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ORIGINAL RESEARCH

The Effect of Visceral Fat Mass on Pancreatic Fistula after Pancreaticoduodenectomy

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ABSTRACT

Background: Obesity is associated with perioperative complications and has been considered a risk factor for surgical outcomes of patients undergoing abdominal surgery. The aim of this study is to evaluate the impact of the amount of visceral fat on postoperative morbidity of patients who underwent pancreaticoduodenectomy (PD). *Methods:* We reviewed 181 patients who underwent surgery for periampullary lesions at the Department of Surgery, Gangnam Severance Hospital, Yonsei University Health System between January 2003 and June 2010. The visceral fat area (VFA) and subcutaneous fat area were calculated by computed tomography software. *Results:* The mean body mass index (BMI) was 23.4 kg/m^2 ($\pm$3.1 kg/m^2), and the mean VFA was 94.4 cm^2 ($\pm$49.5 cm^2). The mean intraoperative blood loss, and the incidence of clinically relevant pancreatic fistula (grade B/C) and clinically relevant delayed gastric emptying (grade B/C) were significantly higher in the high-VFA group ($\geq$100 cm^2). In univariate analysis, the incidence of clinically relevant pancreatic fistula (grade B/C) was significantly higher in the high-BMI group ($\geq$25 kg/m^2), the high-VFA group($\geq$100 cm^2), the large intraoperative blood loss and transfusion group, and in patients with pathology of nonpancreatic origin (ampulla, bile duct, or duodenum). In multivariate analysis, the high-VFA group ($\geq$100 cm^2) and patients with pathology of nonpancreatic origin were identified as independent factors for clinically relevant pancreatic fistula. *Conclusion:* VFA is a better indicator for the development of pancreatic fistula after PD than BMI. High VFA ($\geq$100 cm^2) is a risk factor for developing a pancreatic fistula after PD.

Keywords: pancreaticoduodenectomy; pancreatic fistula; visceral fat area; obesity

INTRODUCTION

Pancreaticoduodenectomy (PD) performed in high-volume centers has become increasingly safe and more efficient [1–4]. However, the morbidity rate remains high with complication rates of about 40% [1–4]. In PD, pancreatic leakage is still one of the leading postoperative complications, often resulting in prolonged hospital stay and operative mortality. Previously reported factors predictive of pancreatic leakage after PD include old age, anastomotic techniques, small pancreatic duct, and soft pancreatic texture [5–10]. Soft pancreas, which is more frequently observed in obese patients, could explain that body mass index (BMI) appears as a risk factor of PF after distal pancreatectomy [11].

Obesity is rapidly becoming a major public health problem in Western countries and Korea. Obesity is related with several chronic diseases including diabetes mellitus, cardiovascular disease, stroke, hypertension, and certain types of cancers. Moreover, it is also associated with perioperative complications and has been considered a risk factor for surgical outcomes of patients undergoing abdominal surgery [12–14]. BMI has been widely used to assess the degree of obesity because it can be simply calculated with weight and height [15, 16]. However, BMI is not always correlated to the degree of a patient's visceral fat because of other factors such as sex and age [17–19]. Many studies suggest that visceral fat is a more useful parameter than BMI in predicting surgical outcomes. Visceral fat

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area (VFA) estimated on computed tomography (CT) images taken at the level of the umbilicus correlate with the total volume of visceral fat [18, 20].

The aim of this study is to evaluate the impact of the amount of visceral fat on postoperative morbidity of patients who underwent PD.

MATERIALS AND METHODS

Patients

One hundred ninety-six patients with benign and malignant periampullary lesions underwent PD at the Department of Surgery, Gangnam Severance Hospital, Yonsei University Health System between January 2003 and June 2010. Fifteen patients were excluded because of incomplete clinicopathologic data. As a result, 181 patients were retrospectively reviewed. This study was approved by the Institutional Review Board of Yonsei University for retrospective chart review and data collection.

Measurement of Visceral Fat Area (VFA)

VFA was measured using CT scan in a previously described manner [12, 15]. One cross-sectional CT scan of 3-mm thick slice was obtained at the level of the umbilicus. The VFA and subcutaneous fat area were calculated by a software program for CT (TeraRecon Aquarius; TeraRecon, USA) with attenuation ranging from −150 to −50 Hounsfield units.

This software enables semiautomatic planimetric measurements of a specific region with specified Hounsfield units. All measuring procedures described above were performed by two radiologists who were blinded to the surgical data at the time of measurement.

