ISSN 1949-8470 (online)

World Journal of *Radiology*

World J Radiol 2024 November 28; 16(11): 629-707

Published by Baishideng Publishing Group Inc

World Journal of Radiology

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NAME OF JOURNAL
World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Thomas J Vogl

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8470/editorialboard.htm

PUBLICATION DATE
November 28, 2024

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World J Radiol 2024 November 28; 16(11): 644-656

DOI: 10.4329/wjr.v16.i11.644

ISSN 1949-8470 (online)

ORIGINAL ARTICLE

Retrospective Study

Pancreatic volume change using three dimensional-computed tomography volumetry and its relationships with diabetes on long-term follow-up in autoimmune pancreatitis

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Specialty type: Radiology, nuclear medicine and medical imaging

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Zhu QT

Received: July 25, 2024
Revised: September 7, 2024
Accepted: September 23, 2024
Published online: November 28, 2024
Processing time: 124 Days and 19.2 Hours

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Abstract

BACKGROUND

Several studies found that early pancreatic atrophy detected by computed tomography (CT) within 6 months was associated with a high incidence of diabetes in patients with type-1 autoimmune pancreatitis (AIP) receiving steroid therapy; however, no long-term follow-up studies have been performed.

AIM

To investigate pancreatic volume (PV) changes using three dimensional (3D)-CT volumetry and their relationship with IgG4 and diabetes in patients with AIP.

METHODS

This retrospective study included 33 patients with type-1 AIP receiving steroid therapy. Patients were divided into diffuse (D-type) and mass-forming type (M-type) AIP. PV was determined by semi-automated 3D-CT volumetry, and changes between initial and follow-up values were calculated. The relationship between PV and serum IgG4 levels was analyzed by Spearman's rank correlation. The PV

atrophy ratio compared with the presumed normal PV at the time of last follow-up CT and its relationship with diabetes were investigated.

RESULTS

There were 16 D-type and 17 M-type patients with long-term follow-up (mean, 95.8 months). The regression curve of mean relative PV change reduced exponentially and rapidly during the first 25 months and then more slowly in both groups. The overall cumulative pancreas re-enlargement rates at 1, 3, 5, 7 and 10 years were 6.1%, 12.2%, 29.2%, 47.5% and 55.0%, respectively. There was a moderate-to-very strong positive correlation ($\rho \geq 0.4$) between PV and serum IgG4 levels in nine (9/13, 69.2%) patients. All 33 patients showed pancreatic atrophy (mean 59.3%) after long-term follow-up. Patients with D-type AIP had a significantly higher atrophy rate and higher incidence of diabetes than M-type patients ($P < 0.05$).

CONCLUSION

PV change initially reduced exponentially and then more slowly and is considered an important factor associated with diabetes. Serum IgG4 levels were positively correlated with PV during follow-up.

Key Words: Autoimmune pancreatitis; Computerized tomography volumetry; Follow-up study; IgG4; Diabetes

Core Tip: To the best of our knowledge, no previous studies have reported on pancreatic volume (PV) changes during long-term follow-up in patients with autoimmune pancreatitis (AIP). In this study, we investigated PV changes using computed tomography volumetry and examined their relationships with IgG4 and diabetes in patients with AIP with long-term follow-up. PV reduced exponentially and rapidly during the first 25 months and then more slowly. IgG4 levels were positively correlated with PV during long-term follow-up in most patients. Pancreatic atrophy occurred during long-term follow-up in all patients, and is considered an important factor associated with diabetes.

Citation: Shimada R, Yamada Y, Okamoto K, Murakami K, Motomura M, Takaki H, Fukuzawa K, Asayama Y. Pancreatic volume change using three dimensional-computed tomography volumetry and its relationships with diabetes on long-term follow-up in autoimmune pancreatitis. *World J Radiol* 2024; 16(11): 644-656
URL: https://www.wjgnet.com/1949-8470/full/v16/i11/644.htm
DOI: https://dx.doi.org/10.4329/wjr.v16.i11.644

INTRODUCTION

Autoimmune pancreatitis (AIP) is being increasingly recognized because of improvements in diagnostic modalities and the use of well-established diagnostic criteria[1]. AIP can be classified as type-1 or type-2 based on pathological findings [2], and as diffuse type (D-type) or mass-forming type (M-type) based on computed tomography (CT) findings[3]. Type-1 AIP is characterized by high serum IgG4 levels and an association with extrapancreatic lesions and is more common than type-2 AIP[2,4-6]. Type-1 AIP shows a good response to steroid therapy[1,7,8] and pancreatic atrophy has been observed in approximately 30% of AIP patients during follow-up[9-12], with progressive loss of the endocrine and exocrine compartments[13,14].

Several studies have evaluated the relationship between pancreatic atrophy on CT within 6 months and the incidence of diabetes in patients with type-1 AIP receiving steroid therapy and found that early volume reduction indicated a high incidence of diabetes[10,11]; however, no long-term follow-up studies have yet been performed. The current retrospective study aimed to investigate the serial long-term changes in pancreatic volume (PV) using semi-automated three dimensional (3D)-CT volumetry. Furthermore, we analyzed their relationships with serum IgG4 levels and diabetes during long-term follow-up in patients with type-1 AIP receiving steroid therapy. We also compared the results between patients with D-type and M-type AIP.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the institutional review board at our institution and associated hospital, and the requirement for informed consent was waived. Using the medical database of our institution and associated hospital, we identified 37 consecutive patients diagnosed with definite type-1 AIP according to the current international consensus diagnostic criteria[1] between May 1998 and September 2021. All patients had been followed-up for > 18 months after the diagnosis of type-1 AIP and all received steroid therapy. The diagnoses of patients diagnosed before 2011 according to the

Table 1 Computed tomography parameters

Parameter	HiSpeed Advantage[1]	Aquilion CX[2] or Aquilion ONE[3]
No. of channels	1	16 or 320
Section collimation in mm	5	1
Section thickness in mm	5	1
Reconstruction interval in mm	2.5	1
Pitch	1.0	0.6-1.0
Tube current in mA	200-250	400-600
Tube voltage in kVp	120	120
Matrix	512 × 512	512 × 512

[1]HiSpeed Advantage (General Electric Medical Systems, Chicago, IL, United States);
[2]Aquilion CX (Aquilion CX TSX-101A/NA; Toshiba Medical Systems, Co. Ltd., Tochigi, Japan);
[3]Aquilion ONE (Aquilion ONE TSX-301A/2A; Toshiba Medical Systems, Co. Ltd.).

previous criteria for AIP[15,16] were reviewed retrospectively according to the international consensus diagnostic criteria. The exclusion criteria were prior pancreatic surgery associated with AIP (n = 1) and lack of sufficient clinical data to evaluate long-term outcomes (n = 3). The final study population thus consisted of 33 patients (mean age 63.1 ± 11.1 years; median 65.0 years; range 37-85 years), including 24 men (mean age 62.3 ± 12.4; median 60.0 years; range 37-85 years) and nine women (mean age 64.7 ± 7.2 years; median 65.0 years; range 53-77 years) at the time of diagnosis of type-1 AIP.

