Intestinal fatty acid-binding protein, a biomarker of intestinal barrier dysfunction, increases with the progression of type 2 diabetes

Yifeng Wang [1, 2], **Licheng Ding** [3], **Jiayue Yang** [4], **Lijun Liu** [Corresp., 1], **Liang Dong** [Corresp. 5]

[1] Department of Emergency and Critical Care Medicine, Second Affiliated Hospital of Soochow University, Soochow, China

[2] Department of Critical Care Medicine, Wuxi People's Hospital affiliated to Nanjing Medical University, Wuxi, China

[3] Department of Emergency Medicine, Affiliated Hospital of Jiangnan University, Wuxi, China

[4] Department of Endocrinology and Metabolism, Wuxi People's Hospital affiliated to Nanjing Medical University, Wuxi, China

[5] Department of Critical Care Medicine, Taizhou Central Hospital Taizhou University, Taizhou, China

Corresponding Authors: Lijun Liu, Liang Dong
Email address: liulijun@suda.edu.cn, dongliangphd@gmail.com

Objective: To investigate serum intestinal fatty acid-binding protein (I-FABP) in two groups of patients with different duration of hyperglycemia in a cross-sectional study.

Materials and methods: In the present study, a total of 280 individuals (158 outpatients and 122 inpatients) suffering from hyperglycemia were recruited between May and September 2019. The clinical information of all participants was collected from the hospital information system, including the duration of hyperglycemia, age, gender, 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 addition, the morbidity of diabetic complications (retinopathy, neuropathy, and nephropathy) in the inpatient group was determined. Furthermore, the difference between 2hPG and FPG (ΔPG), the difference between 2hC-pep and FC-pep (ΔC-pep), and the difference between 2hIns and FIns (ΔIns) were calculated. The level of serum I-FABP, a biomarker of intestinal barrier (IB) dysfunction, was estimated by an enzyme-linked immunosorbent assay.

Results: For the outpatient group, the median duration of hyperglycemia was less than a year; the serum I-FABP level was positively correlated with age ($R = 0.299$, $P < 0.001$). For the inpatient group, the median duration of hyperglycemia was ten years; correlation analysis showed that the serum I-FABP level was positively associated with age and ΔPG ($R = 0.286$, $P = 0.001$; $R = 0.250$, $P = 0.006$, respectively) while negatively associated with FC-pep and 2hC-pep ($R = -0.304$, $P = 0.001$; $R = -0.241$, $P = 0.008$, respectively); multiple linear regression analysis showed that the serum I-FABP level was positively associated with the duration of hyperglycemia ($\beta = 0.362$, $P < 0.001$); moreover, patients with retinopathy had a significantly higher I-FABP level than those without retinopathy ($P = 0.001$).

Conclusions: In the outpatients whose duration of hyperglycemia was less than a year, the serum I-FABP level was positively associated with age. In the inpatients with different courses of diabetes, the serum I-FABP level was positively associated with the duration of hyperglycemia and glycemic variability but negatively associated with islet beta-cell function; moreover, the serum I-FABP level was higher in patients with retinopathy than in those without retinopathy, suggesting that the IB dysfunction got worse with the progression of diabetes.

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Yifeng Wang[1, 2], Licheng Ding[3], Jiayue Yang[4], Lijun Liu[1], Liang Dong[5]

[1] Department of Emergency and Critical Care Medicine, Second Affiliated Hospital of Soochow University, No. 1055 Sanxiang Road, Soochow, 215004, Jiangsu, China

[2] Department of Critical Care Medicine, Wuxi People's Hospital affiliated to Nanjing Medical University, No. 299 Qingyang Road, Wuxi, 214023, Jiangsu, China

[3] Department of Emergency Medicine, Affiliated Hospital of Jiangnan University, No. 200 Huihe Road, Wuxi, 214062, Jiangsu, China

[4] Department of Endocrinology and Metabolism, Wuxi People's Hospital affiliated to Nanjing Medical University, No. 299 Qingyang Road, Wuxi, 214023, Jiangsu, China

[5] Department of Critical Care Medicine, Taizhou Central Hospital affiliated to Taizhou University, No. 999 Donghai Avenue, Taizhou, 318000, Zhejiang, China

Corresponding authors:

(1) Lijun Liu

Department of Emergency and Critical Care Medicine, Second Affiliated Hospital of Soochow University, No. 1055 Sanxiang Road, Soochow, 215004, Jiangsu, China

E-mail: liulijun@suda.edu.cn

Contact number: +8613962192756

(2) Liang Dong

Department of Critical Care Medicine, Taizhou Central Hospital affiliated to Taizhou University,

No. 999 Donghai Avenue, Taizhou, 318000, Zhejiang, China

E-mail: dongliangphd@gmail.com

Contact number: +8613812281996

Abstract

Objective: To investigate serum intestinal fatty acid-binding protein (I-FABP) in two groups of patients with different duration of hyperglycemia in a cross-sectional study.

Materials and methods: In the present study, a total of 280 individuals (158 outpatients and 122 inpatients) suffering from hyperglycemia were recruited between May and September 2019. The clinical information of all participants was collected from the hospital information system, including the duration of hyperglycemia, age, gender, 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 addition, the morbidity of diabetic complications (retinopathy, neuropathy, and nephropathy) in the inpatient group was determined. Furthermore, the difference between 2hPG and FPG (ΔPG), the difference between 2hC-pep and FC-pep (ΔC-pep), and the difference between 2hIns and FIns (ΔIns) were calculated. The level of serum I-FABP, a biomarker of intestinal barrier (IB) dysfunction, was estimated by an enzyme-linked immunosorbent assay.

