Intestinal fatty acid-binding protein, a biomarker of intestinal barrier dysfunction is positively associated with the duration of hyperglycemia

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Objective: To investigate the relationship between serum intestinal fatty acid-binding protein (I-FABP) and hyperglycemia in a cross-sectional study.

Materials and methods: In this present study a total of 280 individuals (158 outpatients and 122 inpatients) suffering with hyperglycemia were recruited during May to September 2019. Clinical information was collected from the hospital information system, that included the duration of hyperglycemia, age, gender, HbA1c, 75-g oral glucose tolerance test including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), fasting C-peptide (FC-pep), 2-hour C-peptide (2hC-pep), fasting insulin (FIns) and 2-hour insulin (2hIns) in all participants, and the morbidity of diabetic complications (retinopathy, neuropathy, and nephropathy) in inpatient subgroup. Further, ΔPG (the difference between 2hPG and FPG), ΔC-pep (the difference between 2hC-pep and FC-pep) and ΔIns (the difference between 2hIns and FIns) were calculated. Serum I-FABP, a biomarker of intestinal barrier (IB) dysfunction, was estimated by ELISA.

Results: Serum I-FABP was significantly associated with duration of hyperglycemia in all participants (β=.333, P<.001) and also in inpatient subgroup (β=.354, P<.001). In the inpatient subgroup, retinopathy positive group had a significantly higher serum I-FABP than retinopathy negative group (P=.001). Besides, serum I-FABP had higher significant association with ΔPG (R=.311, P<.001) than HbA1c (R=.196, P=.001) in all participants, however, this association disappeared in followed multiple linear regression analysis.

Conclusions: Serum I-FABP is positively associated with the duration of hyperglycemia, which suggested that the IB dysfunction got worse with the progression of diabetes.

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Abstract

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Results: Serum I-FABP was significantly associated with duration of hyperglycemia in all participants (β=.333, P<.001) and also in inpatient subgroup (β=.354, P<.001). In the inpatient subgroup, retinopathy positive group had a significantly higher serum I-FABP than retinopathy negative group (P=.001). Besides, serum I-FABP had higher significant association with ΔPG (R=.311, P<.001) than HbA1c (R=.196, P=.001) in all participants, however, this association disappeared in followed multiple linear regression analysis.

Conclusions: Serum I-FABP is positively associated with the duration of hyperglycemia, which suggested that the IB dysfunction got worse with the progression of diabetes.

52 **Keywords:** Intestinal fatty acid-binding protein (I-FABP), Intestinal barrier (IB) dysfunction,

53 Hyperglycemia, Diabetes

Introduction

Diabetes has become a global public health issue with growing morbidity and financial burden in the past decades. Recently, diabetes was considered as a risk factor of worse prognosis in patients with COVID-19[1]. Interestingly, as the most typical clinical features of diabetes, hyperglycemia was confirmed to be an essential predictor of adverse outcomes in diabetic as well as in nondiabetic patients in a previous study[2]. The association between hyperglycemia and adverse outcome in nondiabetic patients is apparent because the reversible hyperglycemia, which is called stress-induced hyperglycemia (SIH), is a secondary symptom of primary disease and a well-known marker of disease severity[3]. However, since hyperglycemia has existed long before other diseases happen in diabetic patients, the relationship between preexisted hyperglycemia and adverse outcome needs to be investigated.

The adverse outcome associated with diabetes can partly explained by the vulnerablity to systemic infection and inflammation in diabetic patients[4]. Nowadays intestinal barrier (IB) dysfunction induced by hyperglycemia[5] was considered to be the underlying mechanism of systemic infection and inflammatory in diabetes. IB is the interface between gut microbiome and human body, preventing gut microbiome and other deleterious intestinal contents coming across the barrier during enteral nutrition absorption, and IB dysfunction will result in translocation of intestinal contents, which could be the direct reason of systemic infection and inflammatory response[6]. In Thaiss' study, hyperglycemia was confirmed to be the independent risk factor of IB dysfunction in animals, furthermore, the association between hyperglycemia and IB dysfunction was observed

to be time-dependent and dose-dependent in vitro[5]. Although the relationship between hyperglycemia and IB dysfunction was clarified in animals and cells-based models[5], the clinical evidence in human was lacking.

