhibit hyperamylasemia due to increased level of S-type isoenzyme. Such conditions include chronic alcoholism, postcoronary bypass, lactic acidosis, anorexia nervosa or bulimia, and malignant neoplasms that secrete amylase. Additionally, hyperamylasemia may result from decreased metabolic clearance of amylase due to renal failure or macroamylasemia, regardless the subtypes of serum amylase.\(^1\)

Hyperamylasemia during the first few days after gastrectomy is very common,\(^2\) and it is usually P-type hyperamylasemia but not S-type.\(^3\) Although the reason of postgastrectomy hyperamylasemia is not clear, possible mechanisms are manipulation of pancreas such as Kocher maneuver, direct injury of pancreatic parenchyme during lymph node or pancreatic capsule dissection, increased intraductal pressure due to drainage disturbance of pancreatic secretion such as afferent loop obstruction.\(^4\)^\(^5\) Postgastrectomy patients with hyperamylasemia mostly do not exhibit progression to acute pancreatitis clinically. Even if a few patients take the clinical course of mild pancreatitis, the pain radiating from the pancreas often gets masked by pain from the surgical wound or physical discomfort related to the operation. Therefore, it is very rare to find a patient with postoperative hyperamylasemia, diagnosed with acute pancreatitis.\(^6\)^\(^7\) Furthermore, it would be even more difficult to diagnose a postgastrectomy patient with complications associated with acute pancreatitis. Indeed postgastrectomy hyperamylasemia has not caused a serious clinical problem and has spontaneously resolved. Therefore, its clinical significance has not called any attention. No specific study has been done to investigate the underlying cause and statistical analysis on postgastrectomy hyperamylasemia. In this study, we investigated clinical significance and possible mechanisms of postgastrectomy hyperamylasemia.

### Materials and Methods

To elucidate the mechanism of postoperative hyperamylasemia after gastrectomy, we performed a retrospective analysis of prospectively collected serum amylase level of 497 consecutive patients without preoperative hyperamylasemia who had undergone gastrectomy by one surgeon for gastric cancer at CHA Bundang Medical Center from 2004 to 2010. Various parameters of serum amylase level on postoperative period were analyzed according to the operative procedure. The parameters of serum amylase include: ratio of patients with more than 250 U/L (twice the upper normal limit), and the mean values of serum amylase.

### Operative techniques

The gastric resections consist of partial gastrectomy(POG), total gastrectomy(TOG), total gastrectomy with splenectomy(TG+SP) or total gastrectomy with splenectomy and distal pancreatectomy(TG+SP+F). The reconstruction methods performed were gastroductodenostomy(GD), gastrojejunostomy(GJ-II) or Roux-en-Y esophagojejunostomy(RY). After FG, reconstruction was performed with B-I or B-II including cases of B-II with Pean anastomosis. After TG, reconstruction was performed with Roux-en-Y esophagojejunostomy, including cases of uncut Roux-en-Y esophagojejunostomy. Furthermore, it was analyzed that performing Kocher maneuver and extent of lymph node dissection (D0, D1 or D2) affected the serum amylase level post-operatively.

We performed Kocher maneuver routinely for B-I in open gastrectomy. After performing B-I with Kocher maneuver, 8 cases were converted to B-II for various reasons. In laparoscopic gastrectomy, Kocher maneuver was not done. After gastrectomy, the total serum amylase level was measured at immediate post operative period and on the first postoperative day routinely. If elevated, it was measured every other day until it returned within normal limits. Gabexate mesilate was administered when the serum amylase level was over 300 U/L.

Multivariate analysis was done for serum amylase levels according to various surgical procedures.

### Statistical analysis

The regression procedures were used as indicated. Statistical significance was defined as p<0.05.

