Autoimmune pancreatitis can transform into chronic features similar to advanced chronic pancreatitis with functional insufficiency following severe calcification

Short Title: AIP can transform into chronic pancreatitis

Keita Kanai, MD[1], Masahiro Maruyama, MD, PhD[1], Fumiko Kameko,[2] Kenji Kawasaki, PhD[3], Junpei Asano, MD[1], Takaya Oguchi, MD[1], Takayuki Watanabe, MD, PhD[1], Tetsuya Ito, MD, PhD[1], Takashi Muraki, MD, PhD[1], Hideaki Hamano, MD, PhD[1], Akihiro Matsumoto, MD, PhD[1], Norikazu Arakura, MD, PhD[4] and Shigeyuki Kawa MD, PhD [5]

[1] Department of Gastroenterology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

[2] Department of Biomedical Laboratory Sciences, Shinshu University School of Health Sciences, 3-1-1 Asahi, Matsumoto 390-8621, Japan

[3] Department of Laboratory Medicine, Shinshu University Hospital, 3-1-1 Asahi, Matsumoto 390-8621, Japan

[4] Endoscopic Examination Center, Shinshu University School of Medicine, 3-1-1 Asahi,

Matsumoto 390-8621, Japan

[5] Center for Health, Safety, and Environmental Management, Shinshu University, 3-1-1 Asahi, Matsumoto 390-8621, Japan

Correspondence: Shigeyuki Kawa, MD, Center for Health, Safety, and Environmental Management, Shinshu University, 3-1-1 Asahi, Matsumoto 390-8621, Japan

E-mail: skawapc@shinshu-u.ac.jp

Tel.: +81-263-37-2156, Fax: +81-263-37-2183

Keywords: autoimmune pancreatitis, calcification, chronic pancreatitis, pancreatic function, IgG4,

Funding: This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan and in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (15K09045).

Abstract

Objectives: Because several studies for autoimmune pancreatitis (AIP) have revealed pancreatic calcification resembling that in chronic pancreatitis (CP), we sought to clarify whether AIP could transform into chronic features similar to advanced CP with severe pancreatic dysfunction.

Methods: Pancreatic functions of 92 AIP patients, 47 definite CP patients, and 30 healthy controls were assessed by fecal elastase-1 concentration (FEC), fasting immunoreactive insulin (IRI), and homeostatic model assessment (HOMA)-R.

Results: The 92 AIP patients included 17 (18%) with severe calcification (SC) and 75 without. FEC levels in AIP and CP patients were significantly lower than that in controls. Exocrine insufficiency defined as FEC <200 μg/g was 39% in AIP without SC, 56% in AIP with SC, and 74% in CP. Fasting IRI and CPR values in CP were significantly lower than those in AIP, with no significant differences between AIP subgroups. The prevalence of endocrine insufficiency according to fasting IRI <5.0 μU/mL was 26% in AIP without SC, 31% in AIP with SC, and 59% in CP, respectively. HOMA-R values were significantly higher in all AIP groups than in CP.

Conclusions: AIP can transform into a state of pancreatic insufficiency following calcification that is less severe than that in definite CP.

Introduction

Pancreatitis presumably caused by autoimmune mechanism had been originally reported in Europe.[1] The disease concept of autoimmune pancreatitis (AIP) was proposed in Japan[2] and later subdivided into type 1 and type 2 AIP. Whereas type 1 AIP is histopathologically designated as lymphoplasmacytic sclerosing pancreatitis, type 2 is defined as idiopathic duct-centric chronic pancreatitis (CP) or AIP with granulocytic epithelial lesions.[3] Type 1 AIP has been characterized by pancreatic swelling, high serum IgG4 concentration, and a favorable response to corticosteroid treatment.[2,4,5] The Japan Pancreas Society published consensus guidelines for AIP in 2011 and later amended them in 2013.[6-8] The international consensus diagnostic criteria (ICDC) for AIP were also proposed in 2011 to enable worldwide AIP diagnosis based on a global standard.[9] Accordingly, awareness of this disease concept has become widespread and an increasing number of AIP patients are being treated.

To date, AIP had been recognized as a reversible state disorder due to its clinical characteristics of histologically lymphoplasmacytic infiltration and favorable response to corticosteroid treatment.[2] However, this concept is now under debate since a number of AIP patients have been reported to exhibit calcification of the pancreas during long-term follow-up resembling that found in advanced ordinary CP. We previously

described that pancreatic calcification developed in over 30% of AIP patients over extended follow-up, wherein stone formation was seen in close association with relapse and narrowing of both Wirsung's and Santorini's ducts.[10,11] We also uncovered that approximately 20% of AIP patients displayed severe calcification that fulfilled the revised Japanese clinical diagnostic criteria for CP[12] and was significantly associated with pancreatic head swelling and non-narrowing of the main pancreatic duct in the pancreatic body.[13] These findings indicated that remnant pancreatic duct narrowing in long-term follow-up led to pancreatic juice stasis and could progress to severe pancreatic calcification. Thus, AIP seems able to transform into a chronic state with imaging findings mimicking those of advanced CP.[13,14]

In ordinary CP such as alcoholic pancreatitis, patients exhibiting the characteristic imaging findings of marked pancreatic calcification, irregular dilation of the pancreatic duct, and pancreatic atrophy also tend to develop pancreatic endocrine and exocrine insufficiency. Accordingly, AIP patients with severe pancreatic calcification that fulfills the image criteria for definite CP may also be at risk for pancreatic insufficiency, although this issue has not been fully investigated. The short-term effects of corticosteroids on endocrine function in AIP are controversial, with some reports showing improvement and others worsening,[15,16] whereas those on exocrine function

appear to be more consistently favorable. In contrast, the long-term changes in exocrine and endocrine function remain unclear for AIP, and it remains uncertain whether it can progress to CP with accompanying functional insufficiency. Our preliminary reports revealed no significant differences in serum amylase or HbA1c levels in AIP cases with and without severe calcification and indicated no apparent correlation between AIP with pancreatic calcification and pancreatic dysfunction akin to that in ordinary CP.[11] However, it is possible that AIP may present endocrine and exocrine abnormalities in a more chronic stage with severe calcification. The present study sought to clarify whether AIP with severe pancreatic calcification resembling that in advanced ordinary CP also displayed pancreatic insufficiency during long-term follow-up and determine if AIP could transform into advanced CP with severe pancreatic insufficiency.