CT protocols and contrast materials

All patients underwent abdominal CT examinations at the time of diagnosis of AIP and during follow-up, including unenhanced and contrast-enhanced (CE) imaging. CE-CT imaging was performed with triple-phase (arterial, portal venous, and equilibrium phases) with delays of 30-40 seconds, 60-70 seconds and 130-160 seconds, respectively, after the initiation of intravenous injection of contrast material, or single-phase with a delay of 100 seconds. CT examinations were performed using a single-detector CT scanner (n = 4) between May 1998 and December 2004, and using a multi-detector CT scanner (n = 33) from January 2005 onward. Detailed CT parameters are summarized in Table 1. All patients received nonionic intravenous contrast material (350 mg iodine/mL) administered at a rate of 2 mL or 3 mL/s and a volume of 100 mL using a mechanical power injector (Dual Shot; Nemoto Kyorindo, Co. Ltd. Tokyo, Japan). CE-CT was performed at least three times during the first year and then at least once approximately every 12 months and/or when dictated by clinical developments to monitor for AIP relapse.

Morphological classification of AIP

Based on the CE-CT findings at the time of diagnosis of AIP (initial CT findings), the patients were divided into D-type and M-type by consensus between two radiologists (Ryuichi Shimada and Yasunari Yamada with 20 and 36 years of experience in abdominal CT, respectively). D-type AIP was defined as enlargement of the entire pancreas with loss of pancreatic lobulation and absence of normal pancreatic clefts, and M-type AIP was defined as focal mass-like enlargement[3].

Measurement of PV and relative PV change

Semi-automated 3D-CT volumetry performed by CE-CT, as an effective method for estimating PV, was carried out as outlined previously[17-19]. PV was measured on transverse CE-CT images using a workstation (SYNAPSE VINCENT; Fujifilm Medical Co., Ltd. Tokyo, Japan), as follows (Figure 1): (1) The outline of the pancreatic parenchyma was traced manually on each slice using a free region of interest (ROI) tool in every 1 mm to 3 mm on CE-CT (when defining ROIs, care was taken to exclude the splenic artery and vein, superior mesenteric vein, portal vein, dilated pancreatic duct, and dilated intrapancreatic bile duct); (2) The boundary of the pancreatic parenchyma was then outlined by extending the ROI using intensity-based semi-automated methods until the entire parenchyma in the slice was included; and (3) The traced pancreatic parenchyma was confirmed by the colored area and manual correction was performed if misdelineation of the pancreatic borders was identified. PV was then quantified. These procedures took approximately four minutes. Data processing was performed by two radiologists in consensus (Ryuichi Shimada and Yasunari Yamada). PV was measured in all patients on initial and serial follow-up CT images. Relative PV change, rather than change in PV, was used to compare patients with D-type and M-type AIP during long-term follow-up, because PV on initial CT differed among AIP patients. Relative PV change was calculated as: Relative PV change = PV on follow-up CT/PV on initial CT × 100%.

Definitions

Pancreatic re-enlargement: Pancreatic re-enlargement is an important criterion for AIP relapse, which also include the recurrence of clinical symptoms, extrapancreatic lesions and re-elevation of serum IgG4 levels[20-22]. Pancreatic re-enlargement was defined as an increase in PV > 10% compared with the previous CT image, after considering measure-

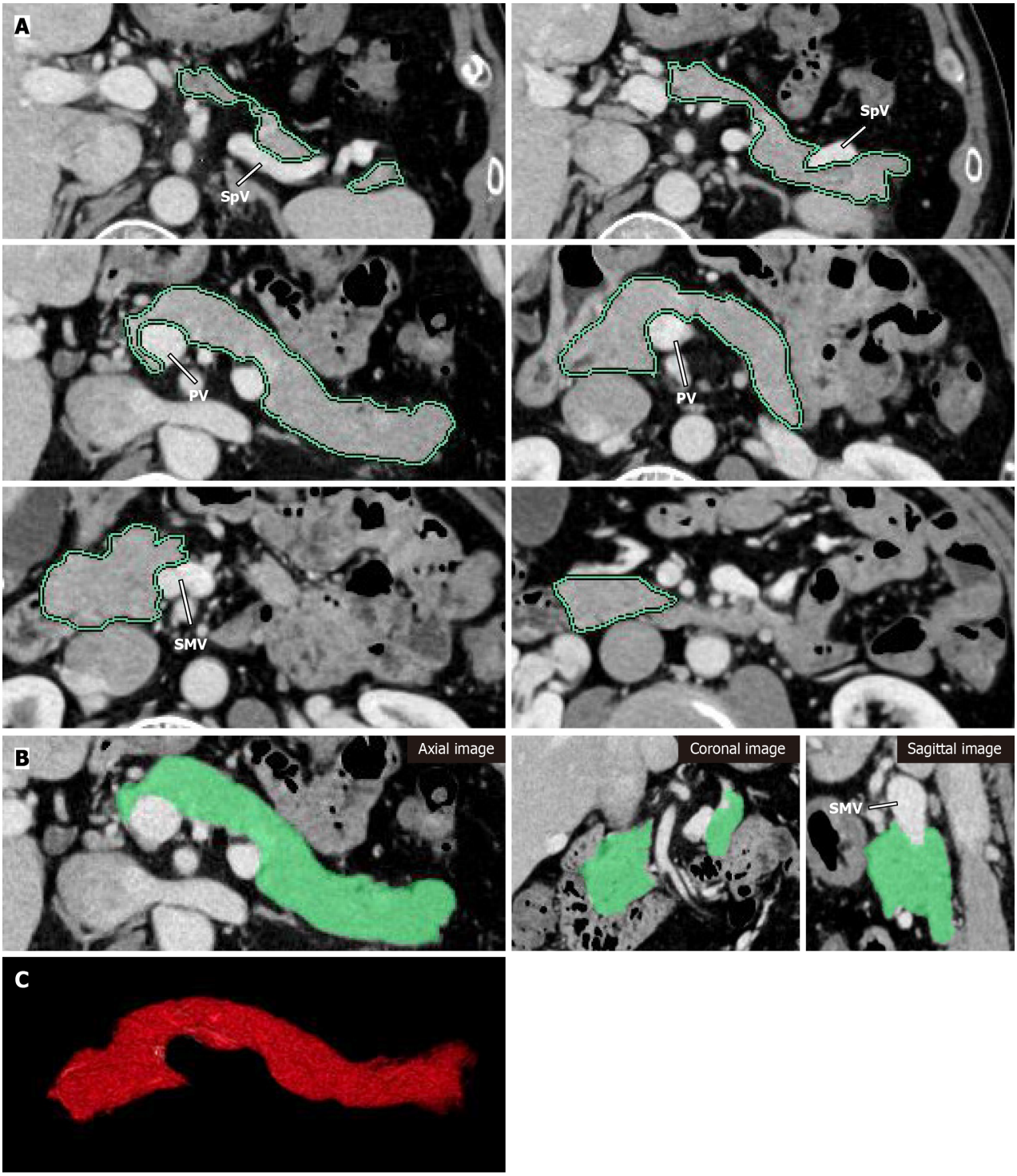

Figure 1 Pancreas volume measurement in a 62-year-old man with a normal pancreas, using portal venous contrast-enhanced computed tomography images. A: Outline of pancreatic parenchyma was traced manually (green line) on each slice using a free region of interest (ROI) tool on contrast-enhanced-CT. While defining ROIs, care was taken to exclude the splenic artery and vein, superior mesenteric vein, and portal vein. The boundary of the pancreatic parenchyma was then outlined by extending the ROI using intensity-based semi-automated methods until the entire parenchyma in the slice was included; B: The traced pancreatic parenchyma was confirmed by the green area and manual correction was performed if misdelineation of the pancreatic borders was identified on axial, coronal, and sagittal images; C: The traced pancreatic parenchyma was transformed to the proximate shape in three dimensions and the pancreatic volume was then quantified. SpV: Splenic vein; PV: Portal vein; SMV: Superior mesenteric vein.

ment errors.

