Pancreatology xxx (2017) 1–6

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Plasma ghrelin suppression as an early predictor for postoperative complications after pancreatoduodenectomy

Kazuki Sasaki [a], Tadafumi Asaoka [a], Hidetoshi Eguchi [a, *], Yasunari Fukuda [a], Yoshifumi Iwagami [a], Daisaku Yamada [a], Yasuhiro Miyazaki [a], Takehiro Noda [a], Tsuyoshi Takahashi [a], Kunihito Gotoh [a], Koichi Kawamoto [a], Yukinori Kurokawa [a], Shogo Kobayashi [a], Shuji Takiguchi [b], Masaki Mori [a], Yuichiro Doki [a]

[a] Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Japan
[b] Gastroenterological Surgery, Graduate School of Medical Sciences, Nagoya City University, Japan

ARTICLE INFO

Article history:
Received 7 July 2017
Received in revised form
29 November 2017
Accepted 1 December 2017
Available online xxx

Keywords:
Clavien-Dindo complication
C-reactive protein
Interleukin-6
Pancreatoduodenectomy
Individual ghrelin ratio

ABSTRACT

Background/Objectives: The gut peptide hormone ghrelin induces appetite and exhibits an anti-inflammatory effect. Serial perioperative changes in ghrelin have been examined in several surgical procedures, but few in pancreatectomy. The present study analyzed perioperative changes in plasma ghrelin levels after pancreaduodenectomy (PD).

Methods: The study included 24 patients undergoing PD between May 2015 and January 2016 at Osaka University Hospital. Plasma ghrelin and interleukin-6 (IL-6) levels, as well as white blood cells (WBCs) and C-reactive protein (CRP), were measured preoperatively and on postoperative day (POD) 1, 3, 7, and 14 by enzyme-linked immunosorbent assay. The relationship between the individual ghrelin ratio relative to preoperative value (IGR) and the development of grade IIIa-V Clavien-Dindo (CD) complications was examined.

Results: Twelve patients (50%) developed grade IIIa CD complications (n = 6 [25%] pancreatic fistula, n = 7 [29%] intraabdominal abscess, n = 3 [13%] post-pancreatectomy hemorrhage, n = 5 [21%] wound infection, and n = 1 [4%] lymphorrhea). The IGR on POD 1 was significantly lower ($p = 0.014$) in patients who developed the complications compared to those who did not, but no significant differences were found in terms of WBC, CRP, or IL-6 on POD 1. When the IGR cut-off was set to 82% by receiver operative curve analysis, the sensitivity was 83%, specificity 75% and area under the curve 0.80. The lower IGR group (≤82%) had more postoperative complications and longer hospital stay.

Conclusions: The IGR on POD 1 after PD is a useful marker for predicting postoperative complications.

Introduction

Ghrelin is a 28-amino-acid peptide hormone discovered in 1999 by Kojima [1] as an intrinsic ligand for growth hormone secretagogue receptor (GHS-R). Ghrelin is produced predominantly by X/A-like cells in the rodent stomach [2] or P/D1 cells in the human stomach [3], as well as the duodenum, jejunum, and pancreas [4]. In addition to growth hormone secretion and an orexigenic effect, ghrelin also has an anti-inflammatory effect by inhibiting the production of proinflammatory cytokines, such as IL-1β and IL-6 [5,6] and suppression of NF-κB. [7,8] Due to its anti-inflammatory effect, a therapeutic effect of ghrelin administration has been reported in acute pancreatitis [9].

Regarding surgical stress, changes in ghrelin vary depending on the surgical procedure. After cholecystectomy, colectomy [10], and appendectomy [11], plasma ghrelin levels have been reported to increase, whereas after bariatric surgery [12], gastrectomy [13], and esophagectomy [14], they decrease due to the removal of the stomach (i.e., vagotomy). In addition, for patients who underwent esophagectomy and had a severely decreased individual ghrelin ratio relative to the preoperative value (IGR) on postoperative day (POD) 1, periods of systemic inflammatory response syndrome (SIRS) were extended [15]. However, the clinical significance of

* Corresponding author. Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan.
E-mail address: heguchi@gesurg.med.osaka-u.ac.jp (H. Eguchi).

https://doi.org/10.1016/j.pan.2017.12.002
1424-3903/

Abbreviations

PD	pancreatoduodenectomy
SSPPD	subtotal-stomach-preserving pancreatoduodenectomy
SIRS	systemic inflammatory response syndrome
IL-6	interleukin-6
ELISA	enzyme linked immunosorbent assay
PJ	pancreatojejunostomy
PG	pancreatogastrostomy
CD	Clavien-Dindo
POPF	postoperative pancreatic fistula
DGF	delayed gastric emptying
PPH	post-pancreatectomy hemorrhage
WBC	white blood cell
POD	postoperative day
ROC:	receiver operating characteristic
AUC	area under the curve
IDC	invasive ductal carcinoma
IPMN	intraductal papillary mucinous neoplasm
IQR	interquartile range
BMI	body mass index
ASA	American Society of Anesthesiologists
CRT	chemoradiation therapy
PV	portal vein
IGR	individual ghrelin ratio
CRP	C-reactive protein

plasma ghrelin levels after pancreatectomy have not been explored in detail.