In this study, serum concentration of intestinal fatty acid-binding protein (I-FABP) was used to indicate the severity of IB dysfunction. I-FABP is an intracellular protein specifically and abundantly expressed in the intestinal epithelial cells, and its increased serum concentration represents intestinal epithelial cell damage and IB dysfunction[7,8]. As a biomarker of IB dysfunction, I-FABP has been used in patients with necrotizing enterocolitis[9], acute mesenteric ischemia[10], strangulated small bowel obstruction[11], Crohn's disease[12], blunt trauma[13], celiac disease[14], acute pancreatitis[15,16], acute decompensated heart failure[17], chronic renal failure[18], septic shock[19], psoriasis[20] and even physiological stressors induced intestine damage[21]. Generally, the nature of convenience and non-invasion makes serum I-FABP a satisfied method to evaluate IB dysfunction in our study[8,22].

Diabetic and prediabetic patients with different severity and duration of hyperglycemia were recruited and their serum I-FABP was measured in our study. Taken together, our study investigated the relationship between serum I-FABP and hyperglycemia in different dimensions in human.

Materials and methods

Study participants

In this cross-sectional study, participants were recruited from outpatient clinic and inpatient ward of Department of Endocrinology and Metabolism, Wuxi People's Hospital affiliated to Nanjing Medical University. The inclusion criteria for outpatients were those who had been tested hyperglycemia or had diabetes related symptoms within a year without using anti-diabetic drugs, while the inclusion criteria for inpatients were those who had been diagnosed with diabetes and newly admitted to the inpatient ward. However, participants were excluded from the study that had below 18 years of age, SIH, type 1 diabetes, change in the lifestyle within a year such as diet and exercise, pregnant within a year, acute complications of diabetes, severe hepatic, renal or heart insufficiency, acute digestive system disease, abdominal surgery in the past half year and acute infection in the past month.

The present study was approved by the Research Ethics Committee of Wuxi People's Hospital affiliated to Nanjing Medical University (HS2019003). Each participants signed informed consent form. This study was registered at the Chinese Clinical Trial Register Center (ChiCTR1900022026) and carried out from May to September in 2019. All data can be obtained from corresponding authors on demand.

Clinical information

Clinical information was collected from the hospital information system, that included the duration of hyperglycemia, age, gender, glycosylated hemoglobin A1c (HbA1c), 75-g oral glucose

tolerance test including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), fasting C-peptide (FC-pep), 2-hour C-peptide (2hC-pep), fasting insulin (FIns) and 2-hour insulin (2hIns) in all participants, and the morbidity of diabetic complications (retinopathy, neuropathy, and nephropathy) in inpatient subgroup. Further, ΔPG (the difference between 2hPG and FPG), ΔC-pep (the difference between 2hC-pep and FC-pep) and ΔIns (the difference between 2hIns and FIns) were calculated.

Serum I-FABP estimation

All the fasting blood samples collected from patients to perform necessary tests were stored at 2-8°C in the clinical laboratory of Wuxi People's Hospital. Then certain serum samples of enrolled patients were aliquoted and stored at -80°C within eight hours for future research. Serum concentration of I-FABP was estimated in duplicates by ELISA (R&D, Catalog Number DFBP20), as per the standardized protocol, and the estimated mean values were used for further analysis.

Statistical Analysis

Statistical analysis was assessed using SPSS 25 (IBM Corporation, Illinois, USA). Non-parametric tests were performed to determine the normality of continuous variables, whereas the non-normal distribution variables were expressed as median (interquartile range). Then, the difference of non-normal distribution variables between two groups was assessed by Mann-Whitney test, the categorical data was assessed by Chi-Square test, and the relationship between two continuous variables was assessed by Spearman correlation coefficient. Multiple linear regression analysis

was used for further adjusted analysis, and finally all the differences were considered significant at a 5% level.

Results

Serum I-FABP in all participants

The clinical information and serum I-FABP of all participants recruited from outpatient clinic and inpatient ward were tabulated in Table 1.1. The duration of hyperglycemia in outpatients was less than a year, while the median duration of hyperglycemia in inpatients was 10 years. Moreover, compared with outpatients, inpatients had higher age, HbA1c, FPG, 2hPG, ΔPG and I-FABP but lower FC-pep, FIns, 2hC-pep, 2hIns, ΔC-pep and ΔIns.