Extrapancreatic lesions: Extrapancreatic lesions were defined as lesions associated with AIP, including involvement of the bile duct, kidney, retroperitoneum, and salivary/lacrimal glands[1,23,24], which were investigated at the time of initial and follow-up CT in all patients.

Table 2 Clinical characteristics of patients with type-1 autoimmune pancreatitis in relation to diffuse or mass-forming type

Variable	All, *n* = 33	D-type, *n* = 16	M-type, *n* = 17	*P* value[a]
Male:Female	24:09	12:04	12:05	1.00
Age at initial CT in years	63.1 ± 11.1 (65.0, 37-85)	64.6 ± 11.0 (65.0, 51-80)	61.6 ± 11.3 (64.5, 37-79)	0.66
Pancreatic re-enlargement	12 (36.4)	7 (43.8)	5 (29.4)	0.48
Mean time to first re-enlargement in months	42.5 ± 27.9 (37.5, 7-93)	50.7 ± 34.0 (52.0, 7-93)	31.0 ± 11.5 (30.0, 18-47)	0.33
Extrapancreatic lesions	9 (27.3)	9 (56.3)	0 (0.0)	< 0.001

Data presented as mean ± standard deviation (median and range) or number (percentage).
[a]*P* values between diffuse and mass-forming types. CT: Computed tomography; D-type: Diffuse type; M-type: Mass-forming type.

Diabetes: Diabetes was defined by one or more of the following criteria: Early-morning fasting serum glucose ≥ 126 mg/dL; casual serum glucose ≥ 200 mg/dL; serum glucose two hours after an oral glucose tolerance test ≥ 200 mg/dL; glycosylated hemoglobin ≥ 6.5% (National Glycohemoglobin Standardization Program); and treatment with antidiabetic drugs, evaluated at least at the time of initial and follow-up CT in all patients.

Treatment strategy
All 33 patients were treated with steroids at an initial dose of 25-50 mg/day for 2-4 weeks, tapered by approximately 5 mg/day every 2-4 weeks, and continued at 2.5-7 mg/day as maintenance therapy. Steroids were increased in patients who relapsed during the acute flare-up period, especially in patients with symptoms.

PV and relative PV change on CT images during follow-up
PV and relative PV change were evaluated on serial CT images during follow-up in patients with type-1 AIP. The PV atrophy ratio was calculated by dividing the difference in presumed normal PV and PV at the time of last follow-up CT by the presumed normal PV. PV is significantly correlated with age[25,26] and sex[27], and the presumed normal PV was therefore defined as the mean PV measured by two radiologists in consensus (Ryuichi Shimada and Yasunari Yamada) in 15 normal subjects age- and sex-matched to each AIP patient, reviewed from the image archiving and communication system in our institution and associated hospital. The following factors that might influence pancreas morphology were considered as exclusion criteria for presumed normal PV measurements: pancreatic pathology such as pancreatitis, pancreatic neoplasm, peripancreatic disease, chronic liver disease, and poor-quality images. PV and relative PV change were also evaluated on serial CT images during follow-up in a control group including 10 subjects with normal pancreases (5 women and 5 men with tongue or maxillary cancer) matched to a median age of 65.0 years in all 33 patients with type-1 AIP.

Evaluation of serum IgG4 Levels and diabetes during long-term follow-up
Serum IgG4 levels were available for 20 of the 33 patients at the time of follow-up CT and were used to analyze the long-term relationship between pancreatic re-enlargement and serum IgG4 levels. The incidence of diabetes was investigated in patients with D-type and M-type AIP at the time of last follow-up CT and the relationships between the incidence of diabetes and pancreatic atrophy were analyzed.

Statistical analysis
Differences between means were analyzed by Student's *t*-test for normally distributed data or the Mann-Whitney *U* test if there was a skewed distribution for numerical variables, and Fisher's exact test for proportions. The relationships between relative PV change and follow-up period were investigated by analysis of covariance in patients with D-type and M-type AIP. The cumulative pancreas re-enlargement rate was analyzed by Kaplan-Meier analysis and compared between patients with D-type and M-type AIP using the log-rank test. Spearman's rank correlation was used to evaluate the relationship between PV and serum IgG4 levels during follow-up. The degree of correlation was classified as very weak ($\rho < 0.2$), weak ($\rho = 0.2$-0.39), moderate ($\rho = 0.4$-0.59), strong ($\rho = 0.6$-0.79), or very strong ($\rho > 0.8$). Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, United States) and a value of $P < 0.05$ was considered to be statistically significant. Data are expressed as mean ± standard deviation or median and range.

RESULTS

Patient characteristics
The clinical characteristics of all 33 patients are shown in Table 2. This study included 16 patients with D-type and 17 patients with M-type AIP at the initial CT diagnosis of type-1 AIP. There was no significant difference in sex ($P > 0.95$) or age ($P = 0.66$) between the two groups.