Results: For the outpatient group, the median duration of hyperglycemia was less than a year; the serum I-FABP level was positively correlated with age ($R = 0.299$, $P < 0.001$). For the inpatient group, the median duration of hyperglycemia was ten years; correlation analysis showed that the serum I-FABP level was positively associated with age and ΔPG ($R = 0.286$, $P = 0.001$; $R = 0.250$, $P = 0.006$, respectively) while negatively associated with FC-pep and 2hC-pep ($R = -0.304$, $P =$

0.001; R = -0.241, P = 0.008, respectively); multiple linear regression analysis showed that the serum I-FABP level was positively associated with the duration of hyperglycemia (β = 0.362, P < 0.001); moreover, patients with retinopathy had a significantly higher I-FABP level than those without retinopathy (P = 0.001).

Conclusions: In the outpatients whose duration of hyperglycemia was less than a year, the serum I-FABP level was positively associated with age. In the inpatients with different courses of diabetes, the serum I-FABP level was positively associated with the duration of hyperglycemia and glycemic variability but negatively associated with islet beta-cell function; moreover, the serum I-FABP level was higher in patients with retinopathy than in those without retinopathy, suggesting that the IB dysfunction got worse with the progression of diabetes.

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

65 Hyperglycemia, Progression of diabetes

Introduction

Diabetes has become a global public health issue with a growing morbidity and financial burden in the past few decades. Recently, diabetes has been considered as a risk factor of a worse prognosis in patients with COVID-19[1]. Interestingly, as the most typical clinical feature of diabetes, hyperglycemia has been 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 outcomes in nondiabetic patients is apparent because reversible hyperglycemia, also known as stress-induced hyperglycemia (SIH), is a secondary symptom of primary disease and a well-known marker of disease severity[3]. However, since hyperglycemia exists long before other diseases appear in diabetic patients, the relationship between preexisting hyperglycemia and adverse outcomes needs to be investigated.

Adverse outcomes associated with diabetes can partly be explained by the vulnerablity of diabetic patients to systemic infection and inflammatory response[4]. Nowadays, intestinal barrier (IB) dysfunction induced by hyperglycemia[5] is considered to be the underlying mechanism of systemic infection and inflammatory response in diabetic patients. The IB is the interface between the gut microbiome and the human body, it prevents the gut microbiome and other deleterious intestinal contents from crossing the barrier during enteral nutrition absorption. In addition, IB dysfunction results in the translocation of intestinal contents, which could be the direct cause of systemic infection and inflammatory response[6]. In a study by Thaiss, hyperglycemia was confirmed to be an independent risk factor for 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 has been clarified in animals and cell-based models[5], the clinical evidence in humans is lacking.

In this study, the 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 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 determination 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 stressor-induced intestinal damage[21]. In addition to serum I-FABP, many other biomarkers are used to measure IB function[8,22]. However, in this study, the serum I-FABP level was determined to evaluate IB dysfunction as it is convenient to measure in a noninvasive manner.

Diabetic and prediabetic patients with different severities and durations of hyperglycemia were recruited, and their serum I-FABP levels were measured in this study.

Materials and methods

Study participants

In this cross-sectional study, participants were recruited from the outpatient clinic and the inpatient ward of the Department of Endocrinology and Metabolism, Wuxi People's Hospital affiliated to Nanjing Medical University. The outpatients were included in this study if they had been tested to be hyperglycemic or had diabetes-related symptoms within a year without taking antidiabetic drugs. The inpatients were included in this study if they had been diagnosed with diabetes and were newly admitted to the inpatient ward. However, participants were excluded from this study if they were younger than 18 years old; had SIH, type 1 diabetes, or a change in lifestyle (e.g., diet or exercise) in the past year; were pregnant in the past year; or had acute complications of diabetes, severe hepatic, renal, or heart insufficiency, acute digestive system disease, or abdominal surgery in the past half year or acute infection in the past month. All patients who agreed to this study and met the inclusion criteria were included in the analysis. Most conditions causing an increase in the serum I-FABP level were excluded according to the criteria, which might have caused a selection bias. Patients who suffered from complications of severe nephropathy were not included in this study. They were admitted to the Nephrology Department rather than the Department of Endocrinology and Metabolism, which resulted in a selection bias.

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

130

131 **Clinical information**

132 The clinical information of all participants was collected from the hospital information system,
133 including the duration of hyperglycemia, age, gender, hemoglobin A1c (HbA1c), 75-g oral glucose
134 tolerance test including fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), fasting C-
135 peptide (FC-pep), 2-hour C-peptide (2hC-pep), fasting insulin (FIns), and 2-hour insulin (2hIns).
136 In addition, the morbidity of diabetic complications (retinopathy, neuropathy, and nephropathy) in
137 the inpatient group was determined. Furthermore, the difference between 2hPG and FPG (ΔPG),
138 the difference between 2hC-pep and FC-pep (ΔC-pep), and the difference between 2hIns and FIns
139 (ΔIns) were calculated.

140

141 **Serum I-FABP estimation**

142 All of the fasting blood samples collected from the patients to perform the necessary tests were
143 stored at 2–8 °C in the clinical laboratory of Wuxi People's Hospital. Then certain serum samples
144 of the enrolled patients were aliquoted and stored at -80 °C within 8 hours for future research. The
145 serum concentration of I-FABP was estimated in duplicate by enzyme-linked immunosorbent
146 assay (R&D, USA and Canada, Catalog Number DFBP20) according to the standardized protocol,
147 and the estimated mean values were used for further analysis.

