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Involvement of intestinal alkaline phosphatase in serum apolipoprotein B-48 level and its association with ABO and secretor blood group types ☆

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Abstract

Serum levels of intestinal alkaline phosphatase (IAP), a protein implicated in transcellular transport of chylomicrons, vary among ABO blood groups. In rat enterocytes, IAP is associated with chylomicron secretion, but the rat expresses only blood group A. It is not known whether chylomicron secretion may be affected in humans who express multiple blood group types. Serum samples from 40 healthy subjects were obtained after overnight fast and 3 h after a high-fat meal, and assayed for IAP and apolipoprotein B-48 (apoB-48), both proteins exclusive to intestine, although only apoB-48 is found in chylomicrons. The two proteins were greater in subjects without blood antigen A (B and O) than in those with this antigen (A and AB); 2.4- and 4.7-fold for IAP and 1.5- and 2.0-fold for apoB-48 before and after the meal, respectively. Moreover, IAP and apoB-48 levels were strongly correlated in the subjects with the secretor phenotype ($r > 0.81$). These results indicate that IAP is strongly involved in chylomicron formation and fatty acid metabolism might change among ABO blood type. In addition, ABO blood type classification in apoB-48 measurement would improve the diagnostic value in the evaluation of metabolic syndrome.

Keywords: ABO blood group; Apolipoprotein B-48; Chylomicron; Intestinal alkaline phosphatase; Secretor phenotype; Triglyceride

Intestinal alkaline phosphatase (IAP; orthophosphoric monoester phosphohydrolase, EC 3.1.3.1) is produced mainly by the epithelial cells of the small intestinal mucosa and is located on the apical membrane [1,2], where IAP is attached to the microvillar membrane by a glycosyl phosphatidylinositol link [3]. Accumulated evidence has shown that IAP in the rat intestinal mucosa plays a key role in the transport of fatty acids and triglyceride (TG) from the intestinal tract to the circulation [4]. After oral fat intake, IAP stimulates production of a unilamellar membrane that moves through the Golgi apparatus along with dietary lipid [2]. This membrane (called surfactant-like particle) surrounds the TG-rich fat droplets that contain apoB-48 and accompanies them as they traverse the epithelial cells [5].

The TG-rich chylomicrons are secreted basolaterally into the intestinal lymph, most likely by reverse pinocytosis. In that process, the IAP-containing membrane that surrounds the fat droplets is separated from the lipid droplets and both components enter the circulation [6]. This sequence of events can explain why oral fat intake results

☆ *Abbreviations:* apo, apolipoprotein; IAP, intestinal alkaline phosphatase; LPL, lipoprotein lipase; secretor, subject with secretor phenotype; non-secretor, subject with non-secretor phenotype; TG, triglyceride.

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in rapid increases in IAP and chylomicrons in the serum [7].

Several studies have confirmed that the serum IAP level is affected by blood group antigen secretor phenotypes. Persons with secretor phenotype are identified by the abundant production of ABO blood antigen in saliva and semen, while those with non-secretor produce the antigen scarcely probably because of the inactivation of the enzyme by a nonsense mutation [8]. Domar et al. [9] reported that serum IAP levels in persons with the non-secretor phenotype (non-secretors) were undetectable or approximately one-tenth smaller than those in persons with the secretor phenotype (secretors) whose gastric, intestinal, and salivary gland epithelial cells secrete abundant soluble ABO blood antigens. However, the explanation for the lower levels of IAP in non-secretors is not known.

In addition to secretor/non-secretor phenotypes, the ABO blood group itself is also associated with differences in the serum IAP levels [9–11]. Domar et al. [9] used a sensitive and specific immunoassay for IAP and showed that even among subjects with the secretor phenotype, those with blood antigen A (groups A and AB) have approximately one-third lower serum IAP levels than those with the other antigens (groups O and B).