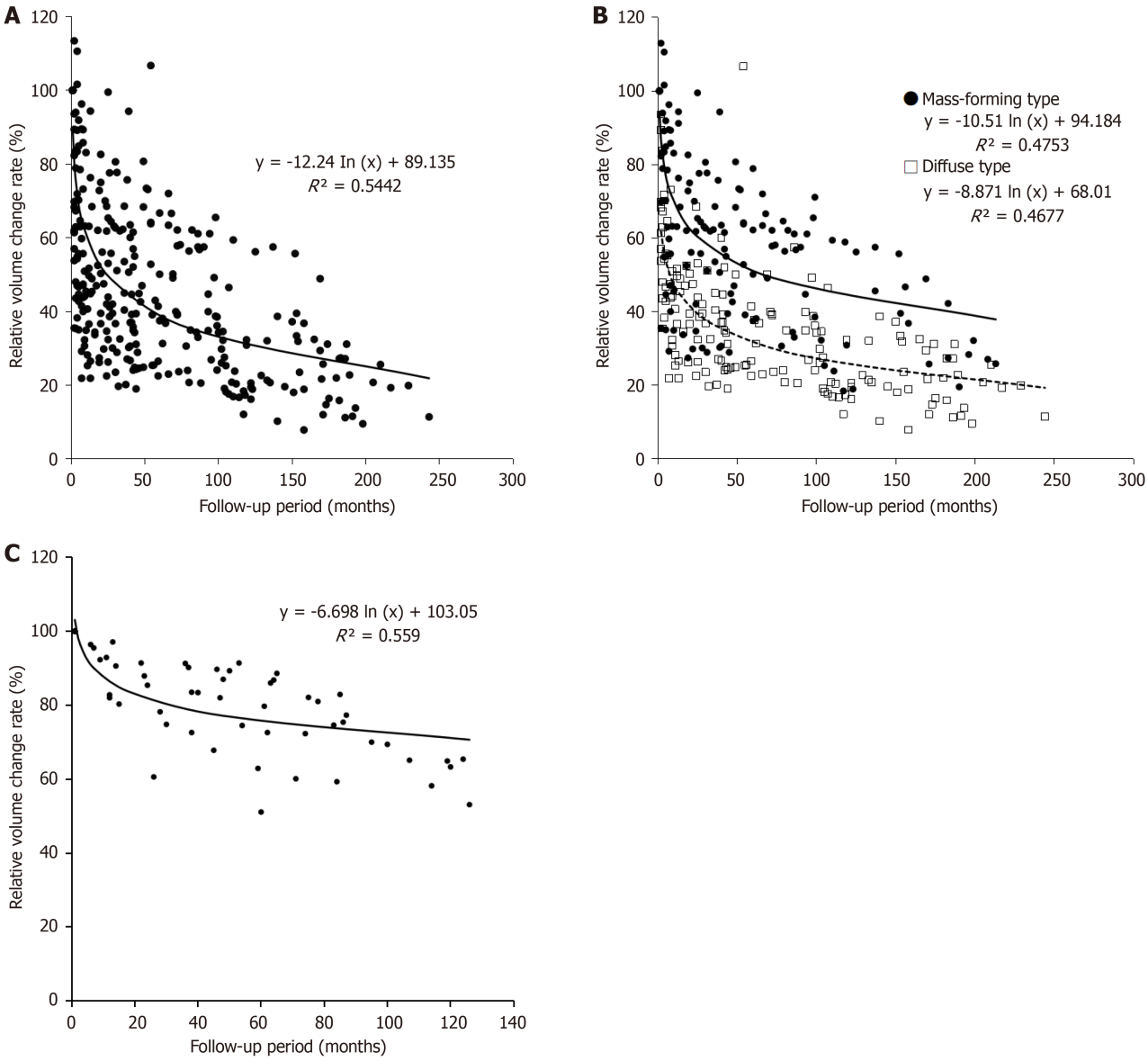

Figure 2 Scatter plot and regression curve. A: Relationship between relative volume change of pancreas and follow-up period in all 33 patients with type-1 autoimmune pancreatitis. Mean relative volume change reduced exponentially and rapidly during the first 25 months of follow-up and then more slowly; B: Diffuse (D-) and mass-forming (M-) types resembled the overall regression curve. The regression curve was lower for patients with D-type compared with M-type autoimmune pancreatitis; C: Relative pancreatic volume change decreased gradually and slightly over time during long-term follow-up in 10 control subjects with normal pancreas.

PV change and relative PV change on CT images during long-term follow-up

The mean period from initial CT for AIP diagnosis to the last follow-up CT in all 33 patients was 95.8 ± 68.2 months, with no significant difference (P = 0.26) between patients with D-type and M-type AIP (Table 3). The mean PV at initial CT was 80.4 ± 25.9 mL in all 33 patients. PV decreased over time during long-term follow-up in all 33 patients, but transient re-enlargement occurred in 12 patients. Scatter plots and regression curves of relative PV change during follow-up are shown in Figure 2A. The mean relative PV change reduced exponentially at a fast rate during the first 25 months of follow-up and then more slowly (Figure 3). The coefficient of determination (R^2) was 0.54 when the approximate curve was determined using the natural logarithmic function: Y = -12.2 ln(x) + 89.13. The mean relative PV changes in patients with D-type (n = 16) and M-type AIP (n = 17) resembled the overall regression curve (Figure 2B), but the curve was lower in patients with D-type [y = -8.9 ln(x) + 68.0 and R^2 = 0.47] compared to M-type AIP [y = -10.5 ln(x) + 94.2 and R^2 = 0.48]. The mean relative PV change at the time of last follow-up CT was 37.6 ± 19.3% in all 33 patients, and the change was significantly lower in patients with D-type compared with M-type AIP (mean 27.4 *vs* 47.1 %, respectively; P = 0.007; Table 3). The mean PV at last follow-up CT was 29.0 ± 15.0 mL in all 33 patients and was significantly lower in D-type compared with M-type AIP (mean 22.6 mL *vs* 35.1 mL, respectively; P = 0.012), similar to the mean relative PV change (Table 3). PV at last follow-up CT was lower than the presumed normal PV in all 33 patients (Supplementary Table 1, Supplementary Table 2 and Supplementary Table 3). The mean PV atrophy ratio compared with the presumed normal PV at the time of last follow-up CT was 59.3% ± 19.8% in all 33 patients and was significantly higher in patients with D-type compared with M-type AIP (mean 68.1 % *vs* 51.0 %, respectively; P = 0.012; Table 3). The mean period from initial CT to last follow-up CT in the control group of 10 subjects was 104.9 ± 21.6 months. The mean PV at initial CT was 65.3 ±

Table 3 Follow-up period and pancreatic volume at initial and last follow-up computed tomography in patients with type-1 autoimmune pancreatitis

Variable	All, *n* = 33	D-type, *n* = 16	M-type, *n* = 17	*P* value[a]
Follow-up period in months	95.8 ± 68.2 (65.0, 19-243)	109.8 ± 74.4 (70, 35-243)	82.6 ± 61.0 (65, 19-212)	0.26
Mean PV at initial CT in cm^3	80.4 ± 25.9 (75.8, 36.2-136.0)	84.4 ± 31.4 (86.0, 36.2-136.0)	76.6 ± 19.8 (72.6, 43.9-117.5)	1
Mean relative PV change[1] at last follow-up CT as %	37.6 ± 19.3 (32.2, 9.5-82.6)	27.4 ± 11.4 (23.5, 9.5-45.0)	47.1 ± 20.6 (31.0, 18.9-82.6)	0.007
Mean PV at last follow-up CT in cm^3	29.0 ± 15.0 (23.2, 10.5-60.3)	22.6 ± 11.1 (19.8, 10.5-47.2)	35.1 ± 15.7 (31.7, 17.8-60.5)	0.013
Mean atrophy ratio of PV at last follow-up CT compared with normal PV as %[2]	59.3 ± 19.8 (65.5, 53.9-94.0)	68.1 ± 15.1 (69.6, 28.5-86.5)	51.0 ± 20.5 (58.9, 11.5-77.0)	0.012

Data presented as mean ± standard deviation (median and range).

[a]*P* values between diffuse and mass-forming types.

[1]Relative pancreatic volume (PV) change = PV on follow-up computed tomography (CT)/PV on initial CT × 100 %;

[2]Atrophy ratio of the pancreatic volume (PV) was calculated by dividing the difference in the normal PV and PV at the time of last follow-up computed tomography by the normal PV. CT: Computed tomography; D-type: Diffuse type; M-type: Mass-forming type; PV: Pancreatic volume.