Materials and Methods

2.1. Study subjects

The medical records of 109 patients with AIP who were treated at Shinshu University Hospital between August 1992 and August 2014 were retrospectively reviewed by cohort study. Of them, we enrolled 92 patients (71 men and 21 women; median age: 74 years, range: 55-90 years) who had been followed for at least 3 years (median follow-up period: 102 months, range: 36-301 months). AIP diagnosis was based on the ICDC for

AIP[9], and all patients showed no image finding resembling those in chronic pancreatitis at diagnosis. All patients were diagnosed as having type 1 AIP. Two control groups were enrolled in this study: 47 patients with definite CP diagnosed based on the revised Japanese clinical diagnostic criteria for CP[12] (44 men and 3 women; median age: 66 years, range: 39-81 years; 42 with alcoholism 5 without) and 30 apparently healthy subjects without any pancreatic and other diseases, such as diabetes mellitus (DM) (23 men and 7 women; median age: 53 years, range: 31-91 years).

2.2. Evaluation of pancreatic imaging

The presence of pancreatic calcification in AIP and CP patients was evaluated using the most recent abdominal computerized tomography (CT) images obtained for each patient.

2.3. Clinical features and laboratory tests

We analyzed the factors of DM and insulin use, use and duration of corticosteroid treatment, relapse, alcohol intake, smoking and serum blood chemistry markers of pancreatic function and AIP activity. Alcohol intake was defined as over 25g daily ethanol consumption and smoking was defined as more than 20 cigarettes smoked per

day. Exocrine function was assessed using fecal elastase-1 concentration (FEC)[17] (Pancreatic elastase ELISA kit, BIOSERV Diagnostics GmbH, Germany) and the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test. Endocrine function was evaluated using serum values of HbA1c, fasting immunoreactive insulin (IRI) for patients treated without insulin, and fasting C-peptide reactivity (CPR). We calculated homeostatic model assessment (HOMA)-R and HOMA-β to evaluate insulin resistance and insulin secretory function, respectively. Pancreatic function and AIP activity markers were determined at the time of the most recent hospital visit for each patient.

As controls, we evaluated similar parameters among definite CP patients and examined FEC levels in healthy subjects. All laboratory tests were performed using commercially available kits and performed according to the manufacturer's instructions.

2.4. Statistical analysis

Pearson's chi-square test was adopted to test for differences between patient subgroups. The Mann-Whitney U and Kruskal-Wallis tests were employed to compare continuous data. All tests were performed using Statflex ver. 6 software (Artech Co., Ltd., Osaka, Japan). *P* values of less than 0.05 were considered to be statistically significant.

2.5. Ethics

This study was approved by the ethics committee of Shinshu University (approval number: 1973).

Results

3.1. Patient characteristics

Among the 92 recruited AIP patients, 17 displayed imaging findings that fulfilled the revised Japanese clinical diagnostic criteria for CP showing characteristic image findings of pancreatic stone and were classified into the AIP with severe calcification (SC) group (14 men and 3 women; median age: 74 years, range: 60-88 years). Nine of these patients had obvious stones in the pancreatic duct (Fig. 1a) and 16 exhibited diffuse calcification in the parenchyma (Fig. 1b). The remaining 75 patients were defined as the AIP without SC group. In comparisons of clinical parameters among the AIP with SC, AIP without SC, and CP groups, the observation period was found to be significantly longer for the AIP with SC group than for the AIP without SC group ($p < 0.05$). Both AIP groups were significantly older than the CP group ($p < 0.05$), while the male-to-female ratio of the CP group was significantly higher than those of the AIP subgroups. AIP with SC patients received prednisolone for a significantly longer period than AIP without SC patients ($p < 0.05$). The CP group included significantly more

alcoholics ($p < 0.0005$ vs. both AIP subgroups, respectively). We found a tendency for several disease activity markers, including IgG, IgG4, soluble interleukin-2 receptor (sIL2-R), and circulating immune complex (CIC), to be lower at final visit in AIP with SC than in AIP without SC (Table 1).

3.2. Evaluation of exocrine function

FEC values were significantly lower in the AIP and CP groups than in healthy controls. FEC in the CP group was significantly lower, and FEC in the AIP with SC group tended to be lower, than that in the AIP without SC group (Table 2, Fig. 2). The incidence of patients with exocrine insufficiency defined as FEC <200 μg/g was 56% (5/9) in AIP with SC and 39% (13/33) in AIP without SC. This difference was not significant. The CP group showed the highest exocrine insufficiency incidence of 74% (20/27), which was significantly greater than that in AIP without SC and indicated that exocrine dysfunction in AIP with SC was intermediary between the other groups (Table 2). A total of 43% (18/42) of AIP patients exhibited exocrine insufficiency irrespective of the presence or absence of pancreatic stones.

BT-PABA test values for the AIP with SC and CP groups were lower than that for AIP without SC, albeit non-significantly (Table 2). There were no remarkable differences in

the prevalence of exocrine insufficiency defined as BT-PABA <70% among the groups. Interestingly, all AIP with SC patients showed impaired exocrine sufficiency.

3.3. Evaluation of endocrine function

The prevalence of complicating DM and insulin use among all AIP patients were 47% (43/92) and 22% (20/92), respectively. These values tended to be higher in the AIP with SC group (Table 3). Fasting IRI in the CP group was significantly lower than values in both AIP subgroups, which were comparable (Table 3, Fig. 3a). The incidence of patients with endocrine insufficiency as defined by fasting IRI <5.0 μU/mL was 59% (20/34) in the CP group. This was significantly higher than the 26% (16/62) for AIP patients without SC. At a frequency of 31% (4/13), endocrine dysfunction AIP with SC appeared to be intermediary between AIP without SC and CP. AIP on the whole exhibited endocrine insufficiency in 27% (20/75) of cases (Table 3).

