Serum A-FABP Is Increased and Closely Associated with Elevated NT-proBNP Levels in Type 2 Diabetic Patients Treated with Rosiglitazone

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Abstract

Background: Adipocyte fatty acid-binding protein (A-FABP) has been shown to play important roles in the development of metabolic syndrome, diabetes, and cardiovascular diseases. In this study we investigated the possible role of A-FABP in the development of cardiac dysfunction related to rosiglitazone treatment.

Methodology/Principal Findings: A total of 84 patients with newly diagnosed type 2 diabetes were treated with rosiglitazone for 48 weeks. Circulating A-FABP and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were determined at baseline and repeated at 24 and 48 weeks. After the 48-week rosiglitazone treatment period, serum levels of both A-FABP and NT-proBNP increased progressively and significantly (P<0.01). Serum levels of A-FABP were demonstrated to be positively correlated with gender and waist circumference both at baseline and the end of the study, and with age, body mass index (BMI), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and NT-proBNP at 48 weeks (all P<0.05). In addition, changes in A-FABP were significantly and positively correlated with changes in NT-proBNP (r=0.239, P=0.039). Furthermore, multiple stepwise regression analysis showed that the changes in A-FABP were independently and positively associated with changes in NT-proBNP after adjusting for confounding factors (β=0.320, P=0.007).

Conclusions/Significance: Rosiglitazone-mediated increase of A-FABP is closely associated with the elevation of NT-proBNP, a well-established marker of cardiac dysfunction. The findings of our study imply that A-FABP may mediate the cross-talk between heart and adipose tissue.

Introduction

Adipocyte fatty acid-binding protein (A-FABP), also known as FABP4, is a cytosolic lipid chaperone that reversibly binds with high affinity to hydrophobic ligands, such as saturated and unsaturated long-chain fatty acids [1]. It is predominantly expressed in mature adipocytes and activated macrophages [2,3]. Emerging evidences suggest that A-FABP plays an important role in lipid-mediated biological processes, and is closely associated with obesity, diabetes, the metabolic syndrome, and the development of atherosclerosis [4–7]. Recently, the relationship between A-FABP and cardiovascular disease has raised much attention. A genetic variant associated with increased A-FABP expression of A-FABP can be induced by PPARγ agonists [14], which can also increase the circulating levels of brain natriuretic peptide (BNP) [15]. Circulating concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) has been proposed as a biomarker of cardiovascular disease and in particular a marker of heart failure, and holds promise as a tool to screen the general population both for prevalence of underlying cardiac structural and functional abnormalities as well as for the future development of cardiovascular events [16,17]. Although the adverse effect of rosiglitazone on fluid dynamics has been proposed as a probable...
mechanism of its greater risk of congestive heart failure, it is unclear whether A-FABP is also involved in the PPARγ agonists-induced changes of cardiovascular function. In the present study, we investigated the long-term effects of rosiglitazone on circulating A-FABP and NT-proBNP levels in patients with newly diagnosed type 2 diabetes (T2DM), and the possible role of A-FABP in the development of cardiac dysfunction.

Methods

Ethics Statement

All subjects gave written informed consent, and the study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People’s Hospital and complied with the Declaration of Helsinki.

Participants

Subjects with newly diagnosed T2DM were recruited from the outpatient clinics of 10 academic hospitals in Shanghai. The diagnosis of T2DM was based on 1999 World Health Organization criteria [18]. The criteria for study inclusion and exclusion have been described previously [19,20]. This study includes data from 84 patients (60 men, 24 women) aged 52.6 ± 8.9 years. All patients were treated with rosiglitazone (Avandia; GlaxoSmithKline, Munich, Germany) for 48 weeks which were comprised of 8 visits. Fasting plasma glucose (FPG) and 2-h postchallenge plasma glucose (2hPG) were monitored at each visit. The initial dose of rosiglitazone was 4 mg/d and escalated to 8 mg/d in patients who failed to attain FPG <7 mmol/l and/or 2hPG <11 mmol/l. Liver function tests were performed every 12 weeks. Lipid profile and arginine stimulation test was used to estimate acute insulin secretion of islet β cells were performed at baseline and repeated at 24 and 48 weeks.

Anthropometric evaluation

A complete physical examination including height, weight, waist circumferences, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were performed on each subject at baseline, 24 weeks and 48 weeks after the initiation of rosiglitazone therapy. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m²). Waist circumference was measured midway between the lowest rib and the superior border of iliac crest on midaxillary line.