On the basis of this evidence, we hypothesized that blood phenotypes might affect chylomicron secretion by regulating IAP expression and/or secretion. Herein, we show that serum levels of IAP (a marker for chylomicron absorption) and apoB-48 (an intestinal marker for chylomicron production [12]) increased more in association with blood group types B and O, and with blood group secretor status. These findings also indicate that the clinical use of apoB-48 measurement, an emerging marker for the risk of metabolic syndrome [13], should incorporate ABO blood type classification.

Subjects and methods

Serum samples. We enrolled 200 students aged 18–22 years, from the Saitama Prefectural Univ. and Medical Technology, Junior College of Saitama Medical School, and determined their ABO blood groups and secretor/non-secretor phenotypes using standard laboratory techniques at Saitama Medical School. Briefly, erythrocytes in EDTA blood were washed with saline and anti-blood type antigen antisera were added. The specific aggregations were determined visually and the blood type was identified. Twenty secretors and non-secretors from the students for this study were chosen randomly to give five subjects with blood groups A, B, AB, and O in each group. All 40 subjects were healthy according to their medical histories and our physical examinations. Blood samples were collected after an overnight fast, and the subjects were then served a standardized high-fat meal. The meal consisted of gruel and bread which contained TG with long chain fatty acids derived from dairy products, as described previously [7]. All the subjects consumed the meal over a period of 10 min. Blood samples were collected 3 h later, which is the time that IAP and TG levels reach their peaks [7]. We centrifuged the blood samples immediately after collection and stored the serum samples at −80 °C until use.

The experimental procedure and its purpose were thoroughly explained to all the subjects and written consent was obtained. The study protocol was approved by the Ethics Committee of Saitama Medical School.

IAP assay. Total serum AP activity was determined with an enzyme catalytic assay kit (ALP K; Wako Pure Chemicals, Osaka, Japan). The AP isozymes in the serum samples were analyzed by PAGE (AlkPhor system, Jokoh, Tokyo, Japan) in duplicate. IAP as a percentage of total AP was determined electrophotographically by AP isozyme patterns [14]. The gels were stained for AP activity and scanned with a Shimadzu, CS-9300PC densitometer. The inter- and intra-assay CVs were <11.1% and <5.9%, respectively.

ApoB-48 assay. We used a specific enzyme-linked immunosorbent assay to determine apoB-48 [15], because apoB-48 is an appropriate marker for measurement of intestinally derived chylomicrons [12,16]. Briefly, apoB-48 specific monoclonal antibody (4C8) was coated onto 96-well microtiter plates. Standard solutions and serum samples diluted 100-fold were added to each well in duplicate. The bound apoB-48 was detected by the biotin and avidin–horseradish peroxidase complex method. The inter- and intra-assay CVs were <8.4% and <7.9%, respectively.

Other analytical methods. We also measured total apoB that includes apoB-100 and apoB-48, TG, and lipoprotein lipase (LPL) because they are involved in the postprandial TG metabolism. Total apoB is an indicator of LDL, VLDL, and chylomicron levels, and LPL is a key enzyme to remove triglyceride on lipoprotein particles. They were assayed with commercially available kits, ApoB HA Test Wako, TG Test Wako (Wako, Osaka, Japan), and MARKIT-M LPL (Dainippon Pharmaceutical, Osaka, Japan).

Statistical analysis. Differences between the mean measured values of the serum samples before and after the meal were assessed with the paired t test. ANOVA was used to evaluate whether or not the blood group affected the levels of serum markers measured in this study. Significances of individual differences were evaluated using the Scheffé test. Spearman correlation coefficients were used to evaluate whether IAP levels were correlated with other serum markers.

Results

Increased serum marker levels after oral fat intake

The levels of all the measured serum markers were increased 3 h after the high-fat meal (Table 1). The mean serum IAP level had approximately doubled and those of apoB-48 and TG showed 1.6-fold increase. The mean levels of total apoB and LPL increased slightly (~10% and 20%, respectively).