Table 4 Correlations between pancreatic volume and serum IgG4 levels in 20 patients with type I AIP during follow-up

D-type, *n* = 6	M-type, *n* = 7	Patients with extrapancreatic lesions (*n* = 7)[1]
-0.31 (0.456)	-0.70 (0.190)	-0.48 (0.230)
0.43 (0.144)[2]	0.10 (0.550)	-0.14 (0.790)
0.45 (0.224)[2]	0.29 (0.425)	0.03 (0.957)
0.48 (0.233)[2]	0.59 (0.045)[2]	0.03 (0.930)
0.85 (0.004)[2]	0.60 (0.048)[2]	0.05 (0.910)
0.86 (0.014)[2]	0.90 (0.037)[2]	0.45 (0.260)
-	0.98 (0.005)[2]	0.60 (0.285)

[1]Data given as correlation coefficient (*P* value);

[2]Moderate-to-very strong significant positive correlation. D-type: Diffuse type; M-type: Mass-forming type.

8.3 mL The PV decreased gradually and slightly over time during long-term follow-up in all 10 control subjects. Scatter plots and the regression line of relative PV change during follow-up show in Figure 2C [y = -6.7 ln(x) + 103.05 and R^2 = 0.52, $P < 0.05$].

Pancreatic re-enlargement and cumulative re-enlargement rates

Pancreatic re-enlargement occurred in 12 patients (12/33, 36.4%) during long-term follow-up, but there was no significant difference ($P = 0.48$) between D-type and M-type AIP (Table 2). One patient had a second re-enlargement. The mean time to re-enlargement was 42.5 ± 27.9 months (median 37.5 months; range 7-93 months), with no significant difference ($P = 0.33$) between patients with D-type and M-type AIP (Table 2). Five patients (5/7, 71.4%) with D-type (Figure 4) and all patients (5/5, 100%) with M-type AIP (Figure 5) showed re-enlargement with the same type of AIP ($P = 0.47$). Based on Kaplan-Meier analysis, the overall cumulative re-enlargement rates of the pancreas in all 33 patients at 1, 3, 5, 7, and 10 years of follow-up were 6.1%, 12.2%, 29.2%, 47.5% and 55.0%, respectively. The overall cumulative re-enlargement rates reached a plateau at 55% after 93 months (7.8 years; Figure 6). The corresponding cumulative re-enlargement rates in patients with D-type AIP were 13.3%, 13.3%, 29.4%, 52.3% and 64.7% and those in patients with M-type AIP were 0%, 5.6%, 29.0%, 40.8% and 40.8%, plateauing at 64.7% after 93 months and 40.8% after 77 months, respectively. D-type AIP was associated with lower cumulative re-enlargement rates than M-type AIP, but the difference was not significant ($P = 0.56$; Figure 4B).

Relationships between change in PV and serum IgG4 levels and between PV and diabetes during long-term follow-up

Serum IgG4 data were available for 20 of the 33 patients at the time of follow-up CT, seven of whom had extrapancreatic lesions. The mean serum IgG4 level at initial CT was 499.5 ± 486.6 mg/dL (median 369.0 mg/dL; range 133-2149 mg/dL). Spearman's rank correlation coefficients between PV and serum IgG4 levels during follow-up are shown in Table 4. Moderate-to-very strong positive correlations (Spearman's $\rho \geq 0.4$) were observed in nine patients (9/13, 69.2%) without

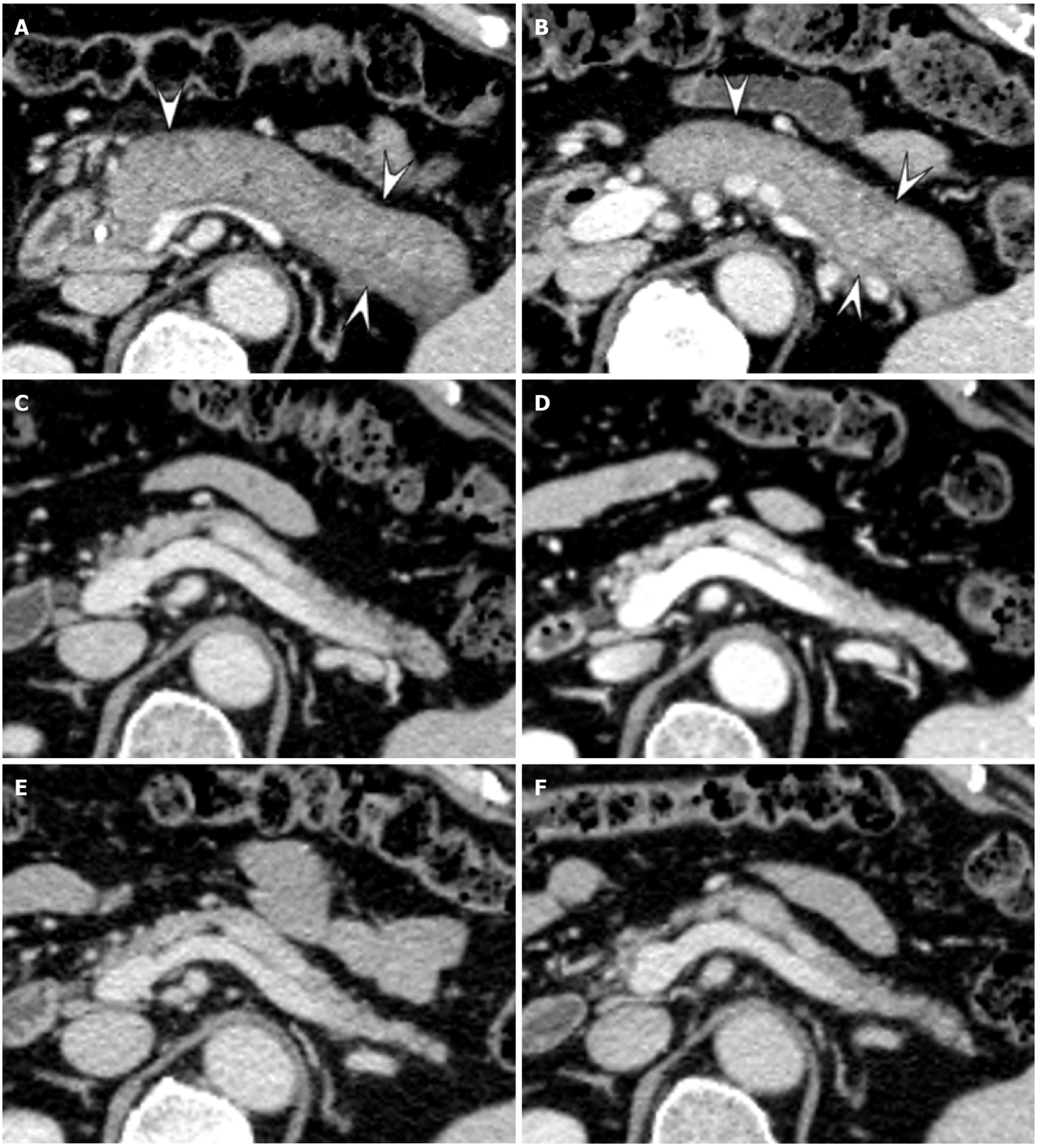

Figure 3 Portal venous contrast-enhanced computed tomography images of 59-year-old man with diffuse-type autoimmune pancreatitis. A: Initial computed tomography showing diffuse enlargement of the pancreas with capsule-like rim (arrowheads); B: One month later, pancreatic volume had decreased (relative volume change 683%) and capsule-like rim was observed; C: Six months later, pancreatic volume had decreased further (relative volume change 207%) and no capsule-like rim was observed; D-F: Relative volume changes after 12, 54 and 86 months were 224%, 21.5% and 20.6%, respectively.