148

149 **Statistical analysis**

Statistical analysis was assessed using SPSS 25 (IBM Corporation, Chicago, IL, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Variables with a non-normal distribution were summarized by the median and interquartile range. Differences between two groups of continuous variables with non-normal distributions were assessed by the Mann-Whitney test. Differences between categorical variables were assessed by the chi-squared test. The relationships between two continuous variables were assessed by the Spearman correlation coefficient. Logarithmic transformation was performed when necessarily. The associations showing a P-value < 0.05 in the correlation analysis were included in the multiple linear regression analysis. Only those metrics with a P-value < 0.05 were kept in the final multiple linear regression models with stepwise variable selection. Finally, all of the differences were considered significant at a 5% level.

Results

Serum I-FABP in the outpatient group

The outpatients were divided into prediabetes group and diabetes group according to the latest diagnosis standards for diabetes[23]. The clinical information and serum I-FABP levels of these two groups are tabulated in Table 1. Compared with the prediabetes group, the diabetes group had a higher HbA1c, FPG, FC-pep, 2hPG, and ΔPG but a lower 2hC-pep, 2hIns, ΔC-pep, and ΔIns. However, there were no statistically significant differences in age, FIns, or serum I-FABP between these two groups.

171 Furthermore, the correlation analysis of the serum I-FABP level was compared with age, HbA1c,
172 FPG, FC-pep, FIns, 2hPG, 2hC-pep, 2hIns, ΔPG, ΔC-pep, and ΔIns. However, age was the only
173 metric that was statistically correlated with the serum I-FABP level in the outpatient group (Table
174 2).
175
176 **Serum I-FABP in the inpatient group**
177 The correlation analysis for the inpatient group showed that the serum I-FABP level was
178 significantly correlated with age, duration of hyperglycemia, FC-pep, 2hC-pep, and ΔPG but not
179 significantly correlated with the other metrics. However, the duration of hyperglycemia was the
180 only metric that was statistically associated with the serum I-FABP level in the multiple linear
181 regression analysis (Table 3).
182
183 Finally, we investigated the relationship between the serum I-FABP level and diabetic
184 complications (retinopathy, neuropathy, and nephropathy). The inpatients were divided into
185 complication-positive group and complication-negative group, and the differences of the serum I-
186 FABP level between the complication-positive group and the complication-negative group were
187 estimated. The results showed that the retinopathy-positive group had a higher serum I-FABP level
188 than the retinopathy-negative group, while the differences of the serum I-FABP level for the two
189 other complications were not statistically significant (Table 4).
190
191 **Serum I-FABP in all participants**

192 The clinical information and serum I-FABP levels of all participants recruited from the outpatient
193 clinic and the inpatient ward are tabulated in Table 5. The median duration of hyperglycemia was
194 less than a year for the outpatients, while it was ten years for the inpatients. Moreover, compared
195 with the outpatients, the inpatients had higher age, HbA1c, FPG, 2hPG, ΔPG, and I-FABP but
196 lower FC-pep, FIns, 2hC-pep, 2hIns, ΔC-pep, and ΔIns.
197
198 Next, correlation analysis of the serum I-FABP level showed a statistical significance with age,
199 duration of hyperglycemia, HbA1c, FC-pep, 2hPG, 2hC-pep, ΔPG, and ΔC-pep. Furthermore,
200 multivariate linear regression analysis showed that the serum I-FABP level was positively
201 associated with the age and the duration of hyperglycemia in all participants (Table 6).
202

203 Discussion

204 A previous study has confirmed the relationship between hyperglycemia and IB dysfunction in
205 animals and cell-based models[5], and our study added evidence from humans to support this
206 relationship. In the present study, we investigated the serum I-FABP levels in diabetic and
207 prediabetic patients who suffered from different severities and durations of hyperglycemia. Our
208 results showed that in the outpatients whose duration of hyperglycemia was less than a year, the
209 serum I-FABP level was positively associated with age. In the inpatients with different courses of
210 diabetes, the serum I-FABP level was positively associated with the duration of hyperglycemia
211 and glycemic variability but negatively associated with islet beta-cell function; moreover, the
212 serum I-FABP level was higher in patients with retinopathy than in those without retinopathy,

213 suggesting that the IB dysfunction got worse with the progression of diabetes.

214

215 **IB dysfunction and severity of hyperglycemia: the serum I-FABP level was not associated**
216 **with FPG, 2hPG, or HbA1c in outpatients.**

217 The study by Thaiss confirmed the dose-dependent relationship between IB dysfunction and
218 hyperglycemia *in vitro*[5]. Since hyperglycemia in the outpatient group was just identified within a
219 year and untreated, this group was suitable for investigation of the relationship between
220 hyperglycemia severity and IB dysfunction. FPG and 2hPG show instantaneous plasma glucose
221 (PG) levels, while HbA1c shows the average PG level in the past 2–3 months[23]. These three metrics
222 were used to determine the severity of hyperglycemia in this study. Unfortunately, none of them
223 showed a statistical correlation with the serum I-FABP level in the outpatient group, and
224 correlation analysis of the inpatient group showed similar results.

225

226 These negative results might be explained by the lower severity of hyperglycemia in our clinical
227 study compared with the *in vitro* study by Thaiss. In their *in vitro* study, IB dysfunction was
228 observed at a glucose level of 8 g/L (about 44 mmol/L)[5], which is rarely achieved in clinical
229 patients. In other words, the hyperglycemia in our study was not severe enough to cause a statistical
230 difference in the serum I-FABP level. Therefore, a well-designed study in humans is needed in the
231 future to answer the dose-dependent relationship between IB dysfunction and hyperglycemia.

232

233 **IB dysfunction and duration of hyperglycemia: the serum I-FABP level was associated with**

the duration of hyperglycemia in inpatients.