### Results

Ten patients (10/497) on immediate postoperative period and one 6th (100/497) on postoperative day 1 showed its level more than 250 U/L. Measuring the serial change of postoperative serum amylase level, elevated serum amylase level on the postoperative day 1 returned to the plateau by the postoperative day 3 in most patients (Fig. 1). On analysis of the ratio of serum amylase level over 250 U/L according to the surgical procedures, 17% of patients with FG showed increased ratio. Cases of TG, TG+SP and TG+SP+F showed 30%, 29% and 40% respectively with significantly higher ratio than FG (p<0.001). Among the cases of TG, splenectomy itself did not affect the level of serum amylase (p=0.95). In addition, patients who received pancreatic resection showed the highest mean value of serum amylase (p<0.001). Lymph node dissection (D1 or D2) showed a higher level of serum amylase: D0, D1, D2: 6, 21% respectively (p=0.022). Kocher maneuver did not have any significant influence on the serum amylase level: 22% in Kocher (+) and 18% in Kocher (−) (p=0.26). The types of anastomosis exhibited difference in the inclination of serum amylase level: 18%, 17%, and 29% according to B-I, B-II, and RY. Certainly RY demonstrated higher ratio than B-I or B-II (p=0.026 Table II). According to the result of multivariate analysis, patients who received pancreatic resection (TG+SP+F) showed significant elevation of serum amylase on POD 1 (p<0.001).

### Discussion

Previous other studies of postgastrectomy hyperamylasemia showed the peak of the serum amylase on postoperative day 1. Gradual declination of serum amylase level resulted in normalization, retrieving the basal plateaus.\(^2\)^\(^7\)^\(^9\)^\(^10\) Other cases with upper abdominal surgery also had demonstrated the elevation of serum amylase level in postoperative day 1, if acute abdominal surgery is not accompanied clinically.\(^11\)^\(^12\)

Analyzing the serum amylase level measured postoperatively according to the different types of resection, the patient group with TG indicated significant increase in the serum amylase level compared to the patient group with FG. However, the analysis on the mean value of serum amylase level showed statistically significant increase only in the patient group with TG+SP+F(Table II).

The patient group with TG exhibited the higher ratio of elevated serum amylase level than the group with FG. Although sample size is small, the group with distal pancreatectomy displayed even greater increase of and
higher mean value of serum amylase than other groups. Splenectomy did not influence the serum amylase level statistically in the patients who received TG (p=0.9951). This implies that the increased serum amylase level is associated with TG regardless of splenectomy. Also, the patients who received Roux-en-Y esophageogastrojejunostomy exhibited hyperamylasemia in greater proportion than the patients who received B-I or B-II. But it is not clear which, the gastrectomy itself or the reconstruction, caused hyperamylasemia.

Postgastrectomy pancreas-related complications, such as pseudocyst, abscess, fistula, or bleeding, are very rare.\(^9\) This study also showed similar results – two patients with postoperative hyperamylasemia developed pancreas-related complications: one peripancreatic abscess, another pancreatic leakage. But the peak serum amylase level of each patient was 237 U/L (PG), 84 U/L (TG+S), 84 U/L (TG+S+P), respectively. Most patients with postoperative hyperamylasemia did not develop clinically significant pancreas-related complications and regarding the two cases of pancreatic complications, postoperative serum amylase level does not help to distinguish the occurrence of postoperative pancreas-related complications. It was reported that in total gastrectomy with distal pancreaticojejunostomy, the occurrence of pancreatic fistula increases.\(^{10}\) According to Furukawa et al.,\(^{11}\) pancreas should be preserved with dissecting the lymph nodes around distal splenic artery.\(^{12}\) This study demonstrated that distal pancreatectomy itself was associated with the elevation of serum amylase. However, not only the sample size of patients with distal pancreatectomy but also the number of patient developed pancreatic fistula was too small to assert any correlation. Kato et al. insisted that proceeding lymph node dissection around distal splenic artery would be a risk factor for developing pancreas-related abscess.\(^{13}\) This study also showed that lymph node dissection was correlated significantly with elevated serum amylase level. Nevertheless, the small number of patient who developed pancreas related complications cannot support correlation between lymph node dissection and development of pancreas related complications. Since rise in the pressure of arterial loop may cause post-operative hyperamylasemia or acute pancreatitis in patients who received B-II anastomosis, we compared the mean value of postoperative serum amylase in patients who received B-II with and without Braun anastomosis (n=11-46). However, statistically significant difference was not observed in the mean value of measured serum amylase level (p=0.22).