Then correlation analysis of serum I-FABP showed statistical significance with age, duration of hyperglycemia, HbA1c, FC-pep, 2hPG, 2hC-pep, ΔPG and ΔC-pep but without other metrics (Table 1.2). Further, multivariate linear regression analysis showed that serum I-FABP was positively associated with age and duration of hyperglycemia in all patients (Table 1.3).

Serum I-FABP in outpatient subgroup

Outpatients were divided into prediabetes group and diabetes group according to the latest diagnosis standard of diabetes[23]. The clinical information and serum I-FABP of these two groups were tabulated in Table 2.1. Compared with prediabetes group, diabetes group had higher HbA1c, FPG, FC-pep, 2hPG and ΔPG but lower 2hC-pep, 2hIns, ΔC-pep and ΔIns. However, there was

no statistically significant difference in age, FIns and serum I-FABP between two groups.

Further, the correlation analysis of serum I-FABP was compared with age, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns, however, age was the only metric that statistically correlated with serum I-FABP in outpatient subgroup (Table 2.2).

Serum I-FABP in inpatient subgroup

The correlation analysis in inpatient subgroup showed that serum I-FABP was significantly correlated with age, duration of hyperglycemia, FC-pep, 2hC-pep and ΔPG, but not significantly correlated with other metrics (Table 3.1). However, the duration of hyperglycemia was the only metric that statistically associated with serum I-FABP in the followed multiple linear regression analysis (P<.001) (Table 3.2).

Furthermore, we investigated the relationship between serum I-FABP and diabetic complications (retinopathy, neuropathy, and nephropathy). Inpatients were divided into complication positive group and complication negative group, the differences of serum I-FABP between complication positive and negative group were estimated. The results showed that retinopathy positive group had a higher serum I-FABP than retinopathy negative group (P=.001), while the differences of serum I-FABP in other two complications were not statistically significant (Table 3.3).

Discussion

Previous study confirmed the relationship between hyperglycemia and IB dysfunction in animals and cells-based models[5] and our study added evidence from human to support this relationship. In the present study, we investigated serum I-FABP in diabetic and prediabetic patients who suffered with different severity and duration of hyperglycemia, and our results showed that serum I-FABP was positively associated with the duration of hyperglycemia, which suggested that the IB dysfunction got worse with the progression of diabetes.

IB dysfunction and age

A previous study suggested that IB dysfunction may be an important event in the aging process conserved across a broad range of species.[24] Age-related loss of the heat-shock transcription factor was confirmed to be involved in the IB dysfunction by accelerating decay of the intestinal subapical terminal web and impairing its interactions with cell junctions in C.elegans[25]. However, the relationship between IB dysfunction and age in human was not studied before.

In our study, the severity and duration of hyperglycemia was similar in outpatient subgroup whose hyperglycemia was just found within a year. The correlation analysis showed that age was the only metric that statistically associated with serum I-FABP, which further proved the relationship between IB dysfunction and age, that is the older ones suffered from more severe IB dysfunction in the newly diagnosed diabetic and prediabetic patients.

IB dysfunction and duration of hyperglycemia

202 Thaiss' study confirmed the time-dependent relationship between IB dysfunction and
203 hyperglycemia in vitro[5]. Similarly in our study, multivariate linear regression analysis in all
204 patients showed that serum I-FABP were statistically associated with age and duration of
205 hyperglycemia. And correlation analysis in inpatient subgroup also showed that both age and
206 duration of hyperglycemia were associated with serum I-FABP. However, the association of age
207 disappeared in the followed multivariate linear regression analysis, leaving duration of
208 hyperglycemia the only metric associated with serum I-FABP in inpatient subgroup. As the
209 relationship between IB dysfunction and age discussed above, and age was an associated factor of
210 serum I-FABP. Still, it might be a confounding factor in the relationship between serum I-FABP
211 and the duration of hyperglycemia. As the duration of hyperglycemia was closely the course of
212 diabetes, our results suggested that the IB dysfunction got worse with the progression of diabetes.
213
214 Afterward, we compared the differences of serum I-FABP between complication positive patients
215 and complication negative patients in inpatient subgroup. Among three types of complications,
216 serum I-FABP in retinopathy positive patients was higher than retinopathy negative patients. For
217 retinopathy complication develops with the progression of diabetes, this result further supported
218 the relevance between IB dysfunction and the progression of diabetes.
219
220 The relevance between IB dysfunction and the progression of diabetes was also supported by the
221 relationship between serum I-FABP and islet function, which was indicated by C-pep in our study.
222 The correlation analysis showed that serum I-FABP was negatively associated with FC-pep and