Surgical Procedure and Perioperative Management

Pylorus preserving pancreaticoduodenectomy (PPPD) and conventional PD were performed as previously reported. [21] All patients underwent dissection of the lymph nodes in the hepatoduodenal ligament, common hepatic artery, and celiac axis. In all cases, the diameter of the pancreatic duct and parenchyma texture were measured after pancreatic transection by the operator. As a policy of our department, antacid drugs for stress ulcer prophylaxis, and octreotide (Sandostatin 150 mg; Novartis International, Basel, Switzerland) were subcutaneously administered to all patients for seven days postoperatively. Gastric suction was stopped within the first three postoperative days. After postoperative day 3, the gastric tube was clamped for 24 hr, and patients were given sips of water between postoperative days 4 and 5. Patients then proceeded to a regular diet within seven days.

Pancreatic fistula is defined by output via an operative drain of any measurable volume of drain fluid on or after postoperative day 3 with the amount of amylase greater than three times the upper normal serum level (>300 IU/l) according to the International Study Group of Pancreatic Fistula (ISGPF) definition [22]. The severity of delayed gastric emptying (DGE) was determined according to the International Study Group of Pancreatic Surgery (ISGPS) classification scheme [23].

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or median and interquartile range (IQR) with skewed distributions. Differences in variables between or among groups were tested using Student's *t-test*, *chi*-square test, or Fisher's exact test. However, nonparametric tests (Kruskal–Wallis or Mann–Whitney test) were used for variables with skewed distributions.

Multivariate analysis was performed using a nonconditional logistic regression model expressed as an odds ratio. The 95% confidential intervals are shown with upper and lower limits. The p-values less than 0.05 were considered significant. To test the independence of the risk and associated factors, significant variables ($p < 0.05$) in univariate analysis were tested in a multivariate logistic regression model.

RESULTS

Patients Characteristics

A total of 181 patients who underwent PD ($N = 44$) or PPPD ($N = 137$) were selected for this study. The mean age of the study population was 61.0 years (±12.0 years) and consisted of 95 men and 86 women.

The median intraoperative blood loss was 1125.6 ml (1028.4–1222.7 ml), the median operative time was 453.0 min (437.5–468.4 min), and the median duration of hospital stay was 27.0 days (25.3–28.7 days). The mean BMI was 23.4 kg/m^2 (±3.1 kg/m^2) and the mean VFA was 94.4 cm^2 (±49.5 cm^2). There were no cases of hospital mortality.

Comparison between High-VFA and Low-VFA Groups

VFA was low (<100 cm^2) in 100 patients and high in 81 patients according to previously reported criteria [24]. There was a significant difference in age, BMI, and metabolic disease (diabetes mellitus (DM), hypertension) between high-VFA and low-VFA groups (Table 1).

TABLE 1 Comparison of patients characteristics and surgical outcomes between high- and low-VFA* groups

	Low VFA (<100 cm^2) $N = 100$	High VFA (≥100 cm^2) $N = 81$	*p*-value
Patients characteristics			
Age (years)	58.8 ± 12.9	63.6 ± 10.2	0.006
Sex (male/female)	47/53	48/33	0.068
BMI† (kg/m^2)	21.9 ± 2.6	25.3 ± 2.7	< 0.001
Metabolic disease			
DM (yes/no)	24/76	34/47	0.008
Hypertension (yes/no)	20/80	29/52	0.014
Operative parameters			
Pancreatic duct size (<3mm/≥3mm)	56/44	50/31	0.437
Pancreatic texture (Soft/Hard)	28/72	30/51	0.128
Pathology origin (pancreas/nonpancreas)	42/58	24/57	0.058
Pathology (malignancy/benign)	84/16	68/13	0.575
Operative technique (PD‡/ PPPD§)	30/70	14/67	0.034
SMV, Portal vein resection (yes/no)	5 / 95	0 / 81	0.066
Intraoperative blood loss (median, ml)	1020.4 (896.9–1143.9)	1255.4 (1102.8–1407.9)	0.017
Operative time (median, min)	443.7 (424.1–463.3)	464.3 (439.5–489.2)	0.191
Amount of transfusion (unit)	1.44 ± 1.7	1.7 ± 1.8	0.412
Hospital stay (median, days)	26.0 (23.7–28.3)	28.2 (25.5–30.8)	0.228
Postoperative course			
Grade of pancreatic fistula (no&A/B&C)	93/7	60/21	< 0.001
Grade of delayed gastric emptying (no&A/B&C)	81/19	53/28	0.014
Postoperative bleeding (yes/no)	0/100	1/80	0.448
Chyle leakage (yes/no)	6/94	2/79	0.219
Complication of gastrostomy site (yes/no)	0/100	2/79	0.199
Wound infection (yes/no)	5/95	9/72	0.106

VFA* Visceral fat area; BMI†: Body mass index; PD‡: Pancreaticoduodenectomy; PPPD§: Pylorus preserving pancreaticoduodenectomy.