Evaluation of fasting CPR showed results similar to those of IRI (Table 3, Fig. 3b). The prevalence of patients with endocrine insufficiency according to fasting CPR <1.5 μU/mL was 68% (25/37) in the CP group, which was significantly higher than the 30% (21/70) for AIP without SC and comparably higher than the intermediary value of 41% (7/17) for AIP with SC. Endocrine insufficiency was 32% (28/87) among all AIP cases

(Table 3).

HOMA-R values in the AIP subgroups were both significantly higher than that in CP (Table 3, Fig. 4a). The prevalence of insulin resistance defined as HOMA-R ≧ 2.5 was also significantly higher in the individual and overall AIP groups than in CP. The results of HOMA-β testing supported those for fasting IRI and CPR: HOMA-β in CP was significantly lower than that in AIP without SC and tended to be lower than that in AIP with SC (Table 3, Fig. 4b). The prevalence of patients with decreased insulin secretion according to HOMA-β <40% was less for all AIP groups versus CP, albeit not significantly (Table 3).

Discussion

4.1. Clinical characteristics of AIP with SC

Among the 92 patients with AIP, we found severe pancreatic calcification that matched the Japanese clinical diagnostic criteria 2009 for CP[12] (i.e., AIP with SC) in 17 patients (18%). AIP with SC had significantly longer periods of observation and treatment than did AIP without SC, indicating that pancreatic calcification required a longer duration of highly active disease state. Because the stagnation of pancreatic juice due to remnant

pancreatic duct stricture seems to be the major cause of stone formation, longer period may be required to complete it.[14] AIP patients were older than CP patients and possessed a lower male-to-female ratio, likely because of the high prevalence of alcoholism in the CP group. AIP with SC displayed somewhat lower values of activity markers at final visit, which suggested that an extended chronic disease period may have resulted in burnout of pancreatic parenchyma.

4.2. Evaluation of pancreatic exocrine function in long-term follow-up AIP patients

We measured FEC as a marker of pancreatic exocrine function in long-term follow-up AIP patients. FEC values were lower in both AIP groups than in healthy controls. Since the AIP without SC group showed a significantly higher FEC value than did the CP group and there was no significant difference between AIP with SC and CP, we considered that exocrine insufficiency in AIP with SC was moderately depressed and intermediary between AIP without SC and CP.

Although many reports have described amelioration of exocrine insufficiency in AIP soon after corticosteroid treatment, few have addressed AIP patients after long-term follow-up. FEC is an established marker of exocrine function in CP, for which exocrine insufficiency determined as FEC <200 μg/g has been reported in 76.5% of calcified CP

cases.[17] This figure coincided with our results of 74%. Maire et al. observed FEC <200 μg/g in 10 of 28 AIP patients (36%) after a more comparable long-term follow-up period (median: 41 months, range: 5-130 months),[18] which was similar to our result of 43%. In addition, the higher ratio of FEC <200 μg/g in the AIP with SC group (56% vs. 39% in the AIP without SC group) suggested that the occurrence of pancreatic calcification had deteriorated exocrine function.

There were no significant differences in BT-PABA results among present study groups. The BT-PABA test has been reported to have several problems that hamper accurate measurement and result in low sensitivity and specificity.[19] However, Uchida et al. observed an amelioration of BT-PABA in 10 of 21 AIP patients (48%) 6 months after corticosteroid treatment, but then witnessed exocrine insufficiency in 6 of the patients afterwards and further deterioration in 4 of the 6 patients over 3 years of follow-up.[20] Accordingly, a proportion of AIP cases appears to progress to exocrine insufficiency, which may be exacerbated by the onset of calcification.

4.3. Evaluation of pancreatic endocrine function in long-term follow-up AIP patients

The complications of DM and insulin treatment were seen in 47% and 22% of AIP patients, respectively, which were not remarkably different from those values in CP.

Although the AIP group exhibited significantly higher fasting IRI and CPR levels than did CP, impaired secretion was found in only 27% and 32% of cases, respectively. Thus, while endocrine dysfunction can occur in AIP during long-term follow-up, it appears to progress more slowly than in CP. Since endocrine function in AIP with SC was more severely impaired than that in AIP without SC, insufficiency may progress quickly after severe pancreatic calcification to a frequency approaching that in CP. Meanwhile, HOMA-β levels were generally better maintained in the AIP groups than in CP and supported the results of fasting IRI and CPR. We observed significantly higher HOMA-R levels in the AIP groups, which may have been related to increased insulin resistance due to corticosteroid treatment for AIP.

Maire et al. reported DM complications in 57% of AIP patients during long-term observation (median: 41 months, range: 5-130 months), which was similar to our result of 47%.[18] Masuda et al. described complicating DM in 11/31 of AIP patients (35%) at 6 months after corticosteroid therapy that was closely associated with pancreatic atrophy.[21] Miyamoto et al. found that DM as estimated by HbA1c was present in 30/69 of AIP patients (46%) and was ameliorated in 10/16 of patients (63%) 3 years after corticosteroid treatment, although HbA1c levels were presumably affected by various therapeutic states.[22] Hirano et al. reported that endocrine function in 51 AIP patients

according to CPR showed improvement in 13%, deterioration in 19%, and no change in 68% of cases over a mean follow-up period of 60 months.[23] They recommended early stage corticosteroid therapy when insulin secretion was normal and treatment cessation during stable endocrine function since corticosteroids deteriorated insulin resistance, as confirmed by our results.[23] Although few studies have monitored long-term endocrine function in AIP, the present investigation showed that endocrine function in some AIP patients worsened over time and became further impaired after severe calcification in a manner similar to that of exocrine function.