223 2hC-pep in all participants and inpatient subgroup, which indicated that the losing of islet function
224 was accompanied with the aggravation of IB dysfunction. However, this association in the multiple
225 linear regression analysis was found to be insignificant. Since islet dysfunction aggravates with
226 the progression of diabetes, C-pep was considered to be a confounding factor in the relationship
227 between serum I-FABP and duration of hyperglycemia. In addition to islet function, insulin
228 secretion function was also investigated in our study. However, FIns, 2hIns, and ΔIns showed no
229 statistical correlation with serum I-FABP, which indicated that insulin secretion function was not
230 associated with IB dysfunction.
231
232 The relationship between IB dysfunction and duration of hyperglycemia can be explained by the
233 accumulation of advanced glycation end products (AGEs) caused by long standing hyperglycemic
234 state in diabetes. AGEs have been proved to contribute to diabetic complications in many studies,
235 and accumulation of AGEs and activation of their receptors (RAGE) induces a stimulation of
236 NADPH oxidase, reactive oxygen intermediate formation, NF-kB activation and gene
237 transcription, which further lead to sustained inflammatory reaction, cell damage and organ
238 dysfunction[26]. Surprisingly, both accumulation of AGEs and overexpression of RAGE were
239 observed in the gastrointestinal tract of diabetic rats[27], that contributed to IB dysfunction in
240 diabetes.
241
242 **IB dysfunction and severity of hyperglycemia**
243 After time-dependent relationship discussed above, dose-dependent relationship was assessed. As

a widely used metric in the diagnosis and follow-up of diabetes, HbA1c shows the average PG level in the past 2-3 months[23]. Correlation analysis showed a positive correlation between serum I-FABP and HbA1c in all patients, but the relationship was neither observed in followed multiple linear regression analysis nor in subgroups, especially in the outpatient subgroup whose hyperglycemia were just identified and untreated, making HbA1c a perfect metric to indicate the severity of hyperglycemia. Although dose-dependent relationship between hyperglycemia and IB dysfunction had been confirmed in previous study[5], IB dysfunction was not associated with the average PG level in the past 2-3 months in our study, and whether this dose-dependent relationship exits in humans needs to be answered in the future.

Compared with sustained hyperglycemia, glycemic variability causes more severe oxidative stress, showed much closer relationship with diabetes complications that makes glycemic variability a more valuable metric than HbA1c in diabetes[28,29]. Glycemic variability consists of the magnitude of PG excursions and the frequency of the fluctuations. In a large multicenter retrospective study, poorly controlled PG was correlated with worse outcomes in patients with COVID-19 and pre-existing type 2 diabetes[1], which proved the relationship between glycemic variability and adverse outcome in other diseases. In our study, ΔPG was used as an indicator of glycemic variability, our results showed that serum I-FABP was positively related to ΔPG in all participants and inpatient subgroup. In other words, the bigger glycemic variability was accompanied with worse IB dysfunction. And another observational study found that type 2 diabetic patients who incapable of maintaining stable PG were more likely to have IB injury[30]. Since ΔPG was not enough to show

the whole day glycemic variability, better designed studies were needed to further estimate the relationship between glycemic variability and IB dysfunction. However, in our study the correlation disappeared in the followed multiple linear regression analysis, making ΔPG a confounding factor in the relationship between serum I-FABP and duration of hyperglycemia.