The mean intraoperative blood loss was significantly larger in the high-VFA group, but there was no significant difference in pancreatic texture, pancreatic duct size, and pathologic origin of disease between the two groups (Table 1).

In postoperative complications, the incidence of clinically relevant pancreatic fistula (grade B/C) and clinically relevant DGE (grade B/C) were significantly higher in the high-VFA group than in low-VFA group (Table 1).

Risk Factors of Clinically Relevant Pancreatic Fistula

In univariate analysis, the incidence of clinically relevant pancreatic fistula (grade B/C) was significantly greater in the high-BMI group (≥25 kg/m^2), the high-VFA group(≥ 100 cm^2), the large intraoperative blood loss and transfusion group, and in patients with pathology of nonpancreatic origin (ampulla, bile duct, or duodenum). The rate of pancreatic fistula did not correlate with sex, age, pathology (malignant versus benign), pancreatic duct size, pancreatic texture, operation method (PD versus PPPD), and superior mesenteric vein (SMV)/portal vein (PV) resection (Table 2).

In multivariate analysis, the high-VFA group (≥100 cm^2) and cancer of nonpancreatic origin (ampulla, bile duct, or duodenum) were identified as independent factors for clinically relevant pancreatic fistula (Table 3).

DISCUSSION

Obesity is rapidly becoming a major public health problem in many countries around the world. According to the 2007 Korea National Health & Nutrition Examination Survey (KNHNES), obesity prevalence has gradually increased in Korea, which is attributed to people's preference for high-calorie diet and sedentary lifestyle and lack of physical exercise. The prevalence rate of BMI ≥ 25 kg/m^2 and BMI ≥ 30 kg/m^2 in Koreans was 29.5% and 3.0% in 2001 according to the KNHENES data of 1988 and 2001 [25–27]. The obesity rate in this study was 30.3% (BMI ≥ 25 kg/m^2) and 2.7% (BMI ≥ 30 kg/m^2) which was similar to the national survey. Obesity is related with several chronic diseases, including DM, cardiovascular disease, stroke, hypertension, and certain cancers: it is also associated with perioperative complications and has been considered a risk factor for surgical outcomes of patients undergoing abdominal surgery [12–14].

BMI has been widely used to assess the degree of obesity because it can be simply calculated with weight and height [15, 16]. BMI and anthropometric measurement of obesity are well correlated to the absolute amount of abdominal adipose tissue. However, BMI

TABLE 2 Univariate analysis of the risk factors for clinically relevant pancreatic fistula (PF) (grade B/C)

	Grade of PF (0&A) $N = 153$	Grade of PF (B&C) $N = 28$	p value
Age (years)	60.6 ± 12.2	63.1 ± 11.1	0.301
Sex			0.412
Male	78	17	
Female	75	11	
Presence of preoperative DM			0.083
Yes	45	13	
No	108	15	
BMI (kg/m^2)			0.014
<25	112	14	
≥25	41	14	
VFA (cm^2)			0.001
<100	93	7	
≥100	60	21	
Diameter of pancreatic duct			0.278
≤3mm	87	19	
>3mm	66	9	
Consistency of pancreas texture			0.193
Soft	46	12	
Hard	107	16	
Pathology origin			0.010
Pancreas	62	4	
nonpancreas (ampulla/bile duct/duodenum)	91	24	
Pathology			0.521
Malignancy	128	24	
Benign	25	4	
Operative technique			
PD	35/118	9/19	0.339
PPPD			
SMV/portal vein resection			0.573
Yes	4	1	
No	149	27	
Intraoperative blood loss (median, ml)	1040.7 (941.5–139.9)	1589.3 (1318.3–1860.3)	0.001
Operative time (median, min)	445.1 (428.3–461.8)	496.0 (457.9–534.1)	0.018
Amount of transfusion (unit)	1.3 ± 1.6	2.7 ± 1.9	0.000