4.4. Differing nature of exocrine and endocrine dysfunction in AIP with SC and ordinary CP

The present study demonstrated that AIP with SC showed milder exocrine and endocrine insufficiencies than did CP, despite fulfilling the Japanese clinical diagnostic criteria for CP. These differences may have stemmed from the varying nature of pancreatic injury between the conditions. Several theories have been proposed for the pathogenesis of ordinary CP.[24] Pathological findings in alcoholic chronic pancreatitis revealed the progression of dense interlobular fibrosis that resulted in destruction of parenchymal cells and formation of stones.[25] On the other hand, as we have pointed out,

remnant narrowing of the pancreatic duct found in some AIP patients likely caused pancreatic juice stagnation and the formation of pancreatic duct stones[11], leading to further secondary injury of pancreatic parenchymal cells.[13,14] Suda et al. reported that whereas interlobular fibrosis combined with a cirrhosis-like appearance and scant inflammatory infiltration was recognized in the tissues of alcoholic CP, inter- and intralobular fibrosis admixed with acinar atrophy and lymphocytic infiltration were intermingled in the tissues of obstructive pancreatitis and AIP,[26] which indicated different underlying pathological findings between the conditions.[25] Lastly, Kishi et al. described prominent pancreatic satellite cell expression in patients with pancreatic duct obstruction.[27] Such pathological changes may also be associated with the difference in exocrine dysfunction severity between AIP and ordinary CP.

Since exocrine and endocrine aberrations were also seen in cases of AIP without SC, direct tissue injury from inflammatory AIP processes may have occurred during long-term follow-up. Even after clinical remission, elevated serum IgG4 was found in over 60% of AIP patients,[28] suggesting the possibility of subclinical inflammatory activity with tissue injury. Compared with CP, AIP tissue damage has somewhat reversible properties as shown in findings after corticosteroid treatment.[29] Ito et al. reported that most ductal basement membranes in AIP were histologically intact and

indicated that exocrine dysfunction in AIP was different from that in CP; ductal cells and bicarbonate secretion remained intact.[16] Song et al. found that type IV collagen was well preserved in AIP tissues as compared with those in CP.[30] Because collagen type IV is a component of the basement membrane that serves as scaffolding and ensures accurate regeneration of tissue form during orderly renewal and repair, the initial structure of the AIP pancreas is regenerated even if considerable pancreatic acinar cell mass is destroyed. This might explain the reversibility or regeneration of AIP tissue to some extent.[29,31] The reversible nature of AIP tissue injury may account for the milder dysfunction found in long-term AIP as compared with CP.

In conclusion, AIP may progress to a state of pancreatic insufficiency after the appearance of calcification that is less severe than in ordinary CP.

References

1. Sarles H, Sarles JC, Muratore R, et al. Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease? *Am J Dig Dis.* 1961;6:688-698.

2. Yoshida K, Toki F, Takeuchi T, et al. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci.* 1995;40:1561-1568.

3. Sugumar A, Kloppel G, Chari ST. Autoimmune pancreatitis: pathologic subtypes and their implications for its diagnosis. *Am J Gastroenterol.* 2009;104:2308-2310.

4. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *New Engl J Med.* 2001;344:732-738.

5. Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet.* 2002;359:1403-1404.

6. Okazaki K, Kawa S, Kamisawa T, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 I. Concept and diagnosis of autoimmune pancreatitis. *J Gastroenterol.* 2014.

7. Kawa S, Okazaki K, Kamisawa T, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 II. Extrapancreatic lesions, differential diagnosis. *J Gastroenterol.* 2014;49:765-784.

8. Kamisawa T, Okazaki K, Kawa S, et al. Amendment of the Japanese Consensus Guidelines for

Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. Journal of gastroenterology. 2014;49:961-970.

9. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas.* 2011;40:352-358.

10. Takayama M, Hamano H, Ochi Y, et al. Recurrent attacks of autoimmune pancreatitis result in pancreatic stone formation. *Am J Gastroenterol.* 2004;99:932-937.

11. Maruyama M, Arakura N, Ozaki Y, et al. Risk factors for pancreatic stone formation in autoimmune pancreatitis over a long-term course. *J Gastroenterol.* 2012;47:553-560.

12. Shimosegawa T, Kataoka K, Kamisawa T, et al. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. J Gastroenterol. 2010;45:584-591.

13. Maruyama M, Arakura N, Ozaki Y, et al. Type 1 Autoimmune Pancreatitis can Transform into Chronic Pancreatitis: A long-term Followed-up Study of 73 Japanese Patients. *International Journal of Rheumatology.* 2013;2013 on line:8.

14. Maruyama M, Watanabe T, Kanai K, et al. Autoimmune pancreatitis can develop into chronic pancreatitis. *Orphanet J Rare Dis.* 2014;9:77.

15. Tanaka S, Kobayashi T, Nakanishi K, et al. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. *Lancet.* 2000;356:910-911.

16. Ito T, Kawabe K, Arita Y, et al. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. *Pancreas.* 2007;34:254-259.

17. Naruse S, Ishiguro H, Ko SB, et al. Fecal pancreatic elastase: a reproducible marker for severe exocrine pancreatic insufficiency. *J Gastroenterol.* 2006;41:901-908.

18. Maire F, Le Baleur Y, Rebours V, et al. Outcome of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol.* 2011;106:151-156.

19. Kitagawa M, Naruse S, Ishiguro H, et al. Evaluating exocrine function tests for diagnosing chronic pancreatitis. *Pancreas.* 1997;15:402-408.

20. Uchida K, Yazumi S, Nishio A, et al. Long-term outcome of autoimmune pancreatitis. *J Gastroenterol.* 2009;44:726-732.

21. Masuda A, Shiomi H, Matsuda T, et al. The relationship between pancreatic atrophy after steroid therapy and diabetes mellitus in patients with autoimmune pancreatitis. *Pancreatology.* 2014;14:361-365.

22. Miyamoto Y, Kamisawa T, Tabata T, et al. Short and long-term outcomes of diabetes mellitus in patients with autoimmune pancreatitis after steroid therapy. *Gut Liver.* 2012;6:501-504.

23. Hirano K, Isogawa A, Tada M, et al. Long-term prognosis of autoimmune pancreatitis in terms of glucose tolerance. *Pancreas.* 2012;41:691-695.

24. Stevens T, Conwell DL, Zuccaro G. Pathogenesis of chronic pancreatitis: an evidence-based

review of past theories and recent developments. *Am J Gastroenterol.* 2004;99:2256-2270.

25. Suda K, Mogaki M, Oyama T, et al. Histopathologic and immunohistochemical studies on alcoholic pancreatitis and chronic obstructive pancreatitis: special emphasis on ductal obstruction and genesis of pancreatitis. *Am J Gastroenterol.* 1990;85:271-276.