Pancreatoduodenectomy (PD) is a major surgery for disease in the area of the pancreatic head and has a possibility of developing various intractable complications, including postoperative pancreatic fistula (POPF) [16], delayed gastric emptying (DGE) [17], and post-pancreatectomy hemorrhage (PPH) [18]. Despite advances in surgical technique and perioperative management [19], the frequency of complications remains high. Therefore, better prediction and management of postoperative complications would enable better decision-making regarding treatment options.

This prospective cohort study investigated the possibility of using ghrelin as a predictive marker of the inflammatory response. The aim of this study was to elucidate the relationship between perioperative serial changes in plasma ghrelin and the postoperative course, especially complications after PD.

Patients and methods

Study design

Clinical data and blood samples were collected prospectively. This study was approved by the Osaka University ethics committee and written informed consent obtained from all patients. Twenty-four patients who underwent PD (or SSPPD in the case without history of gastrectomy) at Osaka University Hospital between May 2015 and January 2016 were enrolled in the study. The other inclusion criterion was disease limited to the area of the pancreatic head. Patients with extended disease, such as liver, omentum, or mesenteric metastasis, were excluded.

Clinical data were obtained from a careful review of electronic health records. Complications were assessed by three surgeons independently. Postoperative complications that developed during the first 2 weeks after the operation were noted. Multiple complications per patient were possible because the number of complications was considered. Complications were graded based on the Clavien-Dindo (CD) classification, ranging from I to V [20,21]. The CD classification is as follows: grade I, only symptom without any intervention; grade II, symptom treated by medications; grade IIIa, symptom requires invasive procedure without general anesthesia; grade IIIb, invasive treatment with general anesthesia; grade IV, requires ICU administration; grade V, death.

Blood samples were obtained from patients before breakfast preoperatively and POD 1, 3, 7, and 14. To obtain plasma, blood was collected in a tube containing ethylene diamine tetraacetic acid (EDTA). After centrifugation at 1500 rpm for 20 min at 4 °C, 10% 1 N hydrochloric acid was added and the sample stored at −80 °C. To obtain serum, blood was collected in a tube containing a separating agent. After centrifugation at 1500 rpm for 20 min at 4 °C, the supernatant was stored at −80 °C. Some blood was used for routine examination, including white blood cell (WBC) count and C-reactive protein (CRP).

Surgical techniques

All operations were performed by an experienced surgical team specializing in hepato-biliary pancreatic surgery. General anesthesia combined with epidural anesthesia was performed unless there were specific reasons not to do so, such as anticoagulant administration. For all cases, cephazolin was administered 30 min before the operation as prophylactic antibiotic.

We performed PD (or SSPPD) primarily to ensure lymph node and connective tissue dissection around the pyloric antrum. All patients underwent regional and lymph node dissection. Standard reconstruction of the gastrointestinal tract included pancreato-enteric anastomosis, bilio-enteric anastomosis, gastroenteric anastomosis, and Braun anastomosis. For pancreato-enteric anastomoses, pancreatojejunostomy (PJ) or pancreatogastrostomy (PG) was selected by the ongoing clinical comparative trial regarding pancreato-enteric reconstruction, or the safety and ease of anastomosis was assessed intraoperatively. Gastro-jejunostomy was reconstructed in an antecolic fashion. Three drains were placed around pancreato-enteric and bilio-enteric anastomoses. Internal pancreatic duct stent was inserted to drain pancreatic juice, and intrahepatic duct tube was placed to drain bile. In the case of PG, a decompression tube was also placed in the stomach. If the postoperative course was uneventful, the drain tubes were removed in order.

Enzyme linked immunosorbent assay (ELISA) for IL-6 and ghrelin

Plasma ghrelin and serum IL-6 levels were measured as described previously. [14,15] There are two main forms of ghrelin, an acylated form and deacylated form. The two forms of plasma ghrelin were measured using the ELISA kits for acyl ghrelin and des-acyl ghrelin (Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan) [22]. Total ghrelin was calculated as the sum of acyl and des-acyl ghrelin. Serum IL-6 was measured using the ELISA kit for IL-6 (Thermo Fisher Scientific K.K., Yokohama, Japan). Measurements were made in duplicate for each sample and the mean value used.

Statistical analysis

JMP® Pro 12.2.0 (SAS Institute Inc., Cary, NC, USA) was used for

Please cite this article in press as: Sasaki K, et al., Plasma ghrelin suppression as an early predictor for postoperative complications after pancreatoduodenectomy, Pancreatology (2017), https://doi.org/10.1016/j.pan.2017.12.002