Biochemical measurements

Blood samples were collected after an overnight fast. Arginine stimulation tests were performed on all the patients. At time 0, arginine hydrochloride (10% arginine hydrochloride of 50 ml,
5 g) was injected intravenously within 30–60 s. Blood samples were drawn at times 0, 2, 4, and 6 min after injection for glucose and insulin measurements [21]. Plasma glucose concentrations were measured using glucose oxidase method. Serum insulin was assayed via radioimmunoassay (Linco Research, St Charles, MO, USA). Glycated hemoglobin A1c (HbA1c) values were determined by high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA, USA). Serum lipid profiles, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by enzymatic procedures using an autoanalyzer (Hitachi 7600–020; Hitachi, Tokyo, Japan). NT-proBNP was assayed by chemiluminescence (Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany). A-FABP levels were assayed by sandwich ELISA (Antibody and Immunoassay Services, the University of Hong Kong). The intra- and inter-assay variations were 4.5 and 6.7%, respectively.

**Evaluation of insulin resistance (IR) and β-cell function**

IR and basal insulin secretion were estimated using the homeostasis model assessment (HOMA) index based on fasting glucose and insulin measurements as follows: HOMA-IR = fasting insulin (mU/l)×FPG (mmol/l)/22.5. HOMA of beta cell function (HOMA-B%) = 20×fasting insulin/(FPG-3.5) [22]. The acute insulin response (AIR) was used to examine the amount of acute phase insulin secretion after arginine stimulation, and was calculated as the mean insulin value of 2, 4, and 6 min minus fasting insulin concentration.

**Statistical analysis**

All analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL). Data were expressed as means ± SD for normal distributions or median (interquartile range) for skewed variables. Data that were not normally distributed as determined by the Kolmogorov-Smirnov test were logarithmically transformed before analysis. To test the effect of rosiglitazone treatment during the examination period, we used repeated-measures ANOVA to compare data from baseline and weeks 24 and 48, and multiple comparisons were performed applying the Bonferroni correction. Pearson’s correlation was used to evaluate the relationships among continuous variables. Multiple stepwise regression analysis was performed to determine the independent parameters correlated with A-FABP, NT-proBNP, and changes in A-FABP and NT-proBNP. P < 0.05 was considered significant.

**Results**

**Clinical characteristics of the patients**

The demographic and biochemical characteristics of the study subjects at baseline and after 24 and 48 weeks treatment with rosiglitazone were summarized in Table 1. Compared to baseline, DBP, FPG, 2hPG, HbA1c, and HOMA-IR all decreased.

### Table 2. Anthropometric and biochemical parameters showing significant correlations with serum A-FABP and NT-proBNP at baseline.

|            | A-FABP Univariate | A-FABP Multivariate | NT-proBNP Univariate | NT-proBNP Multivariate |
|------------|-------------------|---------------------|----------------------|------------------------|
|            | r                  | P                   | β                    | P                      |
| Age        | 0.033              | 0.769               |                      |                       |
| Gender (women) | 0.208              | 0.034               | 0.207               | 0.048                  |
| Waist circumference | 0.203              | 0.039               |                      |                       |
| BMI        | 0.205              | 0.062               | 0.345               | 0.020                  |
| SBP        | 0.038              | 0.731               |                      |                       |
| DBP        | 0.056              | 0.610               |                      |                       |
| TC         | -0.028             | 0.803               |                      |                       |
| TG         | 0.134              | 0.176               |                      |                       |
| HDL-c      | -0.116             | 0.241               |                      |                       |
| LDL-c      | 0.175              | 0.076               |                      |                       |
| FPG        | -0.069             | 0.555               |                      |                       |
| 2hPG       | 0.142              | 0.207               |                      |                       |
| Fasting insulin | -0.085             | 0.440               |                      |                       |
| HbA1c      | -0.139             | 0.161               |                      |                       |
| HOMA-IR    | 0.178              | 0.123               |                      |                       |
| HOMA-B%    | 0.045              | 0.672               |                      |                       |
| AIR        | 0.089              | 0.367               |                      |                       |
| A-FABP     | 0.112              | 0.258               |                      |                       |

β, Standardized regression coefficients.

*A* Pearson correlation analyses were performed.

*A* multiple stepwise regression analysis was performed. Variables included in the original model are age, gender, waist circumference, BMI, and LDL-c.

*A* multiple stepwise regression analysis was performed. Variables included in the original model are age, gender, SBP, TG, HDL-c, LDL-c, FPG, HbA1c, HOMA-IR, and AIR.

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significantly at week 24 and 48, whereas HDL-c increased significantly at week 48 (all \( P < 0.01 \)).