26. Suda K, Takase M, Fukumura Y, et al. Histopathologic characteristics of autoimmune pancreatitis based on comparison with chronic pancreatitis. *Pancreas.* 2005;30:355-358.

27. Kishi S, Takeyama Y, Ueda T, et al. Pancreatic duct obstruction itself induces expression of alpha smooth muscle actin in pancreatic stellate cells. *The Journal of surgical research.* 2003;114:6-14.

28. Kawa S, Hamano H, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. Reply. *New Engl J Med.* 2001;345:148-148.

29. Saito T, Tanaka S, Yoshida H, et al. A case of autoimmune pancreatitis responding to steroid therapy. Evidence of histologic recovery. *Pancreatology.* 2002;2:550-556.

30. Song MH, Kim MH, Jang SJ, et al. Comparison of histology and extracellular matrix between autoimmune and alcoholic chronic pancreatitis. *Pancreas.* 2005;30:272-278.

31. Song MH, Kim MH, Lee SK, et al. Regression of pancreatic fibrosis after steroid therapy in patients with autoimmune chronic pancreatitis. *Pancreas.* 2005;30:83-86.

Acknowledgments: We thank Trevor Ralph for his English editorial assistance.

Potential competing interests: None

Qualify for (co-)authorship: All authors met the contributions to (a) conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; (c) final approval of the version to be published.

Figure Legends

Figure 1: CT imaging findings of calcified AIP which fulfills the diagnostic criteria in Japanese clinical diagnostic criteria for CP. **(a)** Stones in pancreatic ducts. **(b)** Diffuse calcifications distributed in the parenchyma throughout the entire pancreas.

Figure 2: Scattergram for fecal elastase-1 concentration (FEC) in AIP without severe calcification (SC), AIP with SC, chronic pancreatitis (CP), and healthy controls. NS: not significant.

Figure 3: Scattergram for **(a)** fasting immunoreactive insulin (IRI) in AIP without severe calcification (SC), AIP with SC, and chronic pancreatitis (CP), and **(b)** fasting C-peptide reactivity (CPR) in AIP without SC, AIP with SC, and CP. NS: not significant.

Figure 4: Scattergram for **(a)** HOMA-R in AIP without severe calcification (SC), AIP with SC, and chronic pancreatitis (CP), and **(b)** HOMA-β values in AIP without SC, AIP with SC, and CP. NS: not significant.

Table 1. Comparison of clinical and laboratory features among test groups

	AIP without SC (n=75)	AIP with SC (n=17)	Ordinary CP (n=47)	*p* value
Clinical features		Median (range)		
Observation period, mo	78 (36-301)	148 (42-211) $^{\Phi}$	88 (6-402)	$^{\Phi}p < 0.005$
Age, y	74 (55-90) *	74 (60-88) *	66 (39-81)	$*p < 0.0005$
Gender (M/F)	57/18	14/3	44/3 $^{\Psi}$	$^{\Psi}p < 0.02$
Alcohol intake (+/-)	35/40 ‡	8/9 ‡	42/5	$^{\ddagger}p < 0.0005$
Smoking (+/-)	40/35 ¶	11/6 ¶	41/6	$^{\P}p < 0.05$
Prednisolone (PSL) (+/-)	61/14	13/4		NS
PSL period (months)	80 (2-1375)	157 (38-209)		$p < 0.05$
Relapse (+/-)	23/52	7/10		NS
Laboratory results at final visit		Median (range)		
IgG	1458 (315-3240) (n=45)	1276 (683-1894) (n=12)		NS
IgG4	228.0 (3-1330) (n=48)	162.5 (42-632) (n=12)		NS
C3	98.0 (59-178) (n=45)	99.5 (72-132) (n=12)		NS
C4	22.1 (11.2-40.3) (n=45)	23.6 (16.9-30.5) (n=12)		NS
sIL-2R	455.0 (129-1625) (n=45)	376.0 (171-909) (n=11)		NS
CIC	3.2 (2.0-9.9) (n=36)	2.2 (2.0-5.9) (n=11)		NS

$^{\Phi}p < 0.005$ vs. AIP without SC, $*p < 0.0005$ vs. CP, $^{\Psi}p < 0.02$ vs. AIP without SC, $^{\ddagger}p < 0.0005$ vs. CP, $^{\P}p < 0.05$ vs. CP

SC: severe calcification*; CP:* chronic pancreatitis; *sIL-2R:* soluble interleukin-2 receptor; *CIC:* circulating immune complex; *NS:* not significant

Table 2. Comparison of pancreatic exocrine function parameters

	AIP without SC	AIP with SC	Ordinary CP	Control
FEC (μg/g)	229.9 (7.7-642.1)	99.0 (5.1-520.3)	80.2 (3.6-542.5) *	488.2 (66.0-1031.7) $^{\Phi}$
	(n=33)	(n=9)	(n=27)	(n=30)
FEC<200μg/g (%)	13/33 (39%)	5/9 (56%)	20/27 (74%) *	5/30 (17%) $^{\Phi}$
Total AIP	18/42 (43%)			
BT-PABA (%)	56.4 (16.9-86.6)	42.5 (11.1-56.9)	48.9 (11.9-126.9)	NS
	(n=18)	(n=5)	(n=21)	
BT-PABA<70% (%)	11/18 (61%)	5/5 (100%)	17/21 (81%)	NS
Total AIP	16/23 (70%)			

Values are expressed as median (range).