extrapancreatic lesions, with no significant difference between patients with D-type and M-type AIP ($P = 0.27$). There was no significant correlation ($P > 0.05$) between PV and serum IgG4 levels in the seven patients with extrapancreatic lesions. Of the 12 patients with pancreatic re-enlargement, eight patients were not associated with extrapancreatic lesions and measured serum IgG4 levels. Serum IgG4 levels were re-elevated in five (62.5%) of the eight patients at the time of pancreatic re-enlargement (elevated values: mean 138.2 ± 78.4 mg/dL; median 129.0 mg/dL; range 67-267 mg/dL). Three patients (3/4, 75%) who only developed extrapancreatic lesions during follow-up had re-elevated serum IgG4 levels (elevated values: mean 287.3 ± 55.7 mg/dL; median 293.0 mg/dL; range 229-340 mg/dL).

Diabetes was observed in 19 patients (19/33, 57.6%) at the time of initial CT, with no significant difference between D-type (11/16, 68.8%) and M-type AIP (8/17, 47.1%) ($P = 0.296$) and in 20 patients (20/33, 60.6%) at the time of the last follow-up CT (mean follow-up 95.8 months), including in significantly more patients with D-type (13/16, 81.3%) compared with M-type AIP (7/17, 41.2%; $P = 0.032$; Supplementary Table 1, Supplementary Table 2, Supplementary

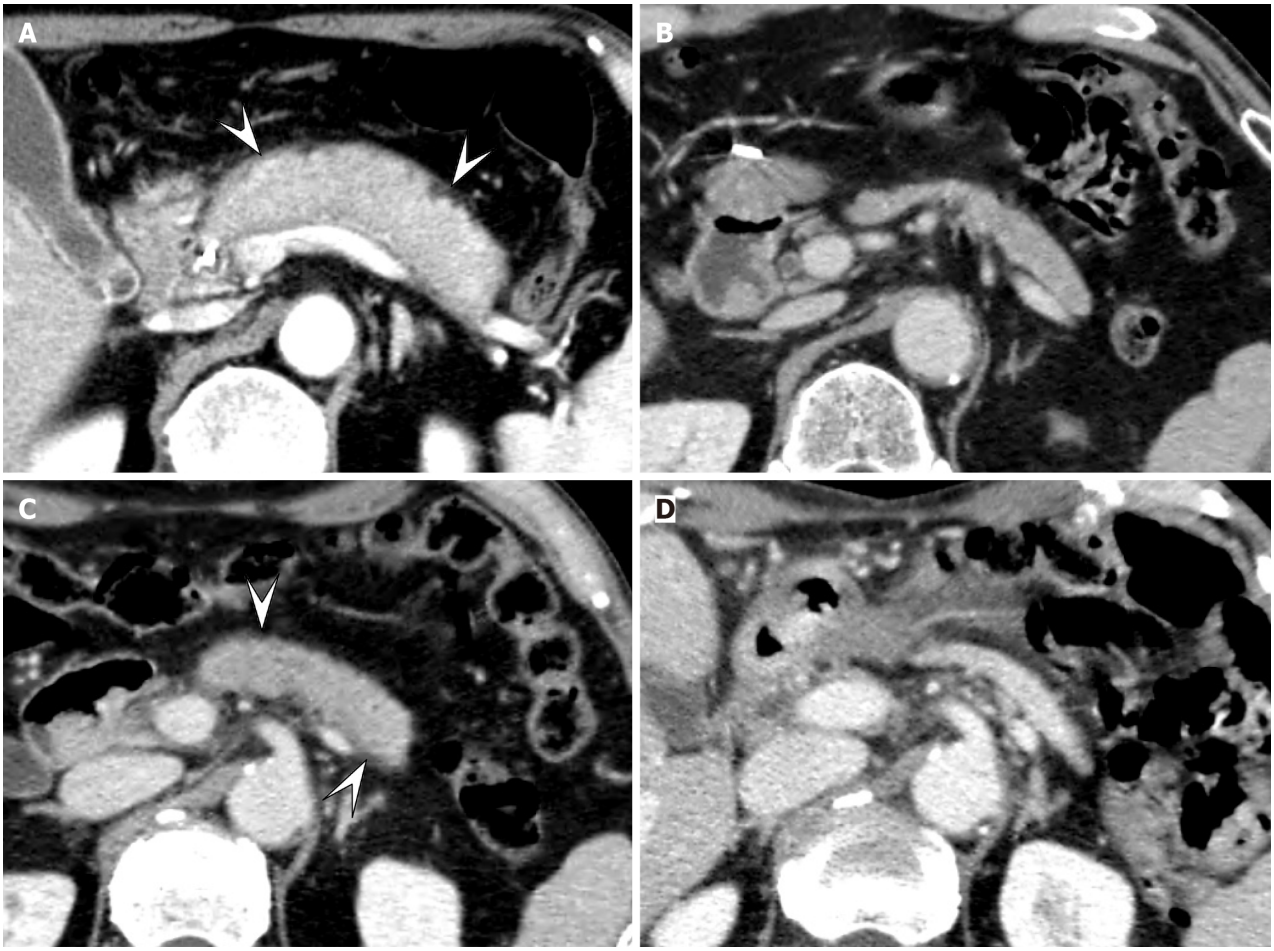

Figure 4 Portal venous contrast enhanced-computed tomography images of a 60-year-old man with diffuse-type autoimmune pancreatitis and re-enlargement during follow-up. A: Initial computed tomography showing diffuse enlargement of the pancreas with capsule-like rim (arrowheads); B: Three years later, pancreatic volume had markedly decreased (relative volume change 414%); C: Seven years later, re-enlargement (diffuse type) of the pancreas with capsule-like rim (arrowheads) was observed (relative volume change 575%); D: One year after re-enlargement, pancreatic volume had decreased again (relative volume change 241%; arrows).

Table 3 and Table 5). The mean PV atrophy ratios compared with presumed normal PV at the time of last follow-up CT were 68.4 ± 13.7% (median 69.6%; range 26.0%-86.5%) in the 22 patients with diabetes and 41.2 ± 18.0% (median 45.0%; range 11.5%-73.8%) in the 11 patients without diabetes (P = 0.001). Patients with D-type AIP had a higher incidence of diabetes than those with M-type AIP (13/16, 81.3% *vs* 7/17, 41.2 %, respectively; P = 0.032).