TABLE 3 Multivariate logistic analysis of the risk factors for pancreatic fistula grade (B&C)

	Odds ratio	95% CI	p-value
High VFA (>100 cm^2)	0.013	1.001–1.026	*0.026*
Nonpancreas origin disease (ampulla/bile duct/duodenum)	1.743	1.588–20.547	*0.015*

Multivariate analysis was performed on logistic regression model expressed as an odds ratio. The 95% confidential intervals did not contain 1.0, so p-values were significant.

does not always accurately reflect the amount of visceral fat because the distribution of fat tissue greatly varies among individuals [18, 19]. In our study, 44.8% of patients did not have a directly proportional positive correlation between VFA and BMI.

The clinical importance of visceral fat accumulation has been highlighted by its association with metabolic syndrome which is characterized by glucose intolerance, obesity, hypertension, and dyslipidemia. In our study, the rate of metabolic syndrome (DM, hypertension) is higher in the high-VFA group. Generally, visceral fat is a major factor influencing the technical difficulty during abdominal surgery. In many other studies, obese patients were associated with high rate of wound infection, long hospital stay, long operation time, large intraoperative blood loss, and high anastomotic fistula. Similar to previous studies, this study showed that high VFA was a significant risk factor for large intraoperative blood loss and long operation time.

In this study, VFA was measured using CT images. Magnetic resonance imaging (MRI) also permits the quantification of VFA with most accurate results derived from whole body analysis using contiguous slices [28,29]. However, MRI overestimated VFA when compared to finding with CT [30, 31]. The superior accuracy of CT can be attibuted to the fact that absolute HU values of pixels directly correspond to the tissue property in CT, while there is no direct association between tissue property and pixel value in MRI.

Pancreatic fistula is a leading postoperative complication of PD, often resulting in prolonged hospital stay and operative mortality. After PD, pancreatic fistula may occur in 5–30% patients, and our result was similar to other studies. Previous studies reported old age, anastomotic techniques, small pancreatic duct, and soft pancreatic texture, as factors predictive of pancreatic leakage after PD [5–10]. Recently, a high amount of visceral fat was reported to be associated with significantly higher rate of overall complications and pancreatic fistula after PD [12]. Our multivariate analysis found VFA as a potential risk factor of pancreatic fistula after PD. The reason why patients with high VFA are more likely to develop pancreatic fistula could be the surgical difficulty associated with deeper and poorer view of surgical field as well as fragile pancreatic tissue. Noun et al. [32] reported obese patients had higher amount of intrapancreatic fat and this large amount of fat was positively correlated with BMI. We did not histopathologically examine the presence of pancreatic steatosis. Thus, we cannot correlate VFA with pancreatic fat amount. However, the high-VFA group in our study showed a tendency for higher incidence of soft pancreatic texture. Future prospective studies should focus on better characterizing pancreatic texture and consistency in obese patients with large amounts of VF to determine the gland features that potentiate pancreatic fistula after pancreatic resection.

Once a patient is diagnosed with pancreatic fistula, aggressive and appropriate conservative management is the key to a successful outcome. A conservative approach to the management of pancreatic fistula is

successful in over 90% patients. However, interventional radiological assistance is sometimes required, but surgical procedure is rarely indicated.

According to our results, VFA is a better indicator than BMI for the development of pancreatic fistula after PD. VFA $\geq$ 100 cm^2 is a risk factor for the development of pancreatic fistula after PD. Adjunctive operative techniques and therapies aimed at reducing the chances of a pancreatic fistula after PD should be considered for high-VFA patients with a disease of a nonpancreatic origin such as the ampulla, bile duct, or duodenum.

Declaration of interest: The authors report no conflicts of interest.

REFERENCES

[1] Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. *Ann Surg*. 2006;244:10–15.

[2] DeOliveira ML, Winter JM, Schafer M, et al. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann Surg*. 2006;244:931–939.

[3] Glasgow RE, Jackson HH, Neumayer L, et al. Pancreatic resection in Veterans Affairs and selected university medical centers: results of the patient safety in surgery study. *J Am Coll Surg*. 2007;204:1252–1260.

[4] Grobmyer SR, Pieracci FM, Allen PJ, et al. Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. *J Am Coll Surg*. 2007;204:356–364.

[5] de Castro SM, Busch OR, van Gulik TM, et al. Incidence and management of pancreatic leakage after pancreatoduodenectomy. *Br J Surg*. 2005;92:1117–1123.