Perspective of the study

Based on the results, we speculated that IB dysfunction happened and developed along with the progression of diabetes. The relationship between hyperglycemia and IB dysfunction offered a new perspective to the clinical phenomenon of diabetes. On one hand, impaired IB enhanced the influx and systemic dissemination of intestinal bacteria, which explained the vulnerability to the infection in diabetic patients[31]. On the other hand, more intestinal contents and bacterial metabolites came across the impaired IB and went into the blood circulation, causing systemic chronic oxidative stress and inflammatory, which not only promoted diabetes complications[32,33] but also contributed to the diabetes directly[34].

The association between hyperglycemia and IB dysfunction was clarified in our study, but the causal relationship between them is yet to be discussed. Previous studies showed that nondiabetic patients who suffered from SIH was more likely to get diabetes in the future[35,36], which brought about a confusing hypothesis that, reversible hyperglycemia could cause irreversible hyperglycemia. It is well recognized that some primary diseases like sepsis, trauma, burns and surgery, which induce SIH[3], could directly cause IB dysfunction[37]. On mechanism,

hyperglycemia-induced IB dysfunction allows for enhanced influx of intestinal contents and the induced infection and inflammatory further intensifies hyperglycemia[3]. Surprisingly, IB dysfunction built a bridge between SIH and diabetes, that is, IB dysfunction not only resulted from but also contributed to hyperglycemia. When improving IB function by treating primary disease exactly alleviated SIH[3], the interventions aiming to improve IB function might be a promising treatment strategy to diabetes.

Besides the new therapeutic approach for hyperglycemia, some wildly used anti-diabetic drugs already showed protective potential for IB. GLP-1, which controlled the meal-related glycemic excursions, alleviated the gut inflammation and promoted the repairment of intestinal epithelial cells[38,39], similar protective effect have also been observed with metformin[40] and berberine[41]. Compared with IB, gut microbiome has drawn more attention in diabetes. Although quite a few studies showed that the gut microbiome influenced the development of diabetes[42,43], the underlying mechanism is still unclear. As the interface between gut microbiome and diabetic patients, IB was a promising candidate for mechanism research.

This study had some limitations: first, participants recruited from inpatient ward were admitted to hospital for different pathological conditions, including but not limited to poor glucose control and diabetes complications. The influence on serum I-FABP came from all those conditions hadn't been thoroughly estimated. Second, participants recruited from inpatient ward had been treated with anti-diabetic drugs; whether those drugs affect the serum I-FABP was not investigated. Third,

patients who suffered from severe nephropathy complications were not included in our study, for they were admitted to Nephrology Department rather than Department of Endocrinology and Metabolism that resulted in selection bias.

Conclusions

To the best of our knowledge this study investigated serum I-FABP in diabetic and prediabetic patients for the first time, and results showed that serum I-FABP is positively associated with the duration of hyperglycemia, which suggested that the IB dysfunction got worse with the progression of diabetes. Considering the participation of gut microbiome in the etiology of diabetes, it was hard to ignore the role of IB, whose dysfunction might cause oxidative stress, systemic inflammatory and infection. By highlighting IB in diabetes related research, we proved a new perspective to interpret this familiar disease.

Acknowledgements

This manuscript has been edited and proofread by *Medjaden* Bioscience Limited.

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Abbreviation

I-FABP: intestinal fatty acid-binding protein

IB: intestinal barrier

HbA1c: glycosylated hemoglobin A1c

OGTT: oral glucose tolerance test

PG: plasma glucose

C-pep: C-peptide

Ins: insulin

FPG: fasting plasma glucose

FC-pep: fasting C-peptide

FIns: fasting insulin

2hPG: 2-hour plasma glucose

2hC-pep: 2-hour C-peptide

2hIns: 2-hour insulin

ΔPG: the difference between 2hPG and FPG

ΔC-pep: the difference between 2hC-pep and FC-pep

ΔIns: the difference between 2hIns and FIns

SIH: stress-induced hyperglycemia

AGEs: advanced glycation end products

RAGE: AGEs receptor

Table 1(on next page)

Table 1.1. Clinical information and serum I-FABP between participants recruited form outpatient clinic and inpatient ward

Table 1.1. Clinical information and serum I-FABP between participants recruited form outpatient clinic and inpatient ward