After dose-dependent relationship discussed above, time-dependent relationship was assessed, the relationship between IB dysfunction and the duration of hyperglycemia was investigated in the study. The median duration of hyperglycemia was less than a year for the outpatient group, while it was ten years for the inpatient group. For the inpatient group, the serum I-FABP level was statistically associated with the duration of hyperglycemia both according to the correlation analysis and the multivariate linear regression analysis.

The relationship between IB dysfunction and the duration of hyperglycemia can be explained by the accumulation of advanced glycation end products (AGEs) caused by the long-standing hyperglycemic state in diabetes. AGEs have been demonstrated to contribute to diabetic complications in many studies, and the accumulation of AGEs and the activation of their receptors (RAGE) induce NADPH oxidase stimulation, reactive oxygen intermediate formation, nuclear factor-κB activation, and gene transcription, which further lead to a sustained inflammatory reaction, cell damage, and organ dysfunction[24]. Surprisingly, both the accumulation of AGEs and the overexpression of RAGE were observed in the gastrointestinal tract of diabetic rats[25], which contributes to IB dysfunction in diabetes.

IB dysfunction and progression of diabetes: the serum I-FABP level was associated with retinopathy, glycemic variability and islet beta-cell dysfunction in inpatients.

As a result of sustained hyperglycemia, diabetic complications develop with the progression of

255 diabetes. In this study, the serum I-FABP level was higher in patients with retinopathy than in
256 those without retinopathy in the inpatient group. As retinopathy is a complication that develops
257 with the progression of diabetes, this result suggested that the IB dysfunction got worse with the
258 progression of diabetes. Unfortunately, patients who suffered from severe nephropathy were not
259 included in this study, this partly explained why the serum I-FABP level was not higher in the
260 patients with neuropathy or nephropathy.
261
262 Previous studies have found that glycemic variability is closely related to diabetic complications.
263 Glycemic variability consists of the magnitude of PG excursions and the frequency of the
264 fluctuations. Compared with sustained hyperglycemia, glycemic variability has more deleterious
265 effects in the pathogenesis of diabetic complications[26,27]. An observational study has found that
266 type 2 diabetic patients incapable of maintaining stable PG levels were more likely to have IB
267 injury[28], in other words, glycemic variability might be associated with IB dysfunction. In this
268 study, ΔPG was used to indicate the glycemic variability, and the results showed that the serum I-
269 FABP level was positively correlated with ΔPG in the inpatient group. Taken together, IB
270 dysfunction was related to glycemic variability and was aggravated with the progression of
271 diabetes. Since ΔPG is not enough to show the whole day glycemic variability, better designed
272 studies are needed to further estimate the relationship between glycemic variability and IB
273 dysfunction.
274
275 In addition, islet beta-cell dysfunction advances with the progression of diabetes[29]. In this study,

276 the serum C-pep and insulin levels were used to indicate islet beta-cell function. The results
277 showed that the serum I-FABP level was negatively associated with the C-pep (FC-pep and 2hC-
278 pep) levels in the inpatient group. However, there was no statistical correlation between the serum
279 I-FABP and insulin (FIns and 2hIns) levels. C-pep is secreted from beta cells at an equimolar
280 concentration as insulin, however, the half-life of C-pep is longer than that of insulin,[30] which
281 makes C-pep a better metric for islet beta-cell function. In this study, the investigation of C-pep
282 suggested that the aggravation of IB dysfunction was accompanied by the loss of islet beta-cell
283 function in the progression of diabetes.
284
285 Although the serum I-FABP level was correlated with ΔPG, FC-pep, and 2hC-pep, these
286 associations disappeared in the multivariate linear regression analysis. Given the roles of diabetic
287 complications, glycemic variability, and advancing islet beta-cell dysfunction in the progression
288 of diabetes, ΔPG, FC-pep, and 2hC-pep were considered to be confounding factors in the
289 relationship between the serum I-FABP level and the duration of hyperglycemia. Since the
290 duration of hyperglycemia closely followed the course of diabetes, this study suggested that the
291 IB dysfunction got worse with the progression of diabetes.
292
293 **IB dysfunction and age: the serum I-FABP level was positively correlated with age in**
294 **outpatients and inpatients.**
295 In the outpatient group, without the influence of the duration of hyperglycemia, the serum I-FABP
296 level was positively correlated with age, suggesting that the older patients suffered from more

297 severe IB dysfunction in the newly diagnosed diabetic and prediabetic patients. A previous study
298 has found that IB dysfunction might be an important event in the aging process, and that is
299 conserved across a broad range of species[31]. Age-related loss of the heat-shock transcription factor
300 has been confirmed to be involved in IB dysfunction by accelerating the decay of the intestinal
301 subapical terminal web and impairing its interactions with cell junctions in *C. elegans*[32]. The
302 current study added evidence regarding the association between IB dysfunction and age in humans.
303
304 Similarly, in the inpatient group, the serum I-FABP level was positively correlated with age.
305 However, the association between I-FABP and age disappeared in the multivariate linear
306 regression analysis, leaving the duration of hyperglycemia as the only metric associated with the
307 serum I-FABP level. Considering that the durations of hyperglycemia get longer when diabetic
308 patients grow older, age might be a confounding factor in the relationship between the serum I-
309 FABP level and the duration of hyperglycemia in the inpatient group.
310
311 **The different behaviors of two groups**
312 At first glance, the results in all participants seem to be the combination of two groups: correlation
313 analysis showed the serum I-FABP level was positively associated with the duration of
314 hyperglycemia, age, and glycemic variability but negatively associated with islet beta-cell
315 function; multivariate linear regression analysis showed that the serum I-FABP level was
316 associated with both age and the duration of hyperglycemia.
317

When all patients were combined, there was some evidence of a relationship, but on further investigation, it turned out that there appeared to be different behaviors in each group, and the difference might be mainly caused by the significant difference in the duration of hyperglycemia. As a result, the relationship between I-FAPB and the other metrics reported for all participants might be driven by the group sizes. Consequently, the results for all participants need to be interpreted with caution.