ABO blood groups and secretor/non-secretor phenotypes affect serum IAP levels

The mean serum IAP levels of the secretors were approximately threefold at fasting ($p = 0.0002$) and eightfold 3 h after the meal ($p < 0.0001$) than those of the non-secretors (Table 1). The serum IAP levels of the secretors increased 2.6-fold after the meal; 21.3 ± 14.3 and 56.0 ± 43.5 IU/L before and after the meal, respectively, and those of the non-secretors showed a slight but statistically significant increase; 6.5 ± 1.7 and 6.9 ± 1.7 IU/L, respectively ($p < 0.0001$) (Fig. 1). The LPL activity of the non-secretors was 21% greater than that of the secretors after the meal, but such differences were not observed before the meal. No association with blood types was found in the serum levels of TG or total apoB.

The ABO blood group was also associated with serum IAP levels in both the secretors and the non-secretors

Table 1
Associations of blood groups with serum levels of five serum markers before and after a standardized high-fat meal

Sampling and blood type	*n* (men)	IAP (IU/L)		ApoB-48 (mg/L)		Total apoB (g/L)		TG (mmol/L)		LPL (μg/L)	
		Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
Fasting[a]											
Total	40 (22)	13.9 ± 14.3	0.11[b]	5.2 ± 1.9	<0.0001[b,**]	0.66 ± 0.13	0.02[b,*]	0.86 ± 0.26	<0.0001[b,**]	74.3 ± 22.1	0.001[b,**]
A	10 (5)	6.3 ± 2.8	0.03[c,**]	3.9 ± 1.4	0.0005[c,**]	0.71 ± 0.11	0.21[c]	0.93 ± 0.20	0.76[c]	77.5 ± 13.2	0.33[c]
AB	10 (5)	9.9 ± 5.6		4.4 ± 1.2		0.59 ± 0.12		0.83 ± 0.42		76.2 ± 18.0	
B	10 (6)	15.9 ± 15.7		6.9 ± 2.2		0.68 ± 0.07		0.87 ± 0.21		80.3 ± 16.7	
O	10 (6)	23.7 ± 20.2		5.7 ± 1.2		0.67 ± 0.19		0.81 ± 0.16		63.3 ± 18.0	
Secretor	20 (10)	21.3 ± 17.3	0.0002[d,**]	4.6 ± 1.9	0.02[d,*]	0.69 ± 0.13	0.16[d]	0.85 ± 0.31	0.74[d]	74.7 ± 28.6	0.77[d]
Non-secretor	20 (12)	6.5 ± 1.7		5.8 ± 1.8		0.63 ± 0.13		0.87 ± 0.22		73.9 ± 13.3	
3 h after meal											
Total	40 (22)	31.5 ± 39.3		8.4 ± 4.2		0.74 ± 0.13		1.38 ± 0.40		88.3 ± 22.6	
A	10 (5)	9.7 ± 9.5	0.07[c]	5.0 ± 1.2	<0.0001[c,**]	0.82 ± 0.13	0.09[c]	1.38 ± 0.27	0.99[c]	88.1 ± 20.8	0.17[c]
AB	10 (5)	12.2 ± 8.4		6.1 ± 1.4		0.73 ± 0.14		1.32 ± 0.27		80.0 ± 15.2	
B	10 (6)	51.1 ± 47.9		11.7 ± 4.4		0.74 ± 0.08		1.36 ± 0.27		98.2 ± 26.3	
O	10 (6)	52.9 ± 48.4		10.9 ± 4.2		0.72 ± 0.17		1.41 ± 0.34		76.1 ± 19.3	
Secretor	20 (10)	56.0 ± 43.5	<0.0001[d,**]	9.9 ± 5.3	0.14[d]	0.73 ± 0.13	0.88[d]	1.32 ± 0.50	0.14[d]	80.0 ± 25.9	0.001[d,**]
Non-secretor	20 (12)	6.9 ± 1.7		7.0 ± 2.0		0.74 ± 0.14		1.43 ± 0.27		96.6 ± 15.2	

[a] Serum samples collected before and after the fatty meal were assayed for IAP, apoB-48, total apoB, TG, and LPL.
[b] After the meal, serum levels of all analytes, except for those of IAP activity, increased significantly.
[c] The associations of serum levels of the markers with ABO blood groups were evaluated by ANOVA.
[d] The differences in the serum levels of the markers between in the secretors and in the non-secretors were compared by Mann–Whitney *U* test before and after the meal.
[*] $p < 0.05$.
[**] $p < 0.01$.

