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Kobayashi, Takashi ; Sato, Yu ; Nishiumi, Shin ; Yagi, Yosuke ; Sakai, Arata ; Shiomi, Hideyuki ; Masuda, Atsuhiro ; Okaya, Shinobu ; Kutsumi…

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Serum apolipoprotein A2 isoforms in autoimmune pancreatitis

Authors' names and affiliations:

Takashi Kobayashi[1], Yu Sato[1], Shin Nishiumi[1], Yosuke Yagi[1,2], Arata Sakai[1], Hideyuki Shiomi[1], Atsuhiro Masuda[1], Shinobu Okaya[3], Hiromu Kutsumi[4], Masaru Yoshida[1,5,6] Kazufumi Honda[3]

[1]Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan

[2]Department of Gastroenterology, Nissay Hospital, Japan

[3]Department of Biomarker of Early Detection for Cancer, National Cancer Center Research Institute, Japan

[4]Center for Clinical Research and Advanced Medicine Establishment, Shiga University of Medical Science, Japan

[5]Division of Metabolomics Research, Department of Internal Related, Kobe University Graduate School of Medicine, Japan

[6]AMED-CREST, AMED, Japan

Corresponding author: Takashi Kobayashi

Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan

e-mail address: kobatak@med.kobe-u.ac.jp

7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

Telephone: +81-78-382-6305; Fax: +81-78-382-6309

Abstract

Recently, apolipoprotein A2 (apoA2) isoforms have been reported as candidate serum/plasma biomarkers of pancreatic cancer. However, the distribution of apoA2 isoforms in patients with autoimmune pancreatitis (AIP) has not been investigated yet. In this study, we evaluated the distribution of serum apoA2 isoforms; i.e., homodimer apoA2-ATQ/ATQ, heterodimer apoA2-ATQ/AT, and homodimer apoA2-AT/AT, in AIP patients and healthy volunteers (HV) using enzyme-linked immunosorbent assays, and the clinical characteristics and serum levels of each apoA2 isoform in 32 AIP patients and 38 HV were investigated. The calculated apoA2-ATQ/AT levels of the AIP patients were significantly lower than those of the HV, which agreed with results obtained for

patients with pancreatic cancer. Interestingly, most of the AIP patients exhibited high levels of apoA2-ATQ along with low levels of apoA2-AT, indicating that the processing of the C-terminal regions of apoA2 dimer was inhibited in the AIP patients. This specific distribution of serum apoA2 isoforms might provide important information about the disease states of AIP patients and aid the differential diagnosis of AIP versus pancreatic cancer.

Keywords:

autoimmune pancreatitis; apolipoprotein A2 isoform; biomarker

Introduction

Apolipoprotein A2 (apoA2) is a major component of high-density lipoproteins (HDL), and it plays an important role in directing the fate of lipid metabolism among HDL. The presence of apoA2 stabilizes HDL particles, making their remodeling more difficult [1]. In humans, most of circulating apoA2 exist as dimer consisting of two identical 77-residue polypeptide chains linked by a disulfide bridge between the Cys-6 residues [2], and there are five types of apoA2 dimer isoform, which have different

amino acid sequences in their C-terminal regions; i.e., homodimer apoA2-ATQ/ATQ, heterodimer apoA2-ATQ/AT, homodimer apoA2-AT/AT, apoA2-AT/A, and apoA2-A/A [3]. In recent years, some studies have revealed that the levels of specific apoA2 isoforms in the serum/plasma of pancreatic cancer patients were significantly different from those seen in healthy individuals, even in the early stages of the disease [3,4]. ApoA2 isoforms are considered to be some of the most promising serum/plasma biomarkers for aiding the early detection of pancreatic cancer. However, the relationships between the serum/plasma levels of apoA2 isoforms and pancreatic diseases, including autoimmune pancreatitis (AIP), have not been fully investigated. AIP is a major immunoglobulin G4-related disease (IgG4-RD) [5,6]. AIP patients often suffer from glucose intolerance and obstructive jaundice due to chronic pancreatic inflammation and sclerosis [7]. Although AIP might not be a risk factor for pancreatic cancer [8], AIP itself often exhibits cancer-like findings on imaging examinations. Therefore, the differential diagnosis of AIP from pancreatic cancer is important and often affects critical clinical decisions. The diagnostic criteria for AIP include characteristic imaging features involving the pancreatic parenchyma and duct, an elevated serum level of IgG4, and the detection of the marked infiltration of IgG4-positive plasma cells into pancreatic tissues during histopathological examinations