Moreover, in all participants and in the inpatient group, the multivariate linear regression models were just ways of determining possible associations between I-FABP and the metrics, the direct causal relationship in humans needs further investigation.

Perspective of the study

Based on the results of this study, we speculated that IB dysfunction occurred and developed along with the progression of diabetes. The relationship between hyperglycemia and IB dysfunction offers a new perspective on the clinical phenomenon of diabetes. On one hand, an impaired IB enhances the influx and systemic dissemination of intestinal bacteria, which explains the vulnerability of diabetic patients to infection[33]. On the other hand, more intestinal contents and bacterial metabolites come across the impaired IB and are released into the blood circulation, causing systemic chronic oxidative stress and inflammatory response, which not only promote diabetic complications[34,35] but also contribute directly to diabetes[36].

339 The association between the duration of hyperglycemia and IB dysfunction was clarified in this
340 study, but the underlying mechanisms have not been discussed. Previous studies showed that
341 nondiabetic patients who suffered from SIH were more likely to get diabetes in the future[37,38],
342 which brought about a confusing hypothesis that reversible hyperglycemia could cause irreversible
343 hyperglycemia. It is well recognized that some primary diseases like sepsis, trauma, burns, and
344 surgery, which induce SIH[3], can directly cause IB dysfunction[39]. Hyperglycemia-induced IB
345 dysfunction allows for an enhanced influx of intestinal contents, and the induced infection and
346 inflammatory response further intensify hyperglycemia[3]. Surprisingly, IB dysfunction builds a
347 bridge between SIH and diabetes, that is, IB dysfunction not only results from but also contributes
348 to hyperglycemia. Since improving IB function by treating the primary disease has been shown to
349 alleviate SIH[3], aiming to improve IB function might be a promising treatment strategy for diabetes.
350
351 Besides the new therapeutic approach for hyperglycemia, some widely used antidiabetic drugs
352 have already shown protective potential for IB. Glucagon-like peptide 1, which controls meal-
353 related glycemic excursions, alleviates gut inflammation and promotes the repairment of intestinal
354 epithelial cells[40,41]. Similar protective effects have also been observed with metformin[42] and
355 berberine[43]. Compared with the IB, the gut microbiome has drawn increasing attention in diabetes
356 research. Although quite a few studies have shown that the gut microbiome influences the
357 development of diabetes[44,45], the underlying mechanism is still unclear. As the interface between
358 the gut microbiome and diabetic patients, the IB is a promising candidate for mechanism research.
359

This study had some limitations. First, the participants recruited from the inpatient ward were admitted to the hospital for different pathological conditions, including but not limited to poor glucose control and diabetic complications. The influence of all these conditions on the serum I-FABP level was not thoroughly investigated. Second, the participants recruited from the inpatient ward had been treated with antidiabetic drugs, whether these drugs affected the serum I-FABP level was not investigated. Third, patients who suffered from severe nephropathy complications were not included in this study. Fourth, the results from all participants were driven by the group sizes because of the significant difference in the duration of hyperglycemia between groups.

Conclusions

To the best of our knowledge, this study investigated the serum I-FABP level in diabetic and prediabetic patients for the first time, and the results showed that in the outpatients whose duration of hyperglycemia was less than a year, the serum I-FABP level was positively associated with age. In the inpatients with different courses of diabetes, the serum I-FABP level was positively associated with the duration of hyperglycemia and glycemic variability but negatively associated with islet beta-cell function; moreover, the serum I-FABP level was higher in patients with retinopathy than in those without retinopathy, suggesting that the IB dysfunction got worse with the progression of diabetes.

Considering the participation of the gut microbiome in the etiology of diabetes, it is difficult to ignore the role of IB, whose dysfunction might cause oxidative stress, systemic infection, and

inflammatory response. By highlighting the IB in diabetes-related research, we offer a new perspective to interpret this familiar disease.

Acknowledgements

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

References

1. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang C, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH, Li H. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* 2020.
2. Cichosz SL, Schaarup C. Hyperglycemia as a Predictor for Adverse Outcome in ICU Patients With and Without Diabetes. *Journal of diabetes science and technology.* 2017;11(6):1272-1273.
3. Mifsud S, Schembri EL, Gruppetta M. Stress-induced hyperglycaemia. *British journal of hospital medicine (London, England : 2005).* 2018;79(11):634-639.
4. Knapp S. Diabetes and infection: is there a link?--A mini-review. *Gerontology.* 2013;59(2):99-104.
5. Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, Braverman S, Tengeler AC, Barak O, Elazar M, Ben-Zeev R, Lehavi-Regev D, Katz MN, Pevsner-Fischer M, Gertler A, Halpern Z, Harmelin A, Aamar S, Serradas P, Grosfeld A, Shapiro H, Geiger B, Elinav E. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science.* 2018;359(6382):1376-1383.
6. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. *Gut.* 2019;68(8):1516-1526.
7. Gajda AM, Storch J. Enterocyte fatty acid-binding proteins (FABPs): different functions of liver and intestinal FABPs in the intestine. *Prostaglandins, leukotrienes, and essential fatty acids.* 2015;93:9-16.
8. Wells JM, Brummer RJ, Derrien M, MacDonald TT, Troost F, Cani PD, Theodorou V, Dekker J, Meheust A, de Vos WM, Mercenier A, Nauta A, Garcia-Rodenas CL. Homeostasis of the gut barrier and potential

biomarkers. *American journal of physiology Gastrointestinal and liver physiology.* 2017;312(3):G171-g193.