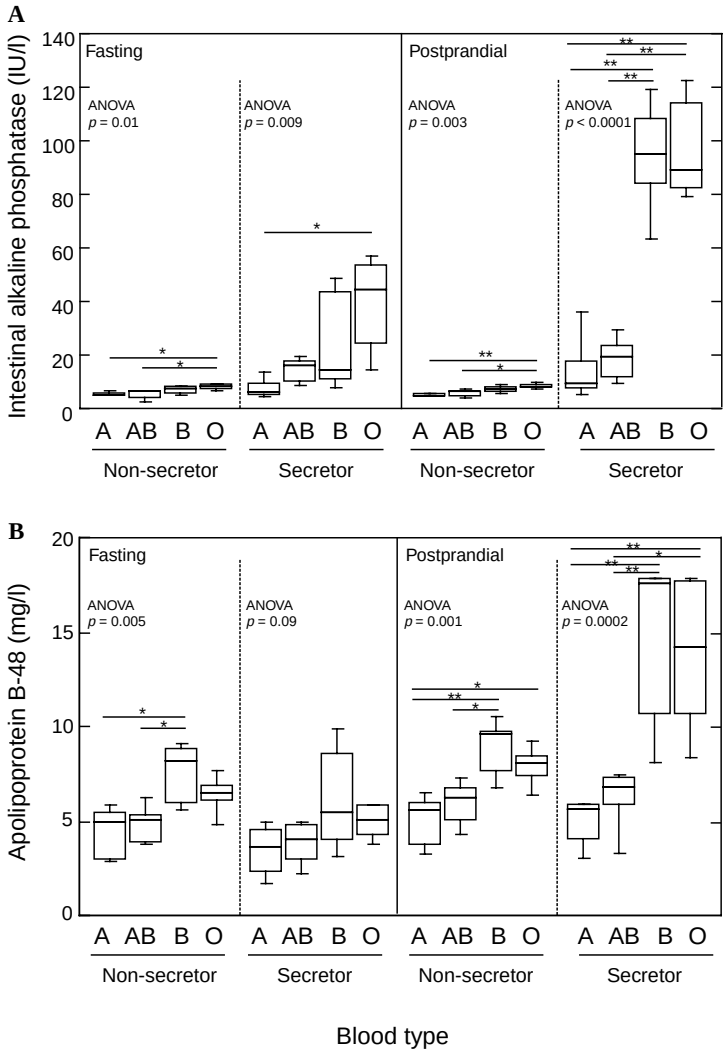

Fig. 1. Associations of ABO blood groups with serum IAP (A) and apoB-48 levels (B). The data were separated according to ABO blood groups and shown as box plots. The center, the top, and the end of each box represent the median, 75th percentile, and 25th percentile of the data, respectively. Error bars indicate the 10th and 90th percentiles of the data. Significant differences among ABO blood types were evaluated by ANOVA and the Scheffé test. $^{*}p < 0.05$; $^{**}p < 0.01$.

(Fig. 2). The serum IAP level was greater in the subjects without blood antigen A (blood groups B and O). These differences are consistent with previous observations [9]. Moreover, in the secretors with blood antigens B and O, the mean IAP levels were increased 3.8- and 2.5-fold, respectively (Fig. 1), while those with blood antigen A showed no significant difference between before and after the fatty meal.