[9]. However, about 10-50% of type 1 AIP patients do not fulfill the serum IgG4 level criterion [10]. Tissue sampling from the pancreas is not easy, and moreover, it carries a risk of pancreatitis, infection, and bleeding. Therefore, it would be useful to identify markers other than the serum IgG4 level that could aid the diagnosis/treatment of AIP. The aim of this study is to investigate the distribution of serum apoA2 isoforms in AIP patients and then to evaluate the utility of apoA2 isoforms as biomarkers of AIP.

Materials and Methods

Subjects

This study was approved by the institutional ethics committee of Kobe University Hospital (No. 1681). Written informed consent was obtained from all patients and healthy volunteers (HV) before registration. Thirty-two AIP patients and 36 HV were registered at Kobe University Hospital between December 2014 and March 2015. All of the AIP patients were diagnosed based on the Japan Society of the Pancreas 2011 (JSP2011) criteria before being registered [9,11]. The HV were asymptomatic individuals who did not have any history of pancreatitis, pancreatic tumors, or diabetes.

Clinical data

All clinical data including regarding the AIP patients' gender, age, body mass index (BMI), history of diabetes, serum amylase levels, pancreatic amylase levels, lipase levels, IgG4 levels, and history of steroid therapy, and the gender, age, and BMI of the HV were obtained from the clinical data system at the closest point to registration; i.e., when the blood samples used to obtain the measurements of the levels of each apoA2 isoform were collected.

Serum samples

All blood sampling procedures were performed using the standard venous blood sampling method. After the blood samples had been allowed to completely coagulate at room temperature for about 30 min, they were centrifuged at 3,000 rpm for 15 min. Serum samples were obtained and then frozen at -80^{o}C until the analysis.

Measurement of apoA2-AT and apoA2-ATQ

The human APOA2 C-terminal enzyme-linked immunosorbent assay (ELISA) kit (Toray Industries Inc., Japan) was used to measure the levels of each apoA2 isoform in this study according to the manufacturer's instructions. This kit contains two types of plate and antibodies, which makes it possible to measure the levels of apoA2-AT and

apoA2-ATQ at the same time. Absorbance was measured at 450 nm. Each sample was measured in triplicate, and the mean value was used as the serum level for that sample.

Relationships between the ELISA results and apoA2 isoforms

ApoA2-ATQ targeted by this ELISA kit includes homodimer apoA2-ATQ/ATQ, heterodimer apoA2-ATQ/AT, and monomer apoA2-ATQ. The results of the apoA2-ATQ ELISA exhibit a good correlation with the serum levels of homodimer apoA2-ATQ/ATQ [4]. ApoA2-AT targeted by this ELISA kit includes homodimer apoA2-AT/AT, heterodimer apoA2-ATQ/AT, heterodimer apoA2-AT/A, and monomer apoA2-AT. The results of the apoA2-AT ELISA display a good correlation with the serum levels of homodimer apoA2-AT/AT [4]. A previously reported formula based on ELISA results for apoA2-AT and apoA2-ATQ was used to calculate the serum level of heterodimer apoA2-ATQ/AT in this study.

Statistics

Numerical data regarding age, height, weight, BMI, blood chemistry, and apoA2 isoforms are presented as the mean and standard deviation (S.D.) for each group, and were compared using the Student's t-test. Categorical data concerning sex, diabetes,

or steroids are presented as distribution charts, and were compared using Pearson's chi-square test. These analyses were performed using the default conditions of JMP12 (SAS Institute Inc.).

Results and Discussion

All 32 of registered AIP patients and all 36 of registered HV were included in this study. Regarding the clinical characteristics of the two groups (**Table 1**), there were no significant intergroup differences in age, sex, or BMI. All of the AIP patients were diagnosed with type 1 AIP based on the JSP2011 criteria. About 80% of them were receiving steroid treatment at the time of their registration. The AIP patients' serum IgG4 levels ranged from 21 to 1,080 mg/dL, and 87.5% of them met the clinical criterion of a serum IgG4 level of >135 mg/dL at the time of registration. The analysis did not reveal any significant correlation among the levels of the apoA2 isoforms and major clinical factors, except for a moderately negative correlation between the serum amylase level and the level of apoA2-AT according to the ELISA (hereafter referred to as the apoA2-AT level (ELISA)) (**Sup. Table 1**).