9. Coufal S, Kokesova A, Tlaskalova-Hogenova H, Frybova B, Snajdauf J, Rygl M, Kverka M. Urinary I-FABP, L-FABP, TFF-3, and SAA Can Diagnose and Predict the Disease Course in Necrotizing Enterocolitis at the Early Stage of Disease. *Journal of immunology research.* 2020;2020:3074313.

10. Salim SY, Young PY, Churchill TA, Khadaroo RG. Urine intestinal fatty acid-binding protein predicts acute mesenteric ischemia in patients. *The Journal of surgical research.* 2017;209:258-265.

11. Kittaka H, Akimoto H, Takeshita H, Funaoka H, Hazui H, Okamoto M, Kobata H, Ohishi Y. Usefulness of intestinal fatty acid-binding protein in predicting strangulated small bowel obstruction. *PLoS One.* 2014;9(6):e99915.

12. Sarikaya M, Ergul B, Dogan Z, Filik L, Can M, Arslan L. Intestinal fatty acid binding protein (I-FABP) as a promising test for Crohn's disease: a preliminary study. *Clinical laboratory.* 2015;61(1-2):87-91.

13. Matsumoto S, Sekine K, Funaoka H, Funabiki T, Shimizu M, Hayashida K, Kitano M. Early diagnosis of hollow viscus injury using intestinal fatty acid-binding protein in blunt trauma patients. *Medicine (Baltimore).* 2017;96(10):e6187.

14. Oldenburger IB, Wolters VM, Kardol-Hoefnagel T, Houwen RHJ, Otten HG. Serum intestinal fatty acid-binding protein in the noninvasive diagnosis of celiac disease. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica.* 2018;126(3):186-190.

15. Kupcinskas J, Gedgaudas R, Hartman H, Sippola T, Lindstrom O, Johnson CD, Regner S. Intestinal Fatty Acid Binding Protein as a Marker of Necrosis and Severity in Acute Pancreatitis. *Pancreas.* 2018;47(6):715-720.

16. Goswami P, Sonika U, Moka P, Sreenivas V, Saraya A. Intestinal Fatty Acid Binding Protein and Citrulline as Markers of Gut Injury and Prognosis in Patients With Acute Pancreatitis. *Pancreas.* 2017;46(10):1275-1280.

17. Kitai T, Kim YH, Kiefer K, Morales R, Borowski AG, Grodin JL, Tang WHW. Circulating intestinal fatty acid-binding protein (I-FABP) levels in acute decompensated heart failure. *Clinical biochemistry.* 2017;50(9):491-495.

18. Okada K, Sekino M, Funaoka H, Sato S, Ichinomiya T, Murata H, Maekawa T, Nishikido M, Eishi K, Hara T. Intestinal fatty acid-binding protein levels in patients with chronic renal failure. *The Journal of surgical research.* 2018;230:94-100.

19. Sekino M, Funaoka H, Sato S, Okada K, Inoue H, Yano R, Matsumoto S, Ichinomiya T, Higashijima U, Matsumoto S, Hara T. Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: A preliminary study. *J Crit Care.* 2017;42:92-100.

20. Sikora M, Stec A, Chrabaszcz M, Waskiel-Burnat A, Zaremba M, Olszewska M, Rudnicka L. Intestinal Fatty Acid Binding Protein, a Biomarker of Intestinal Barrier, is Associated with Severity of Psoriasis. *Journal of clinical medicine.* 2019;8(7).

21. March DS, Marchbank T, Playford RJ, Jones AW, Thatcher R, Davison G. Intestinal fatty acid-binding protein and gut permeability responses to exercise. *Eur J Appl Physiol.* 2017;117(5):931-941.

22. Piton G, Capellier G. Biomarkers of gut barrier failure in the ICU. *Curr Opin Crit Care.* 2016;22(2):152-160.

23. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S14-s31.

24. Wautier MP, Guillausseau PJ, Wautier JL. Activation of the receptor for advanced glycation end products and consequences on health. *Diabetes & metabolic syndrome.* 2017;11(4):305-309.

25. Chen PM, Gregersen H, Zhao JB. Advanced glycation end-product expression is upregulated in the gastrointestinal tract of type 2 diabetic rats. *World journal of diabetes.* 2015;6(4):662-672.

26. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care.* 2019;42(3):400-405.

27. Nusca A, Tuccinardi D, Albano M, Cavallaro C, Ricottini E, Manfrini S, Pozzilli P, Di Sciascio G. Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes/metabolism research and reviews.* 2018;34(8):e3047.

28. Shen L, Ao L, Xu H, Shi J, You D, Yu X, Xu W, Sun J, Wang F. Poor short-term glycemic control in patients with type 2 diabetes impairs the intestinal mucosal barrier: a prospective, single-center, observational study. *BMC endocrine disorders.* 2019;19(1):29.

29. Bergman RN, Finegood DT, Kahn SE. The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes. *Eur J Clin Invest.* 2002;32:35-45.

30. Polonsky KS, Rubenstein AH. C-PEPTIDE AS A MEASURE OF THE SECRETION AND HEPATIC EXTRACTION OF INSULIN - PITFALLS AND LIMITATIONS. *Diabetes.* 1984;33(5):486-494.