*$p < 0.02$ vs. AIP without SC, total AIP

$^{\Phi}p < 0.02$ vs. AIP without SC, AIP with SC, total AIP, and Ordinary CP

FEC: fecal elastase-1 concentration; *BT-PABA: N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid; *NS:* not significant

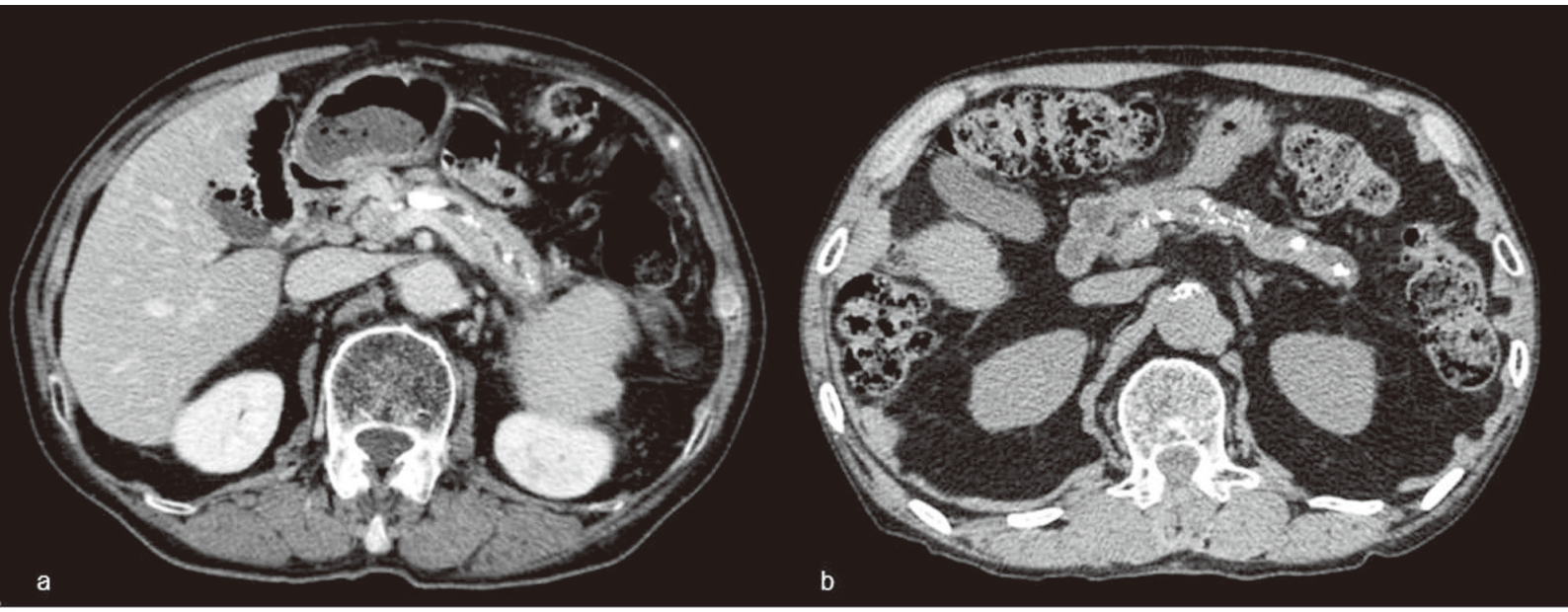
Table 3. Comparison of pancreatic endocrine function parameters

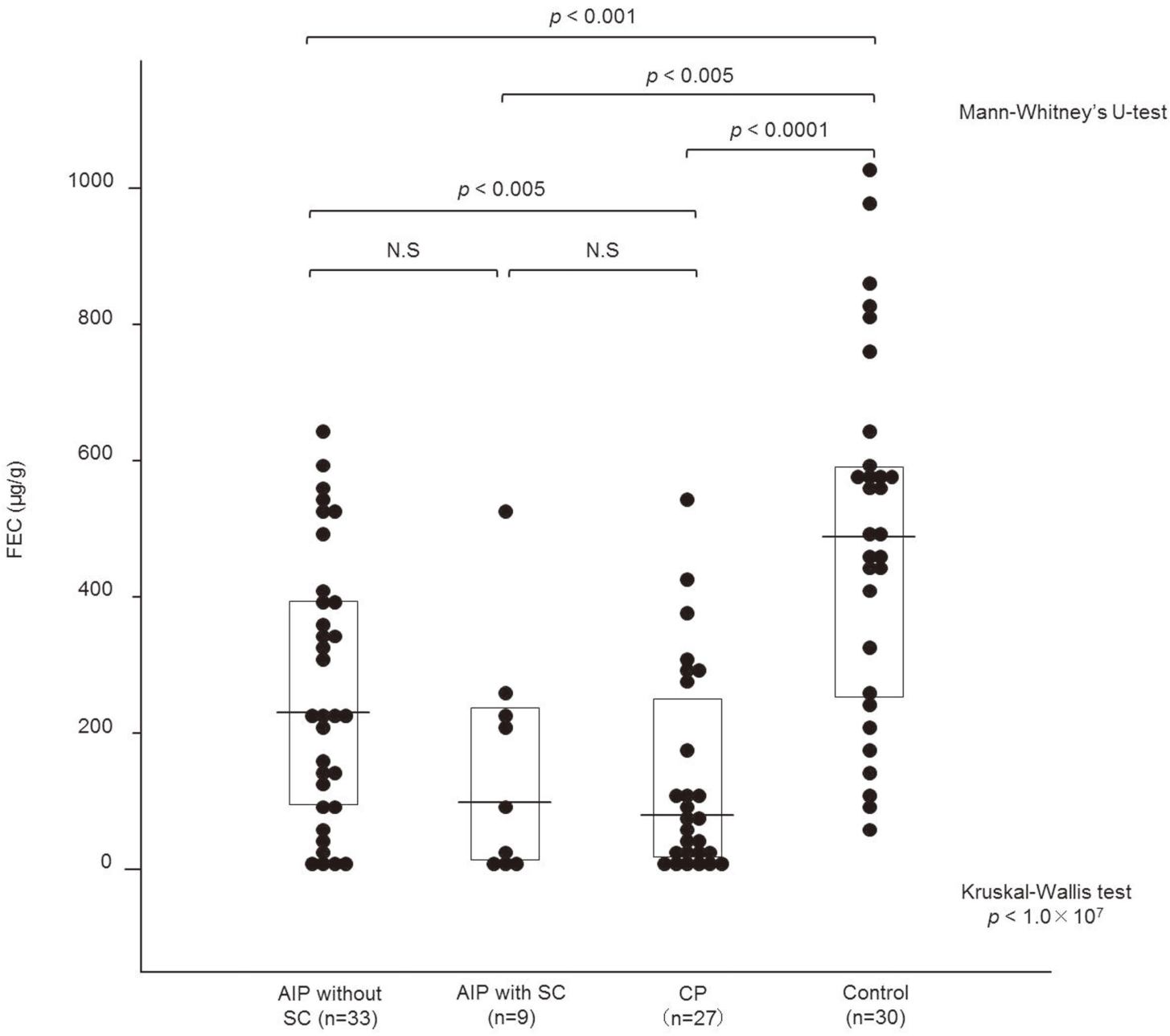
	AIP without SC	AIP with SC	Ordinary CP	*p* value
	Total AIP			
Diabetes mellitus (+/-) (%)	33/42(44)	10/7 (59)	15/30 (33)	NS
Total AIP (+/total) (%)	43/92 (47)			
Insulin use (+/-)	15/60 (20)	5/12 (29)	10/35 (22)	NS
Total AIP (+/total) (%)	20/92 (22)			
	median (range)			
IRI (μU/mL)	9.8 (1.2 -222.5) $^{\Phi}$	10.2 (3.4-44.1) $^{\Phi}$	3.9 (1.0-28.7)	$^{\Phi}p < 0.05$
	(n=62)	(n=13)	(n=34)	
IRI <5.0 μU/mL (%)	16/62 (26) *	4/13 (31)	20/34 (59)	$^{*}p < 0.002$
Total AIP (+/total) (%)	20/75 (27) *			
CPR (ng/mL)	2.3 (0.2-8.1) $^{\Phi}$	2.5 (0.3-8.7) $^{\Phi}$	0.9 (0.2-7.5)	$^{\Phi}p < 0.05$
	(n=70)	(n=17)	(n=37)	
CPR <1.5 μU/mL (%)	21/70 (30) $^{\Psi}$	7/17 (41)	25/37 (68)	$^{\Psi}p < 0.0005$
Total AIP (+/total) (%)	28/87 (32) $^{\Psi}$			
HOMA-R	2.9 (0.5-82.4) ¶	3.2 (1.2-22.4) ¶	1.0 (0.3-9.7)	$^{\P}p < 0.01$
	(n=56)	(n=10)	(n=28)	
HOMA-R ≧2.5 (%)	33/56 (59) $^{\Phi}$	7/10 (70)$^{\Phi}$	8/28 (29)	$^{\Phi}p < 0.05$
Total AIP (+/total) (%)	40/66 (61) $^{\Phi}$			
HOMA-β (%)	78.2 (3.6-920.7) ¶	84.4 (14.6-255.0)	42.4 (4.4-297.0)	$^{\P}p < 0.01$
	(n=56)	(n=10)	(n=28)	
HOMA-β <40% (%)	17/56 (30)	3/10 (30)	14/28 (50)	NS
Total AIP (+/total) (%)	20/66 (30)			