	Outpatient	Inpatient	P-value
Male/Female, n	90/68	72/50	.807
Age, y **	47.5 (33, 56)	56 (51.75, 67)	<.001
Duration, y **	< 1	10 (3, 14)	<.001
HbA1c, %**	5.9 (5.5, 6.5)	8.0 (6.8, 9.3)	<.001
FPG, mmol/L *	6.57 (5.77, 8.04)	7.43 (5.86, 9.08)	.037
FC-pep, ng/mL **	2.69 (1.92, 3.45)	1.92 (1.29, 2.67)	<.001
FIns, mu/L *	10.66 (6.29, 14.74)	7.77 (5.21, 12.74)	.020
2hPG, mmol/L **	10.55 (7.87, 14.71)	18.97 (14.37, 21.38)	<.001
2hC-pep, ng/mL **	9.22 (7.03, 12.39)	5.19 (3.59, 7.69)	<.001
2hIns, mu/L **	55.34 (35.06, 109.25)	38.11 (21.67, 69.28)	.001
ΔPG, mmol/L **	3.80 (1.91, 7.16)	10.32 (6.71, 12.95)	<.001
ΔC-pep, ng/mL **	6.78 (4.27, 9.36)	3.33 (2.13, 5.17)	<.001
ΔIns, mu/L **	47.02 (26.69, 91.97)	30.51 (16.84, 56.10)	.002
I-FABP, pg/mL**	1289 (909, 1629)	1831 (1243, 2642)	<.001

I-FABP = intestinal fatty acid-binding protein, FPG = fasting plasma glucose, FC-pep = fasting C-peptide, FIns = fasting insulin, 2hPG = 2-hour plasma glucose, 2hC-pep = 2-hour C-peptide, 2hIns = 2-hour insulin, ΔPG = 2hPG – FPG, ΔC-pep = 2hC-pep – FC-pep, ΔIns = 2hIns – FIns.

* P<.05. ** P<.01.

Table 2(on next page)

Table 1.2. Correlation analysis of serum I-FABP with age, hyperglycemia duration, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in all participants

Table 1.2. Correlation analysis of serum I-FABP with age, hyperglycemia duration, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in all participants

		R	P-value
I-FABP	Age **	.398	<.001
	Duration **	.413	<.001
	HbA1c **	.196	.001
	FPG	-.019	.755
	FC-pep **	-.220	<.001
	FIns	-.072	.282
	2hPG **	.250	<.001
	2hC-pep **	-.214	<.001
	2hIns	-.075	.265
	ΔPG **	.311	<.001
	ΔC-pep **	-.171	.004
	ΔIns	-.058	.392

I-FABP = intestinal fatty acid-binding protein, FPG = fasting plasma glucose, FC-pep = fasting C-peptide, FIns = fasting insulin, 2hPG = 2-hour plasma glucose, 2hC-pep = 2-hour C-peptide, 2hIns = 2-hour insulin, ΔPG = 2hPG – FPG, ΔC-pep = 2hC-pep – FC-pep, ΔIns = 2hIns – FIns.

** P<.001.

Table 3(on next page)

Table 1.3. Multiple linear regression in all participants

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		B	β	t	P-value
I-FABP	Duration **	53.519	.333	5.436	<.001
	Age **	13.857	.198	3.225	.001

I-FABP = intestinal fatty acid-binding protein.

** P<.01.

Table 4(on next page)

Table 2.1. Clinical information and serum I-FABP between different courses of diabetes in outpatient subgroup

Table 2.1. Clinical information and serum I-FABP between different courses of diabetes in outpatient subgroup

	Prediabetes	Diabetes	P-value
Male/Female, n **	42/53	48/15	<.001
Age, y	45 (32, 57)	49 (34, 55)	.790
HbA1c, % **	5.5 (5.3, 5.8)	6.9 (6.4, 9.1)	<.001
FPG, mmol/L **	5.94 (5.41, 6.47)	8.54 (7.64, 10.89)	<.001
FC-pep, ng/mL **	2.39 (1.86, 3.16)	2.97 (2.29, 3.62)	.004
FIns, mu/L	10.21 (5.91, 14.36)	11.98 (7.37, 15.13)	.136
2hPG, mmol/L **	8.46 (6.93, 10.28)	15.73 (13.55, 19.25)	<.001
2hC-pep, ng/mL **	9.96 (7.61, 12.83)	7.35 (5.89, 11.15)	.001
2hIns, mu/L **	64.26 (42.18, 122.03)	46.56 (28.78, 69.34)	.003
ΔPG, mmol/L **	2.52 (1.00, 4.00)	7.28 (4.81, 9.21)	<.001
ΔC-pep, ng/mL **	7.56 (5.57, 10.36)	4.63 (3.03, 7.96)	<.001
ΔIns, mu/L **	57.25 (33.78, 105.98)	34.82 (18.20, 58.76)	<.001
I-FABP, pg/mL	1354 (948, 1634)	1231 (883, 1604)	.442