The AIP patients exhibited significantly higher levels of apoA2-ATQ according to the ELISA (hereafter referred to as the apoA2-ATQ level (ELISA)) than the HV (52.3

μg/mL vs. 31.9 μg/mL, p<0.0068). This result indicated that the serum level of homodimer apoA2-ATQ/ATQ in AIP patients was higher than in the HV. On the other hand, they displayed significantly lower apoA2-AT levels (ELISA) than the HV (27.5 μg/mL vs. 88.2 μg/mL, p<0.0001). This result indicated that the serum level of homodimer apoA2-AT/AT in AIP patients was lower than in the HV. As for the serum levels of heterodimer apoA2-ATQ/AT calculated based on the ELISA results, they were significantly lower in the AIP patients than in the HV (28.9 μg/mL vs. 45.5 μg/mL, p=0.0024) (**Figures 1 and 2**). Some studies have found that pancreatic cancer patients had lower total blood levels of the apoA2 dimer than healthy controls [3,12]. Honda et al. reported that pancreatic cancer patients exhibited significantly lower serum levels of heterodimer apoA2-ATQ/AT than HV [4]. Our results regarding the heterodimer apoA2-ATQ/AT levels of the AIP patients were similar to those described in the latter study. Felix et al. reported that AIP patients displayed significantly higher serum total apoA2 levels than pancreatic cancer patients, but the difference between the serum total apoA2 levels of the AIP patients and healthy controls was not significant [13]. Therefore, the reduced levels of heterodimer apoA2-ATQ/AT seen in the AIP patients in our study might not have been due to a drop in the total level of the apoA2 dimer. Honda et al. proposed a unique distribution of apoA2 isoforms in pancreatic cancer

patients, which depends on the processing pattern of amino acids in the C-terminal regions of the apoA2 dimer [14]. One is the hyper-processing (ATQ/ATQ<AT/AT) pattern; i.e., low levels of apoA2-ATQ (ELISA) along with high levels of apoA2-AT (ELISA), and the other is the hypo-processing (ATQ/ATQ>AT/AT) pattern; i.e., high levels of apoA2-ATQ (ELISA) along with low levels of apoA2-AT (ELISA). Interestingly, these two types of processing pattern were observed at equal frequencies in pancreatic cancer patients [14]. In our study, the hypo-processing (ATQ/ATQ>AT/AT) pattern was most common among the AIP patients, indicating that the processing of amino acids in the C-terminal regions of apoA2 dimer might be inhibited in AIP patients (**Figure 3**). Felix et al. also revealed that the levels of gelatinase B/matrix metalloproteinase 9 (MMP-9), the neutrophil gelatinase B–associated lipocalin/MMP-9 complex, and gelatinase A/MMP-2 were significantly higher in AIP patients than in pancreatic cancer patients [15]. In addition, in some AIP patients the levels of enzymes from pancreatic tissues might be increased due to active inflammation induced by AIP. Indeed, in our study, 6 (18.6%) of the AIP patients had increased serum amylase levels, and 28 (87.5%) of the AIP patients displayed elevated serum IgG4 levels. In general, pancreatic cancer patients rarely have increased serum amylase levels or clinically acute pancreatitis. These differences in the total apoA2 level

and the distribution patterns of apoA2 isoforms between AIP and pancreatic cancer might reflect pathological and enzymatic differences between the two conditions, although the mechanism underlying the observed alterations in amino acid sequence of the C-terminal regions of apoA2 dimer has not been elucidated yet. Therefore, these results indicate that the frequency of apoA2 isoforms might provide important information for discriminating between AIP and pancreatic cancer or a healthy state. Furthermore, Julovi et al. revealed that apoA2 enhances pancreatic cancer cell proliferation through scavenger receptor class B type-1 (SR-B1) [16], and the frequency of each apoA2 isoform might provide useful information that would increase our understanding of pancreatic inflammation and cancer. Regarding apolipoproteins other than apoA2, it was also revealed that the level of apolipoprotein A1 (apoA1) was related to the severity of acute pancreatitis. Peng et al. reported that the concentrations of HDL and apoA1 are inversely related to organ failure and death in patients who are predicted to develop severe pancreatitis [17]. Huh et al. demonstrated that the ratio of apoB to apoA1 was positively correlated with the severity of acute pancreatitis and that it had high predictive value for predicting severe acute pancreatitis [18]. Furthermore, Montecucco et al. reviewed the relationships among acute/chronic systemic inflammation, autoimmune diseases, and apoA1/HDL [19]. The findings of these

studies suggest that pancreatic inflammation might alter the lipid metabolism of HDL, including their apolipoproteins.