DISCUSSION

In this study, we investigated PV changes in patients with type-1 AIP receiving steroid therapy using semi-automated CT volumetry and analyzed their relationships with serum IgG4 levels and diabetes during long-term follow-up. The mean relative PV change compared with PV at the time of diagnosis reduced exponentially and rapidly during the first 25 months and then more slowly. Pancreatic atrophy, compared with the presumed normal PV, occurred in all patients (mean 59.3% ± 19.8%) at the time of last follow-up CT (mean follow-up 95.8 months). The cumulative pancreas re-enlargement rate reached a plateau at 55% after 93 months (7.8 years). There was a moderate-to-very strong positive correlation ($\rho \geq 0.4$) between PV and serum IgG4 levels in nine patients (9/13, 69.2%). Patients with D-type AIP had significantly greater atrophy and a higher incidence of diabetes after long-term follow-up compared with patients with M-type AIP ($P < 0.05$). Pancreatic atrophy after long-term follow-up is thus considered an important factor associated with diabetes.

To the best of our knowledge, no previous studies have reported the relative PV changes compared with PV at the time of diagnosis in patients with AIP over a long-term follow-up period. The mean follow-up period in all 33 patients in the current study was 95.8 ± 68.2 months, with no significant difference (P = 0.26) between D-type and M-type AIP. The regression curve of relative PV change during follow-up decreased gradually and slightly over time in control subjects with a normal pancreas, while the regression curve exponentially and rapidly decreased during the first 25 months and then more slowly in patients with AIP and was lower in patients with D-type compared with M-type AIP. The mean PV atrophy ratio at the time of last follow-up CT compared with the presumed normal PV was 59.3% in all 33 patients and

Table 5 Incidence of diabetes in patients with type-1 autoimmune pancreatitis at the time of initial and follow-up computed tomography

Diabetes	Initial CT			Last follow-up CT		
	All	D-type	M-type	All	D-type	M-type
Yes	19	11	8	20	13	7
No	14	5	9	13	3	10

CT: Computed tomography; D-type: Diffuse type; M-type: Mass-forming type.

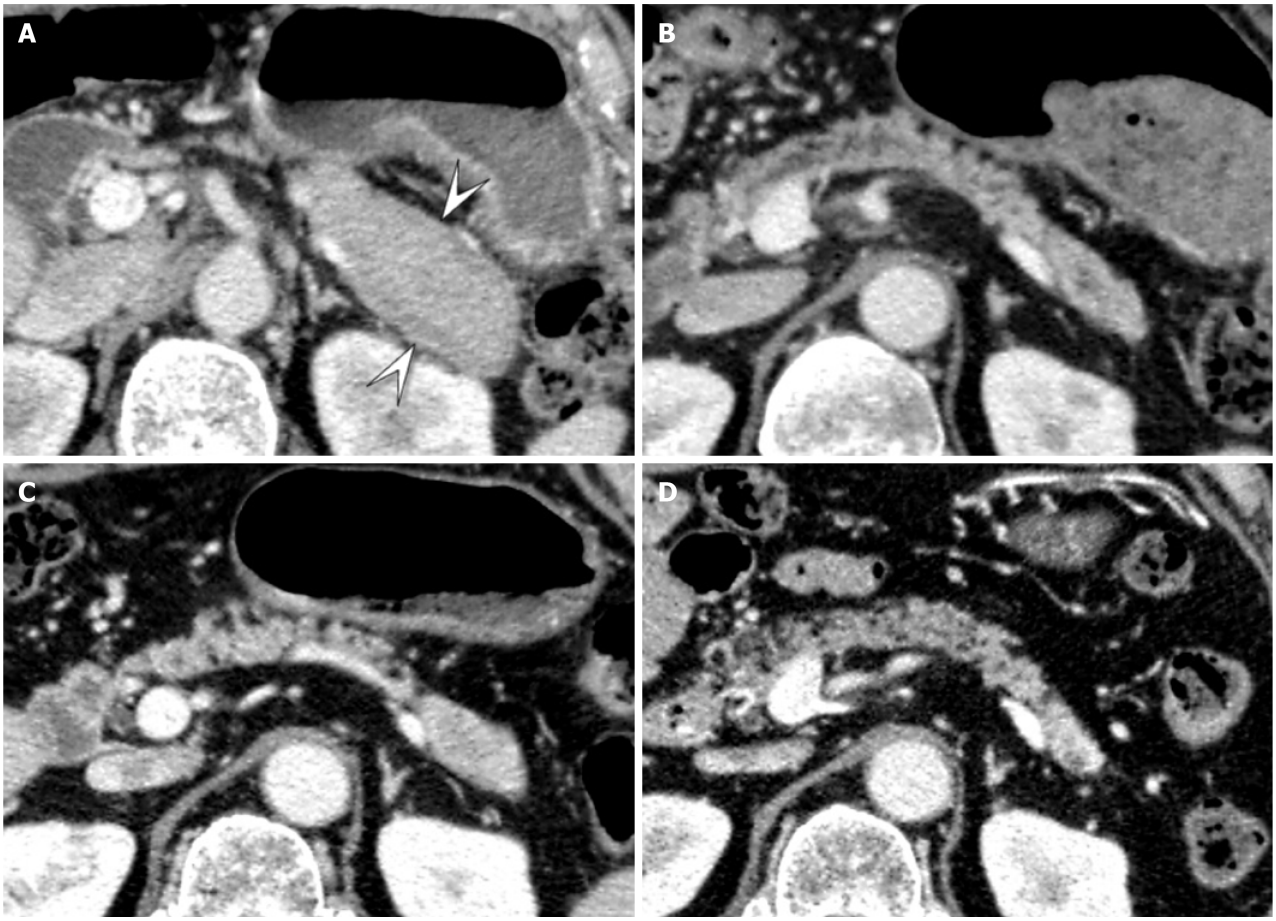

Figure 5 Portal venous contrast-enhanced computed tomography images of a 67-year-old man with mass-forming type autoimmune pancreatitis and re-enlargement during follow-up. A: Initial computed tomography showing enlarged pancreatic tail with capsule-like rim (arrowheads); B: Six months later, pancreatic volume had markedly decreased (relative volume change 598%); C: Four years later, re-enlargement of the pancreatic tail with no capsule-like rim (arrowheads) was observed (relative volume change 683%); D: One year after re-enlargement, pancreatic volume had decreased again (relative volume change 589%).

was significantly higher in patients with D-type compared with M-type AIP (mean 68.1 % *vs* 51.0 %, respectively; P = 0.012). A previous radiologic-pathologic correlation study in patients with type-1 AIP reported a dense lymphoplasmacytic inflammatory infiltrate in the enlarged pancreatic parenchyma, while inflammatory cells were observed mainly around medium and large interlobular ducts in the non-enlarged pancreatic parenchyma[28]. Dense lymphoplasmacytic inflammation in the pancreas may lead to fibrosis and progressive atrophic changes, and the pancreatic parenchyma may show more severe atrophy in D-type AIP because of the dense and diffuse lymphoplasmacytic inflammatory infiltrate compared with M-type AIP.

In the current study, pancreatic re-enlargement occurred in 12 (36.4%) of all 33 patients during a mean follow-up of 95.8 months, with no significant difference between the D-type and M-type groups (P = 0.48). Seventy percent of D-type patients and 100% of M-type patients showed the same type of pancreatic enlargement on initial CT images and CT images at re-enlargement. These results may provide important information for evaluating re-enlargement during long-term observations of patients with type-1 AIP receiving steroid therapy.