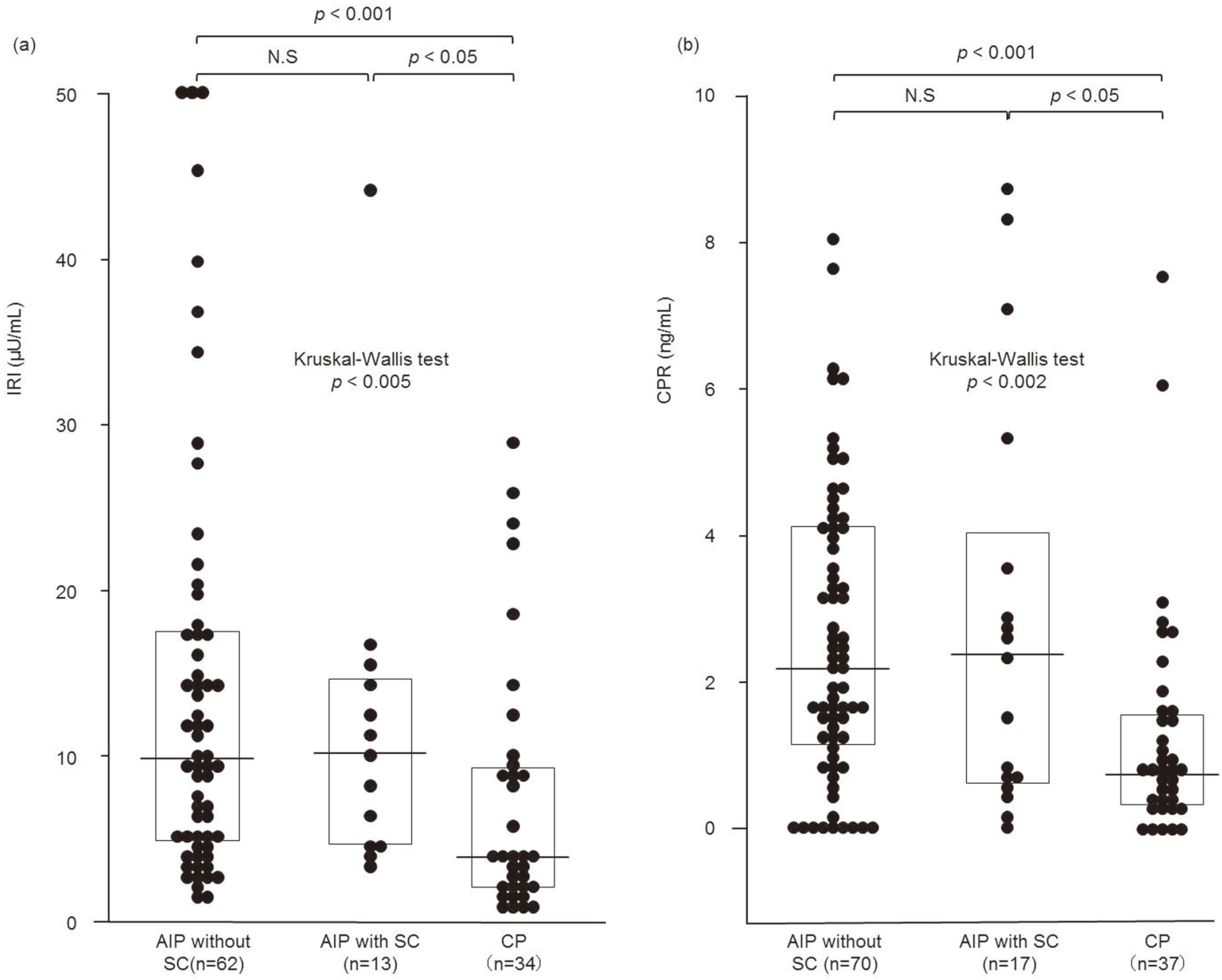
Values are expressed as median (range).