In summary, we detected a reduced level of heterodimer apoA2-ATQ/AT and a specific apoA2 isoform hypo-processing pattern in the sera of AIP patients. This specific serum apoA2 isoform distribution pattern might provide important information about AIP and facilitate the differential diagnosis of pancreatic diseases, including AIP and pancreatic cancer.

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Figure/table legends

Table 1. Characteristics of autoimmune pancreatitis patients and healthy volunteers

Steroid doses are shown as the daily dosage of prednisolone. The p-values were

calculated using the Student's t-test. AIP, autoimmune pancreatitis; HV, healthy volunteers; BMI, body mass index; P-amylase, pancreatic isoform of amylase; IgG4, immunoglobulin G4

Figure 1. The calculated serum heterodimer apoA2-ATQ/AT levels of the autoimmune pancreatitis patients and healthy volunteers

The calculated serum heterodimer apoA2-ATQ/AT levels of the autoimmune pancreatitis (AIP) patients are shown as closed circles on the left side (mean: 28.9 μg/mL) and those of the healthy volunteers (HV) are shown as open circles on the right side (mean: 45.5 μg/mL). The horizontal lines represent the mean serum heterodimer apoA2-ATQ/AT levels of the AIP patients and HV. The p-value was calculated using the Student's t-test.

Figure 2. The serum apoA2-AT and apoA2-ATQ levels (according to ELISA) of the autoimmune pancreatitis patients and healthy volunteers

The serum apoA2-AT and apoA2-ATQ levels of the autoimmune pancreatitis patients are shown as closed circles, and those of the healthy volunteers are shown as open circles. X axis, the levels of apoA2-AT according to ELISA; Y axis, the levels of

apoA2-ATQ according to ELISA

Figure 3. The distribution pattern of apoA2 dimer isoforms in autoimmune pancreatitis and pancreatic cancer

The direction of the arrow indicates the relative serum level of apoA2 dimer in autoimmune pancreatitis (AIP) or pancreatic cancer compared with that seen in the healthy controls. This summary is based on results obtained by Honda et al. [4,14], Xue et al. [12], Felix et al. [13], and our study. The hyper-processing pattern involves low levels of apoA2-ATQ along with high levels of apoA2-AT according to ELISA (ATQ/ATQ<AT/AT). The hypo-processing pattern involves high levels of apoA2-ATQ along with low levels of apoA2-AT according to ELISA (ATQ/ATQ>AT/AT).

Table 1. Characteristics of autoimmune pancreatitis patients and healthy volunteers

	AIP	HV	P-value
Number	32	36	
males	24	27	1
females	8	9	
Age (y.o.)			
mean	69.2	67.9	0.56
range	47-84	46-83	
BMI (kg/m^2)			
mean	21.5	23.3	0.06
range	15.9-36.2	17.0-31.1	
Diabetes			
yes	15	0	<0.01
insulin	9	0	<0.01
Amylase (U/L)			
mean	104	N/A	-
range	35-384	N/A	
P-amylase (U/L)			
mean	45	N/A	-
range	6-235	N/A	
Lipase (U/L)			
mean	71	N/A	-
range	6-550	N/A	
IgG4 (mg/dL)			
mean	291	N/A	-
range	21-1,080	N/A	
Steroids (mg/day)			
0	7	36	<0.01
0<dosage≤10	24	0	
10<	1	0	

Steroids are shown as the daily dosage of prednisolone. For age and BMI, the P-values were calculated using the Student's t-test. For diabetes, insulin and steroids, the P-value were calculated using Pearson's chi-square test. AIP, autoimmune pancreatitis; HV, healthy volunteers; BMI, body mass index; P-amylase, pancreatic isoform of amylase; IgG4, immunoglobulin G4; N/A,

not available

Figure 1.