ABO blood group is associated with serum apoB-48 levels

Serum apoB-48 levels were strongly associated with ABO blood groups both before and after the meal (Table 1). Like IAP, serum apoB-48 levels were greater in the subjects with blood groups B and O than in the others. Note that prominent postprandial increases in apoB-48 were observed in the secretors with blood antigens B and O (2.4- and 2.8-fold, respectively).

Association of serum apoB-48 levels with secretor/non-secretor phenotypes

Although the mean postprandial level of apoB-48 was 1.3-fold greater than in the non-secretors before the fatty meal, the difference was only half that seen for IAP (2.6-fold). Moreover, an increase of apoB-48 after the meal (2.15-fold; $p < 0.001$) was observed in the secretors, compared to 1.2-fold in the non-secretors ($p < 0.001$). Thus, secretor status led to a much greater increase after a meal for both apoB-48 and IAP.

Serum IAP and apoB-48 are quantitatively correlated

Spearman rank sum test analyses showed that serum IAP and apoB-48 levels were quantitatively correlated in the secretors both before and after the meal (Fig. 2); the coefficients of correlation before and after the meal were

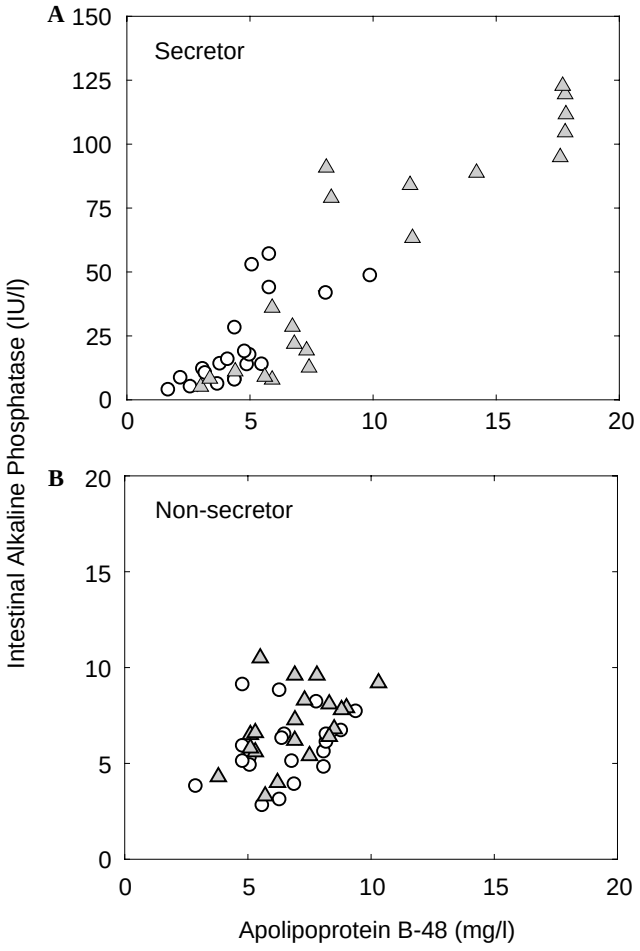

Fig. 2. Relationship between serum IAP and apoB-48 levels before and after a high-fat meal. The open circles and gray triangles indicate the measured values of serum samples before and after the meal, respectively. The coefficients of correlation (Spearman rank sum test) before and after the meal were 0.81 and 0.92 in the secretors (A) and 0.30 and 0.47 in the non-secretors (B), respectively.

0.81 and 0.92, respectively. In the non-secretors, the correlations were weak because of the low IAP levels; the coefficients of correlation before and after the meal were 0.30 and 0.47, respectively. No relationship was observed between the levels of IAP and those of TG, LPL, and total apoB (data not shown).

Discussion

The intestinal and serum levels of IAP, a molecule implicated in chylomicron secretion in the rat [2,5,6], vary among ABO blood groups in humans [9–11]. In this study, we found that IAP and apoB-48 levels were both associated with ABO blood groups and with secretor status. Serum IAP and apoB-48 levels were lower in the subjects with blood antigen A, and serum IAP and apoB-48 were quantitatively correlated in the secretors.