31. Dambroise E, Monnier L, Ruisheng L, Aguilaniu H, Joly JS, Tricoire H, Rera M. Two phases of aging separated by the Smurf transition as a public path to death. *Scientific reports.* 2016;6:23523.

32. Egge N, Arneaud SLB, Wales P, Mihelakis M, McClendon J, Fonseca RS, Savelle C, Gonzalez I, Ghorashi A, Yadavalli S, Lehman WJ, Mirzaei H, Douglas PM. Age-Onset Phosphorylation of a Minor Actin Variant Promotes Intestinal Barrier Dysfunction. *Developmental cell.* 2019;51(5):587-601.e587.

33. Trevelin SC, Carlos D, Beretta M, da Silva JS, Cunha FQ. Diabetes Mellitus and Sepsis: A Challenging Association. *Shock (Augusta, Ga).* 2017;47(3):276-287.

34. Jha JC, Ho F, Dan C, Jandeleit-Dahm K. A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes. *Clinical science (London, England : 1979).* 2018;132(16):1811-1836.

35. Volpe CMO, Villar-Delfino PH, Dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. *Cell death & disease.* 2018;9(2):119.

36. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clinics in dermatology.* 2018;36(1):14-20.

37. Kar P, Plummer MP, Abdelhamid YA, Giersch EJ, Summers MJ, Weinel LM, Finnis ME, Phillips LK, Jones KL, Horowitz M, Deane AM. Incident Diabetes in Survivors of Critical Illness and Mechanisms Underlying Persistent Glucose Intolerance: A Prospective Cohort Study. *Critical Care Medicine.* 2019;47(2):E103-E111.

38. Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, Moodie S, Horowitz M, Shaw JE, Deane AM. Stress Induced Hyperglycemia and the Subsequent Risk of Type 2 Diabetes in Survivors of Critical Illness. *Plos One.* 2016;11(11):12.

39. Greis C, Rasuly Z, Janosi RA, Kordelas L, Beelen DW, Liebregts T. Intestinal T lymphocyte homing is associated with gastric emptying and epithelial barrier function in critically ill: a prospective observational study. *Critical care (London, England).* 2017;21(1):70.

40. Smits MM, van Raalte DH, Tonneijck L, Muskiet MH, Kramer MH, Cahen DL. GLP-1 based therapies: clinical implications for gastroenterologists. *Gut.* 2016;65(4):702-711.

493 41. Anbazhagan AN, Thaqi M, Priyamvada S, Jayawardena D, Kumar A, Gujral T, Chatterjee I, Mugarza E,
494 Saksena S, Onyuksel H, Dudeja PK. GLP-1 nanomedicine alleviates gut inflammation. *Nanomedicine :*
495 *nanotechnology, biology, and medicine.* 2017;13(2):659-665.
496 42. Rodriguez J, Hiel S, Delzenne NM. Metformin: old friend, new ways of action-implication of the gut
497 microbiome? *Current Opinion in Clinical Nutrition and Metabolic Care.* 2018;21(4):294-301.
498 43. Gong J, Hu M, Huang Z, Fang K, Wang D, Chen Q, Li J, Yang D, Zou X, Xu L, Wang K, Dong H, Lu F.
499 Berberine Attenuates Intestinal Mucosal Barrier Dysfunction in Type 2 Diabetic Rats. *Frontiers in*
500 *pharmacology.* 2017;8:42.
501 44. Hills RD, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut Microbiome: Profound
502 Implications for Diet and Disease. *Nutrients.* 2019;11(7):40.
503 45. Canfora EE, Meex RCR, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM.
504 *Nature Reviews Endocrinology.* 2019;15(5):261-273.
505

Abbreviation:

I-FABP: intestinal fatty acid-binding protein

IB: intestinal barrier

HbA1c: 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)

Clinical information and the serum I-FABP level between the different stages of diabetes for the outpatient group.

Table 1. Clinical information and the serum I-FABP level between the different stages of diabetes for the outpatient group.

	Prediabetes	Diabetes	P-value
Male/Female, n **	42/53	48/15	<0.001
Age, y	45 (32, 57)	49 (34, 55)	0.790
HbA1c, % **	5.5 (5.3, 5.8)	6.9 (6.4, 9.1)	<0.001
FPG, mmol/L **	5.94 (5.41, 6.47)	8.54 (7.64, 10.89)	<0.001
FC-pep, ng/mL **	2.39 (1.86, 3.16)	2.97 (2.29, 3.62)	0.004
FIns, mu/L	10.21 (5.91, 14.36)	11.98 (7.37, 15.13)	0.136
2hPG, mmol/L **	8.46 (6.93, 10.28)	15.73 (13.55, 19.25)	<0.001
2hC-pep, ng/mL **	9.96 (7.61, 12.83)	7.35 (5.89, 11.15)	0.001
2hIns, mu/L **	64.26 (42.18, 122.03)	46.56 (28.78, 69.34)	0.003
ΔPG, mmol/L **	2.52 (1.00, 4.00)	7.28 (4.81, 9.21)	<0.001
ΔC-pep, ng/mL **	7.56 (5.57, 10.36)	4.63 (3.03, 7.96)	<0.001
ΔIns, mu/L **	57.25 (33.78, 105.98)	34.82 (18.20, 58.76)	<0.001
I-FABP, pg/mL	1354 (948, 1634)	1231 (883, 1604)	0.442

I-FABP = intestinal fatty acid-binding protein, HbA1c = hemoglobin A1c, 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.

** $P < 0.01$.

Table 2(on next page)

Correlation analysis of the serum I-FABP level for the outpatient group.

Table 2. Correlation analysis of the serum I-FABP level for the outpatient group.