The overall cumulative pancreas re-enlargement rates at 1, 3, 5 and 7 years of follow-up in the current study were 6.1%, 12.2%, 29.2% and 47.5%, respectively, and reached a plateau at 55% after 93 months (7.8 years). This suggests that acute

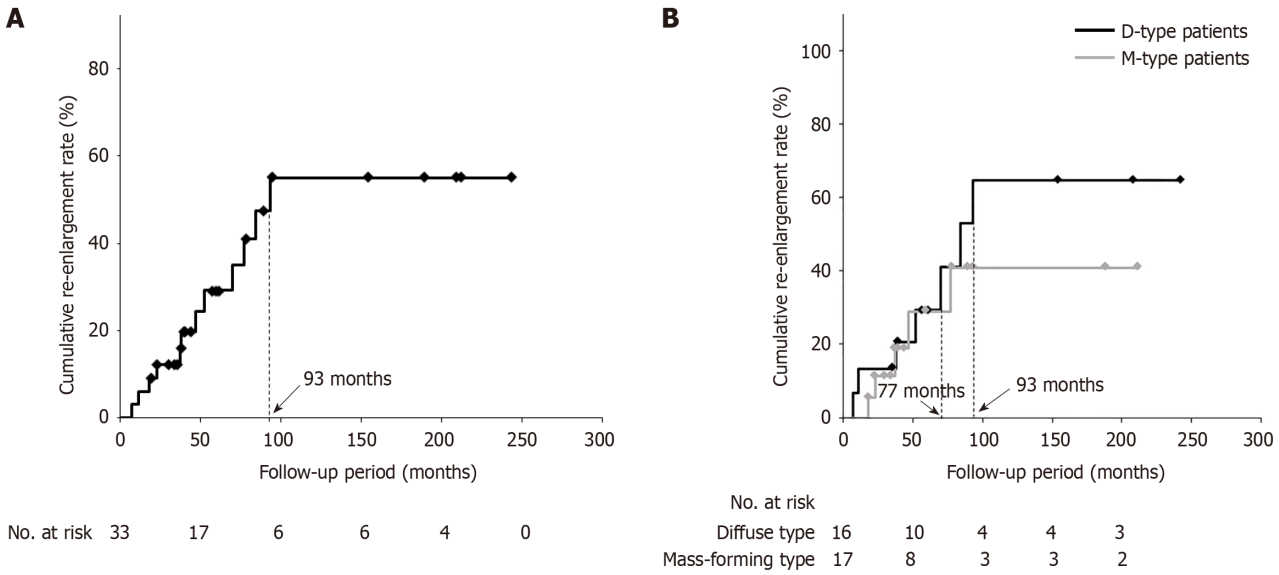

Figure 6 Cumulative re-enlargement rates during follow-up in patients with type-1 autoimmune pancreatitis. A: Overall cumulative re-enlargement rates for all 33 patients at 1, 3, 5, 7 and 10 years of follow-up were 61%, 12.2%, 29.2%, 47.5% and 55.0%, respectively. The overall cumulative re-enlargement rates reached a plateau at 55% after 93 months (7.8 years); B: Cumulative re-enlargement rates were 133%, 13.3%, 29.4%, 52.3% and 64.7% in patients with diffuse-type (D-type) and 0%, 5.6%, 29.0%, 40.8% and 40.8% in patients with mass-forming type (M-type) autoimmune pancreatitis (AIP), and reached plateaus at 64.7% after 93 months (7.8 years) and at 40.8% after 77 months, respectively. Patients with D-type AIP showed lower cumulative re-enlargement rates than patients with M-type AIP, but the difference was not significant (P = 0.56).

inflammation may be unlikely during pancreatic re-enlargement because of severe fibrosis of the pancreatic parenchyma after approximately eight years. These results may provide useful information to help determine the optimal follow-up period in patients with type-1 AIP receiving steroid therapy.

Although re-elevation of serum IgG4 levels has not been considered an indicator of relapse in patients with type-1 AIP [20,28,29], several studies have reported that re-elevated serum IgG4 may predict relapse[23,30-32]. These reports, however, defined relapse as pancreatic re-enlargement, recurrence of clinical symptoms, and extrapancreatic lesions on radiological imaging, and no previous studies have investigated the relationship between PV and serum IgG4 levels during follow-up in patients with type-1 AIP. The current study revealed a moderate-to-very strong positive correlation ($\rho \geq 0.4$) between PV and serum IgG4 Levels in nine patients (9/13, 69.2%) without extrapancreatic lesions.

Previous reports associated pancreatic atrophy with the loss of insulin secretory capacity[33] and usually considered it a marker of advanced disease associated with an increased incidence of diabetes[34,35]. Masuda *et al*[9] reported that patients with AIP with pancreatic atrophy 6 months after steroid therapy had a high incidence of diabetes, and new-onset diabetes was closely associated with pancreatic atrophy after steroid therapy. The current study investigated the relationship between PV atrophy ratio compared with the presumed normal PV and diabetes after long-term follow-up (mean 95.8 months) in patients with type-1 AIP receiving steroid therapy, and found significantly greater pancreas atrophy in patients with diabetes compared with patients without diabetes (P = 0.003). In addition, patients with D-type AIP had a significantly higher incidence of diabetes compared with those with M-type AIP (P = 0.032), possibly because of greater pancreas atrophy in D-type compared with M-type AIP. This result may provide valuable information regarding the management of diabetes in patients with type-1 AIP receiving steroid therapy.

Our study had several limitations. First, the number of enrolled patients was small, and further studies in larger patient populations and with long-term follow-up are required. Second, this was a retrospective study and may thus have included inevitable selection bias. Third, we only studied patients with type-1 AIP because this is more common worldwide than type-2 AIP[4]. Fourth, steroid therapy is generally not indicated in patients with type-1 AIP without symptoms, obstructive jaundice, and extrapancreatic lesions[21,36], and further analysis may be needed to compare patients with type-1 AIP with and without steroid therapy.

CONCLUSION

The pancreas showed an exponential volume reduction during the first 25 months and then a slower reduction in patients with type-1 AIP receiving steroid therapy. The overall cumulative pancreatic re-enlargement rates reached a plateau at 55.0% after 93 months (7.8 years). Serum IgG4 Levels were positively correlated with PV during long-term follow-up in most patients. Patients with D-type AIP had significant greater atrophy and a higher incidence of diabetes compared with patients with M-type AIP. These results suggest that pancreatic atrophy after long-term follow-up is an important factor associated with diabetes.

FOOTNOTES

Author contributions: Shimada R and Yamada Y designed and conducted the study; Shimada R wrote the paper; Yamada Y contributed to the analysis; Okamoto K and Motomura M provided clinical advice; Asayama Y, Murakami K, Fukuzawa K, and Takaki H supervised the study.

Institutional review board statement: The study was approved by the institutional review board in Oita University Faculty of Medicine and Oita Red Cross Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymized clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors report no relevant conflicts of interest for this article.

Data sharing statement: The data used to support the findings to this study are available from the corresponding author upon request.

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S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Zhao YQ

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