I-FABP = intestinal fatty acid-binding protein, FPG = fasting plasma glucose, FC-pep = fasting C-peptide, FIns = fasting insulin, 2hPG = 2-hour plasma glucose, 2hC-pep = 2-hour C-peptide, 2hIns = 2-hour insulin, ΔPG = 2hPG – FPG, ΔC-pep = 2hC-pep – FC-pep, ΔIns = 2hIns – FIns.

** P<.01.

Table 5(on next page)

Table 2.2. Correlation analysis of serum I-FABP with age, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in outpatient subgroup

Table 2.2. Correlation analysis of serum I-FABP with age, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in outpatient subgroup

		R	P-value
I-FABP	Age **	.299	<.001
	HbA1c	-.027	.734
	FPG	-.052	.515
	FC-pep	.031	.696
	FIns	.010	.899
	2hPG	-.025	.757
	2hC-pep	.104	.197
	2hIns	.063	.435
	ΔPG	.003	.973
	ΔC-pep	.103	.199
	ΔIns	.080	.322

I-FABP = intestinal fatty acid-binding protein, FPG = fasting plasma glucose, FC-pep = fasting C-peptide, FIns = fasting insulin, 2hPG = 2-hour plasma glucose, 2hC-pep = 2-hour C-peptide, 2hIns = 2-hour insulin, ΔPG = 2hPG – FPG, ΔC-pep = 2hC-pep – FC-pep, ΔIns = 2hIns – FIns.

** P<.01.

Table 6(on next page)

Table 3.1. Correlation analysis of serum I-FABP with age, hyperglycemia duration, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in inpatient subgroup

Table 3.1. Correlation analysis of serum I-FABP with age, hyperglycemia duration, HbA1c, FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep and ΔIns in inpatient subgroup

		R	P-value
I-FABP	Age **	.286	0.001
	Duration **	.350	<0.001
	HbA1c	.045	.625
	FPG	-.126	.168
	FC-pep **	-.304	.001
	FIns	-.145	.244
	2hPG	.149	.105
	2hC-pep **	-.241	.008
	2hIns	-.219	.081
	ΔPG **	.250	.006
	ΔC-pep	-.163	.076
	ΔIns	-.209	.097

I-FABP = intestinal fatty acid-binding protein, FPG = fasting plasma glucose, FC-pep = fasting C-peptide, FIns = fasting insulin, 2hPG = 2-hour plasma glucose, 2hC-pep = 2-hour C-peptide, 2hIns = 2-hour insulin, ΔPG = 2hPG – FPG, ΔC-pep = 2hC-pep – FC-pep, ΔIns = 2hIns – FIns.

** P<.01.

Table 7 (on next page)

Table 3.2 Multiple linear regression in inpatient subgroup

Table 3.2 Multiple linear regression in inpatient subgroup

		B	β	t	P-value
I-FABP	Duration **	59.986	.354	4.073	<.001

I-FABP = intestinal fatty acid-binding protein.

** P<.01.

Table 8(on next page)

Table 3.3 Relationship between serum I-FABP and diabetic complications in inpatient subgroup

Table 3.3 Relationship between serum I-FABP and diabetic complications in inpatient subgroup

Complications	Positive cases (%)	I-FABP		
		Positive	Negative	P-value
Retinopathy **	48 (39.3)	2164 (1749, 3262)	1585 (1168, 2467)	.001
Neuropathy	51 (41.8)	1949 (1373, 2953)	1697 (1169, 2617)	.126
Nephropathy	34 (27.9)	1836 (1206, 2719)	1829 (1256, 2638)	.833

I-FABP = intestinal fatty acid-binding protein.

** P<.01.