The degree of lymph node dissection did not affect to amylase level POD 1 statistically. (D1/D2, p=0.659) Major limitation in this study would arise from which isoenzymes, the P- or S- type, contribute most for the elevation of serum amylase. If we can measure isoenzyme activity of P-type during postoperative period, it will help us to figure out where the hyperamylasemia comes from. Lack of the direct measurement of the amylase from the drain would be another limiting factor in this study. The amylase level directly measured from peritoneal fluid would reflect subjective measure in pancreatic leakage. Also, based on the standard protocol of national health insurance, patients who had shown serum amylase level over 300 U/L, were indicated for administration of gabexate mesilate. Most patients had shown normalisation of serum amylase level on POD 3. Under the circumstance of administration of gabexate mesilate, it is quite lucid to allage spontaneous resolution of serum amylase level.

**Conclusions**

Serum amylase level hits the peak level on POD 1 and gets normalized on POD 3 in post-gastrectomy patients. Most patients with hyperamylasemia did not develop pancreas related complication, and the serum amylase level had got normalized. In this study, we can certainly state that the frequency of hyperamylasemia increased in cases of total gastrectomy with Roux-en-Y esophageogastrojejunostomy, of pancreas resection and of lymph node dissection.

**Acknowledgements**

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**REFERENCES**


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**Table 1. Serum amylase level on postoperative day 1 according to the surgical procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>Mean± Range</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG</td>
<td>387</td>
<td>196 (23-1446)</td>
<td>67</td>
<td>17*</td>
</tr>
<tr>
<td>TG</td>
<td>21</td>
<td>218 (88-691)</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>TG+S</td>
<td>84</td>
<td>213 (22-1030)</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>TG+S+P</td>
<td>5</td>
<td>590 (40-2230)</td>
<td>2</td>
<td>40*</td>
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<tr>
<td>D0</td>
<td>16</td>
<td>144 (33-259)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>D1</td>
<td>24</td>
<td>188 (33-548)</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>D2</td>
<td>457</td>
<td>207 (22-2230)</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>Kocher(-)</td>
<td>286</td>
<td>230 (22-2230)</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>Kocher(+)</td>
<td>231</td>
<td>230 (24-1469)</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>B-I</td>
<td>157</td>
<td>191 (23-1446)</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>B-II</td>
<td>110</td>
<td>227 (22-2230)</td>
<td>34</td>
<td>29*</td>
</tr>
</tbody>
</table>

* Mean serum amylase level (U/L) on postoperative day 1
* Statistically significant

\(^{1}\) Kocher maneuver was not performed.
\(^{2}\) Kocher maneuver was performed.

PO: partial gastrectomy; TG: total gastrectomy; TG+S: total gastrectomy with splenectomy; TG+S+P: total gastrectomy with splenectomy and distal pancreatectomy; D0; D1 or D2 lymph node dissection; D0; D1 or D2; B-I: gastroduodenostomy; B-II: gastrojejunostomy; RY: Roux-en-Y esophageogastrojejunostomy.
Analysis of Postgastrectomy Serum Amylase

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Abstract

Purpose : To elucidate the mechanism of postgastrectomy hyperamylasemia, we analyzed serum amylase level after gastrectomy.

Materials and Methods : We retrospectively reviewed the prospectively collected data of serum amylase level of 497 patients who had undergone gastrectomy for gastric cancer from 2004 to 2010. Amylase level was measured at immediate postoperative period and on postoperative day 1. Amylase level was analyzed according to the operative procedures, such as the types of gastric resection, reconstruction methods, whether performing Kocher maneuver or not, and the extent of lymph node dissection.

Results : The serum amylase showed its peak level on postoperative day 1, and it returned to the plateau level by the postoperative day 3 in most patients. The proportion of patients with serum amylase more than 250 U/L on postoperative day 1 was analyzed based on the operative procedures. Lymph node dissection was engaged in higher level of serum amylase: D0, D1, D2: 6, 21, 21% respectively (P=0.022). Kocher maneuver didn’t have any effect on amylase level. Total gastrectomy with or without splenectomy (30%, 29% respectively) showed higher level than partial gastrectomy (17%) (P=0.004). Distal pancreatectomy showed significantly high serum amylase. The types of anastomosis exhibited the ratio difference of 18%, 17%, and 29% according to gastroduodenostomy, gastrojejunostomy or Roux-en-Y esophagojejunostomy (P=0.026).

Conclusion : Lymph node dissection, total gastrectomy with Roux-en-Y esophagojejunostomy, and pancreas resection exhibited higher serum amylase level on postoperative day 1 after gastrectomy.

Key Words : hyperamylasemia, gastrectomy, amylases

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