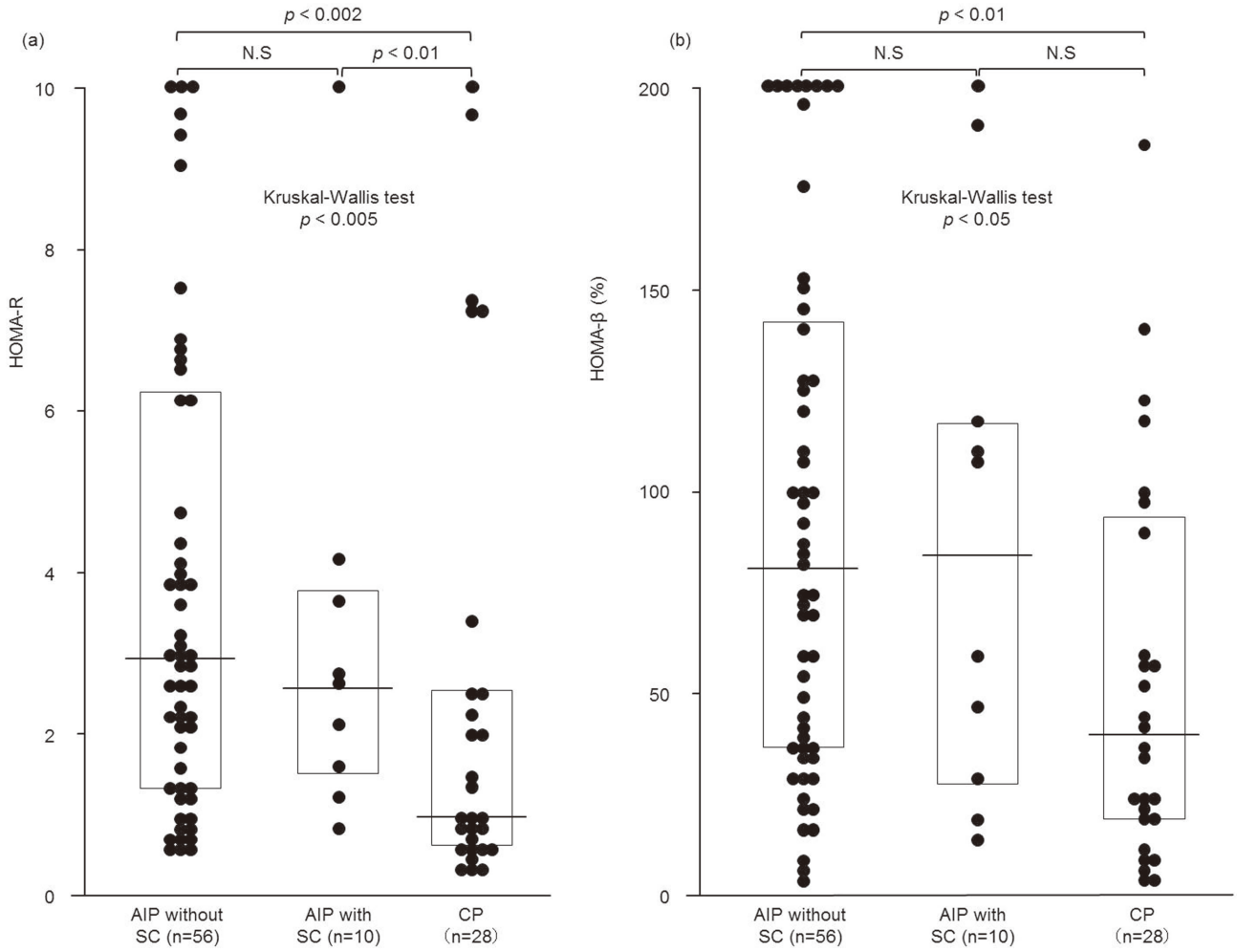
$^{\Phi}p < 0.05$ vs. CP, $^{*}p < 0.002$ vs. CP, $^{\Psi}p < 0.0005$ vs. CP, $^{\P}p < 0.01$ vs. CP

IRI: immunoreactive insulin; *CPR:* C-peptide reactivity; *HOMA-R:* homeostasis model assessment ratio; *HOMA-β:* homeostasis model assessment-beta cells; *NS:* not significant


a
b


p < 0.001
p < 0.005
p < 0.0001
Mann-Whitney's U-test
p < 0.005
N.S
N.S
1000
800
600
400
200
0
FEC (μg/g)
Kruskal-Wallis test
p < 1.0× 10^7
AIP without SC (n=33)
AIP with SC (n=9)
CP (n=27)
Control (n=30)


(a)
p < 0.001
N.S
p < 0.05
IRI (μU/mL)
50
40
30
20
10
0
Kruskal-Wallis test
p < 0.005
AIP without SC(n=62)
AIP with SC (n=13)
CP （n=34）
(b)
p < 0.001
N.S
p < 0.05
CPR (ng/mL)
10
8
6
4
2
0
Kruskal-Wallis test
p < 0.002
AIP without SC (n=70)
AIP with SC (n=17)
CP （n=37）


(a)
p < 0.002
N.S
p < 0.01
Kruskal-Wallis test
p < 0.005
HOMA-R
10
8
6
4
2
0
AIP without SC (n=56)
AIP with SC (n=10)
CP (n=28)
(b)
p < 0.01
N.S
N.S
Kruskal-Wallis test
p < 0.05
HOMA-β (%)
200
150
100
50
0
AIP without SC (n=56)
AIP with SC (n=10)
CP (n=28)