[6] Hosotani R, Doi R, Imamura M. Duct-to-mucosa pancreaticojejunostomy reduces the risk of pancreatic leakage after pancreatoduodenectomy. *World J Surg*. 2002;26:99–104.

[7] Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg*. 2004;8:951–959.

[8] Miedema BW, Sarr MG, van Heerden JA, et al. Complications following pancreaticoduodenectomy. Current management. *Arch Surg*. 1992;127:945–950.

[9] van Berge Henegouwen MI, De Wit LT, Van Gulik TM, et al. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage versus resection of the pancreatic remnant. *J Am Coll Surg*. 1997;185:18–24.

[10] Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. A*nn Surg* 1995;222:580–892.

[11] Sledzianowski JF, Duffas JP, Muscari F, et al. Risk factors for mortality and intra-abdominal morbidity after distal pancreatectomy. *Surgery* 2005;137:180–185.

[12] House MG, Fong Y, Arnaoutakis DJ, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg*. 2008;12:270–278.

[13] Kodera Y, Ito S, Yamamura Y, et al. Obesity and outcome of distal gastrectomy with D2 lymphadenectomy for carcinoma. *Hepatogastroenterology* 2004;51:1225–1228.

[14] Merkow RP, Bilimoria KY, McCarter MD, et al. Effect of body mass index on short-term outcomes after colectomy for cancer. *J Am Coll Surg*. 2009;208:53–61.

[15] Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;444:881–887.

[16] Mathieu P, Poirier P, Pibarot P, et al. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension* 2009;53:577–584.

[17] Baumgartner RN, Heymsfield SB, Roche AF. Human body composition and the epidemiology of chronic disease. *Obes Res*. 1995;3:73–95.

[18] Maurovich-Horvat P, Massaro J, Fox CS, et al. Comparison of anthropometric, area- and volume-based assessment of abdominal subcutaneous and visceral adipose tissue volumes using multi-detector computed tomography. *Int J Obes*. 2007;31:500–506.

[19] Seidell JC, Visscher TL. Body weight and weight change and their health implications for the elderly. *Eur J Clin Nutr.* 2000;54:S33-S39.

[20] Chung SJ, Kim D, Park MJ, et al. Metabolic syndrome and visceral obesity as risk factors for reflux oesophagitis: a cross-sectional case-control study of 7078 Koreans undergoing health check-ups. *Gut* 2008;57:1360–1365.

[21] Park JS, Hwang HK, Kim JK, et al. Clinical validation and risk factors for delayed gastric emptying based on the International Study Group of Pancreatic Surgery (ISGPS) Classification. *Surgery* 2009;146:882–887.

[22] Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an International Study Group (ISGPF) definition. *Surgery* 2005;138:8–13.

[23] Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007;142:761–768.

[24] The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for Study of Obesity. New criteria for "obesity disease" in Japan. *Circ J.* 2002;66:987–992.

[25] The Korean National Health Nutrition Examination Survey 1998. In: WelfareKMoHa, ed. Seoul, Korea: Korean Ministry of Health and Welfare; 1999

[26] The Korean National Health Nutrition Examination Survey 2002. In: Welfare KMoHa, ed. Seoul, Korea: Korean Ministry of Health and Welfare; 2001

[27] Park HS, Park CY, Oh SW, et al. Prevalence of obesity and metaboilic syndrome in Korean adults. *Obes Rev.* 2008;9:104–107.

[28] Ross R, Leger L, Morris D, et al. Quantification of adipose tissue by MRI: relationship with anthropometric variables. *J Appl Physiol.* 1992;72:787–795.

[29] Machann J, Thamer C, Schnoedt B, et al. Standardized assessment of whole body adipose tissue topography by MRI. *J Magn Reson Imaging* 2005;21:455–462.

[30] Sobol W, Rossner S, Hinson B, et al. Evaluation of a new magnetic resonance imaging method for quantitating adipose tissue areas. *Int J Obes Relat Metab Disord.* 1991;15:589–599.

[31] Seidell JC, Bakker CJ, van der Kooy K. Imaging techniques for measuring adipose-tissue distribution—a comparison between computed tomography and 1.5-T magnetic resonance. *Am J Clin Nutr.* 1990;51:953–957.

[32] Noun R, Riachy E, Ghorra C, et al. The impact of obesity on surgical outcome after pancreaticoduodenectomy. *JOP* 2008;9:468–476.