		R	P-value
I-FABP	Age **	0.299	<0.001
	HbA1c	-0.027	0.734
	FPG	-0.052	0.515
	FC-pep	0.031	0.696
	FIns	0.010	0.899
	2hPG	-0.025	0.757
	2hC-pep	0.104	0.197
	2hIns	0.063	0.435
	ΔPG	0.003	0.973
	ΔC-pep	0.103	0.199
	ΔIns	0.080	0.322

I-FABP = intestinal fatty acid-binding protein, HbA1c = hemoglobin A1c, 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.

** $P < 0.01$.

Table 3(on next page)

Correlation analysis and multiple linear regression analysis of the serum I-FABP level for the inpatient group.

Table 3. Correlation analysis and multiple linear regression analysis of the serum I-FABP level for the inpatient group.

	Correlation Analysis		Multiple Linear Regression	
	R	P-value	β	P-value
Age	0.286	0.001	0.098	0.317
Duration	0.350	<0.001	0.362	<0.001
HbA1c	0.045	0.625	-	-
FPG	-0.126	0.168	-	-
FC-pep	-0.304	0.001	-0.090	0.352
FIns	-0.145	0.244	-	-
2hPG	0.149	0.105	-	-
2hC-pep	-0.241	0.008	-0.064	0.494
2hIns	-0.219	0.081	-	-
ΔPG	0.250	0.006	0.149	0.110
ΔC-pep	-0.163	0.076	-	-
ΔIns	-0.209	0.097	-	-

The corresponding model was $Y = 7.292 + 0.027 * X$, Y: ln(I-FABP), X: Duration, and $R^2 = 0.131$ in the multiple linear regression. I-FABP = intestinal fatty acid-binding protein, HbA1c = hemoglobin A1c, 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. β = standardized β-coefficient.

Table 4(on next page)

Relationship between the serum I-FABP level and diabetic complications for the inpatient group.

Table 4. Relationship between the serum I-FABP level and diabetic complications for the inpatient group.

Complications	Positive cases (%)	I-FABP		
		Positive	Negative	P-value
Retinopathy **	48 (39.3)	2164 (1749, 3262)	1585 (1168, 2467)	0.001
Neuropathy	51 (41.8)	1949 (1373, 2953)	1697 (1169, 2617)	0.126
Nephropathy	34 (27.9)	1836 (1206, 2719)	1829 (1256, 2638)	0.833

I-FABP = intestinal fatty acid-binding protein.

** $P < 0.01$.

Table 5(on next page)

Clinical information and serum I-FABP levels of participants recruited from the outpatient clinic and the inpatient ward.

Table 5. Clinical information and serum I-FABP levels of participants recruited from the outpatient clinic and the inpatient ward.

	Outpatient	Inpatient	P-value
Male/Female, n	90/68	72/50	0.730
Age, y **	47.5 (33, 56)	56 (51.75, 67)	<0.001
Duration, y **	<1	10 (3, 14)	<0.001
HbA1c, %**	5.9 (5.5, 6.5)	8.0 (6.8, 9.3)	<0.001
FPG, mmol/L *	6.57 (5.77, 8.04)	7.43 (5.86, 9.08)	0.037
FC-pep, ng/mL **	2.69 (1.92, 3.45)	1.92 (1.29, 2.67)	<0.001
FIns, mu/L *	10.66 (6.29, 14.74)	7.77 (5.21, 12.74)	0.020
2hPG, mmol/L **	10.55 (7.87, 14.71)	18.97 (14.37, 21.38)	<0.001
2hC-pep, ng/mL **	9.22 (7.03, 12.39)	5.19 (3.59, 7.69)	<0.001
2hIns, mu/L **	55.34 (35.06, 109.25)	38.11 (21.67, 69.28)	0.001
ΔPG, mmol/L **	3.80 (1.91, 7.16)	10.32 (6.71, 12.95)	<0.001
ΔC-pep, ng/mL **	6.78 (4.27, 9.36)	3.33 (2.13, 5.17)	<0.001
ΔIns, mu/L **	47.02 (26.69, 91.97)	30.51 (16.84, 56.10)	0.002
I-FABP, pg/mL**	1289 (909, 1629)	1831 (1243, 2642)	<0.001

I-FABP = intestinal fatty acid-binding protein, HbA1c = hemoglobin A1c, 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.

* $P < 0.05$. ** $P < 0.01$.

Table 6(on next page)

Correlation analysis and multiple linear regression analysis of the serum I-FABP level for all participants.

Table 6. Correlation analysis and multiple linear regression analysis of the serum I-FABP level for all participants.

	Correlation Analysis		Multiple Linear Regression	
	R	P-value	β	P-value
Age	0.398	<0.001	0.248	<0.001
Duration	0.413	<0.001	0.311	<0.001
HbA1c	0.196	0.001	0.012	0.843
FPG	-0.019	0.755	-	-
FC-pep	-0.220	<0.001	0.030	0.609
FIns	-0.072	0.282	-	-
2hPG	0.250	<0.001	0.045	0.461
2hC-pep	-0.214	<0.001	0.018	0.763
2hIns	-0.075	0.265	-	-
ΔPG	0.311	<0.001	0.122	0.064
ΔC-pep	-0.171	0.004	0.012	0.843
ΔIns	-0.058	0.392	-	-

The corresponding model was $Y = 6.749 + 0.026 * X_1 + 0.009 * X_2$, Y: ln(I-FABP), X_1: Duration, X_2: Age, and $R^2 = 0.232$ in the multiple linear regression. I-FABP = intestinal fatty acid-binding protein, HbA1c = hemoglobin A1c, 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. β = standardized β-coefficient.