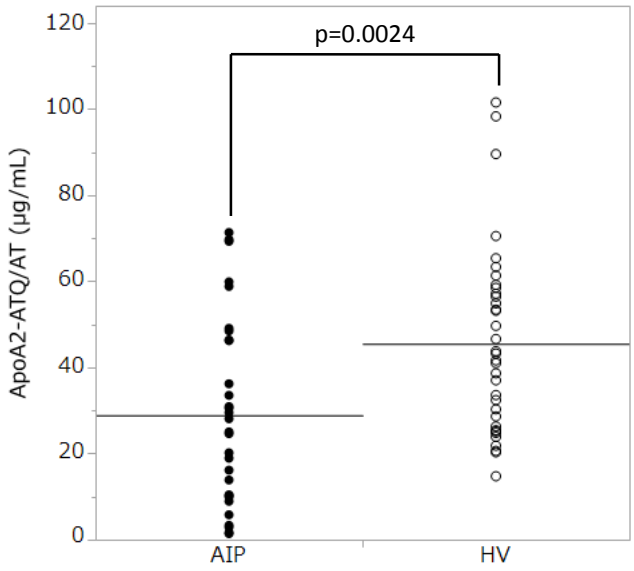


Figure 2.

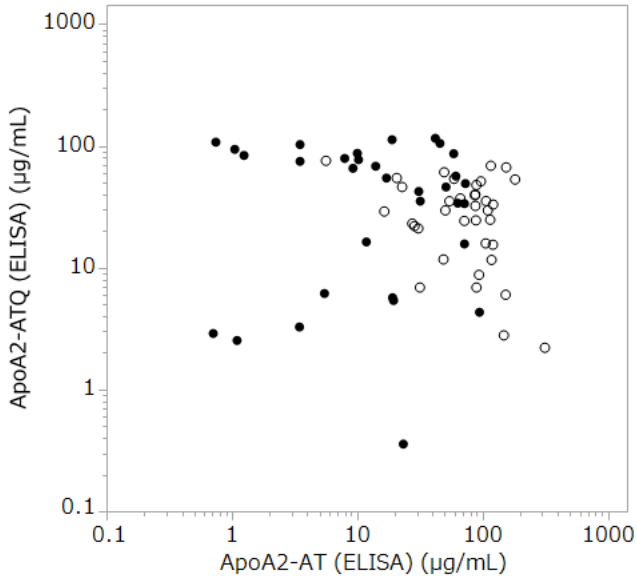
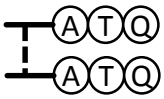
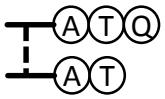
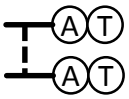

1000
100
10
1
0.1
ApoA2-ATQ (ELISA) (µg/mL)
0.1
1
10
100
1000
ApoA2-AT (ELISA) (µg/mL)

Figure 3.

	Total apoA2 dimer	ApoA2-ATQ/ATQ	ApoA2-ATQ/AT	ApoA2-AT/AT
				
AIP	→	↑	↓	↓
Pancreatic cancer Hyper-processing pattern	↓	↓↓	↓↓	→ or ↑
Pancreatic cancer Hypo-processing pattern	↓	→ or ↑	↓↓	↓↓

Supplementary Table 1. The correlation coefficients for the relationships between the results of the apoA2-ATQ or apoA2-AT ELISA, the calculated apoA2-ATQ/AT level, and major clinical factors

Correlation coefficient	ApoA2-ATQ (ELISA)	ApoA2-AT (ELISA)	Calc ApoA2-ATQ/AT	Age	BMI	HbA1c	Amy	P-amy	Lip	IgG4
ApoA2-ATQ (ELISA)	1									
ApoA2-AT (ELISA)	-0.31	1								
Calc ApoA2-ATQ/AT	0.32	0.52	1							
Age	0.03	-0.05	-0.06	1						
BMI	-0.16	0.26	0.10	-0.02	1					
HbA1c	-0.07	0.04	-0.24	0.15	0.32	1				
Amy	-0.01	-0.50	-0.17	0.10	-0.21	-0.22	1			
P-amy	-0.11	-0.33	-0.16	0.10	-0.02	-0.12	0.91	1		
Lip	-0.16	-0.09	-0.06	0.05	-0.06	-0.01	0.62	0.83	1	
IgG4	0.11	-0.33	-0.35	-0.04	-0.07	0.07	0.18	0.17	0.06	1

Each correlation coefficient was calculated using Pearson’s correlation analysis.