Two hypotheses, not mutually exclusive, have been proposed to explain the association between ABO blood group type and serum IAP concentration. First, Langman et al. [10] reported less AP activity in the intestines of persons with blood antigen A, suggesting a genetic down-regulation of IAP in these individuals. Taking our findings into consideration, we suppose that the ABO blood group affects the expression and/or secretion of IAP and that this regulation consequently changes the efficiency of chylomicron secretion. This hypothesis is supported by the strong correlation between serum IAP and apoB-48 levels on the one hand, and of these markers with blood group types on the others.

Second, IAP is rapidly cleared from the circulation by the liver in animals and humans [17,18], and by other organs in humans [18]. The slow- and fast-moving forms of human IAP separated by electrophoresis have the approximate molecular size of 720 and 150 kDa, respectively, due to the difference of polymerization and differ in the plasma half life by 5-fold (7.5 h for slow-moving form and 1.5 h for fast-moving form) [19]. Thus, there is sufficient variation in plasma forms of IAP that further modification of the enzyme could alter its clearance. Bayer et al. [19] have postulated that this clearance could be regulated through adsorption of IAP by blood group antigen A on human erythrocytes. Since IAP levels are lower in subjects who are blood group A as compared with types B and O, these authors suggested that binding to erythrocytes should lead to more rapid elimination of circulating IAP from the plasma. Erythrocytes produce soluble ABO antigens, and it seems possible that these complexes may further enhance the glycosylation-mediated removal of IAP. It is possible that this process might be regulated either by the type of blood group present on the erythrocytes or other plasma membrane surfaces, e.g., in the liver, or by the secretor status that regulates the appearance of soluble blood groups in body fluids. In support of this latter possibility, the associations of secretor/non-secretor phenotypes with IAP and apoB-48 levels were different from the association with blood group types. IAP levels were much lower than apoB-48 levels in the non-secretors compared to secretors. Considering that ABO blood antigens on erythrocytes bind to IAP [19,20], it seems likely that IAP is rapidly eliminated by erythrocytes from the plasma in non-secretors, whereas the abundant soluble ABO antigens preferentially bind to IAP and thereby prevent the elimination in secretors. Thus, investigators should take secretor/non-secretor phenotypes into consideration when studying IAP in serum [21].

Involvement of IAP in chylomicron formation has been extensively studied in rats [2,4,5], but investigators have differed as to whether the two phenomena are mechanistically related. In the present study, we observed a strong correlation between serum IAP and apoB-48 levels in the secretors, which is consistent with the findings of Malagelada et al. [22] and Domar et al. [21] in humans. Moreover, Linscheer et al.[23] demonstrated the marked reduction of the fatty acid absorption of the small intestine by L-pheynlalanine, an IAP inhibitor. Those findings strongly suggest that IAP is involved in the fat absorption and chylomicron formation. On the other hand, Nalui et al. [24] reported that

the inhibition of chylomicron formation by Pluronic L81 in rats did not change the secretion of IAP into intestinal lymph. It is possible, however, that IAP could participate in the transport of fat droplets, while Pluronic L-81 blocks lipid secretion independent of IAP secretion [6].

ApoB-48 have been used as a static marker for the metabolism of triglyceride-rich lipoprotein, whose increase is a characteristic of the development of metabolic syndrome [12,13]. Simple and reliable apoB-48 assay methods have become available that facilitate its clinical use [15]; however, the association of serum levels of apoB-48 with blood group types is not recognized. We would like to propose incorporating blood type classification into the clinical evaluation of apoB-48 levels that may improve its usefulness and reliability.

In conclusion, we observed that the serum IAP and apoB-48 levels were similarly associated with the ABO blood groups, especially after a fatty meal. These findings indicate that the ABO blood groups might be involved in chylomicron secretion via regulation of the expression and/or secretion of IAP in the intestinal mucosa and change postprandial TG metabolism.

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