Serum levels of A-FABP and NT-proBNP are higher in women than in men at both baseline (both \( P < 0.01 \)) and the end of the study (both \( P < 0.05 \)). As shown in Figure 1, 24 and 48 weeks after the treatment with rosiglitazone, serum levels of A-FABP increased progressively and significantly in both genders (all \( P < 0.001 \)). As compared with week 24, A-FABP levels also significantly increased at the study end (\( P < 0.001 \)). Serum NT-proBNP demonstrated similar increasing trend, with significant higher levels at 48 weeks for men and at both 24 and 48 weeks for women compared to baseline (all \( P < 0.01 \)).

Correlation analysis and multiple linear regression analysis showing parameters related to A-FABP and NT-proBNP

At baseline (Table 2), univariate analysis revealed significant correlations of serum A-FABP with gender (women) and waist circumference (both \( P < 0.05 \)). Serum NT-proBNP was positively correlated with age and gender (women) (both \( P < 0.05 \)), and negatively correlated with HbA1c, HOMA-IR, and AIR (all \( P < 0.05 \)). On multiple stepwise regression analysis, gender (\( P = 0.048 \)) and BMI (\( P = 0.020 \)) were independently related to A-FABP, and age (\( P < 0.001 \)), LDL-c (\( P = 0.032 \)), and HOMA-IR (\( P = 0.019 \)) were independently correlated with NT-proBNP.

After 48 weeks of rosiglitazone therapy (Table 3), serum levels of A-FABP were demonstrated to be positively correlated with age, gender, waist circumference, BMI, TC, TG, LDL-c, and NT-proBNP (all \( P < 0.05 \)). Serum NT-proBNP was shown to be positively correlated with age, gender, SBP, HDL-c, and A-FABP, and negatively correlated with BMI, FPG, fasting insulin, HOMA-IR, and AIR (all \( P < 0.05 \)). On multiple stepwise regression analysis, age (\( P = 0.002 \)), gender (\( P = 0.009 \)), BMI (\( P = 0.023 \)), TG (\( P = 0.019 \)), and LDL-c (\( P = 0.002 \)) were independently and positively related to A-FABP, whereas age (\( P < 0.001 \)), gender (\( P = 0.036 \)), and HOMA-IR (\( P = 0.026 \)) were independent factors for NT-proBNP. However, the relationship between A-FABP and NT-proBNP was abolished after multi-adjustment.

Table 3. Anthropometric and biochemical parameters showing significant correlations with serum A-FABP and NT-proBNP after the 48-week rosiglitazone treatment.

|                                | A-FABP |          |          | NT-proBNP |          |          |
|--------------------------------|--------|----------|----------|-----------|----------|----------|
|                                |        | Univariate | Multivariate |          | Univariate | Multivariate |
|                                |        |           |           |           |           |           |
| Age                            | 0.376  | <0.001    | 0.312    | 0.002    | 0.587    | <0.001    |
| Gender (women)                 | 0.285  | 0.009    | 0.243    | 0.009    | 0.355    | 0.001    |
| Waist circumference            | 0.217  | 0.049    |          |          | -0.127   | 0.259    |
| BMI                            | 0.231  | 0.035    | 0.229    | 0.023    | -0.231   | 0.038    |
| SBP                            | 0.171  | 0.125    |          |          | 0.227    | 0.043    |
| DBP                            | 0.161  | 0.147    |          |          | -0.084   | 0.461    |
| TC                             | 0.480  | <0.001   |          |          | 0.014    | 0.897    |
| TG                             | 0.351  | 0.001    | 0.241    | 0.019    | -0.100   | 0.369    |
| HDL-c                          | -0.068 | 0.539    |          |          | 0.281    | 0.011    |
| LDL-c                          | 0.451  | <0.001   | 0.303    | 0.002    | 0.021    | 0.850    |
| FPG                            | 0.051  | 0.663    |          |          | -0.237   | 0.035    |
| 2hPG                           | -0.181 | 0.107    |          |          | -0.059   | 0.603    |
| Fasting insulin                | 0.148  | 0.179    |          |          | -0.394   | <0.001   |
| HbA1c                          | 0.077  | 0.493    |          |          | -0.019   | 0.868    |
| HOMA-IR                        | 0.003  | 0.981    |          |          | -0.426   | <0.001   |
| HOMA-B%                        | 0.031  | 0.790    |          |          | -0.137   | 0.252    |
| AIR                            | 0.034  | 0.757    |          |          | -0.275   | 0.013    |
| A-FABP                         | 0.250  | 0.024    |          |          |          |          |

/\, Standardized regression coefficients.
\* Pearson correlation analyses were performed.
\*\* A multiple stepwise regression analysis was performed. Variables included in the original model are age, gender, waist circumference, BMI, TC, TG, LDL-c, and NT-proBNP.
\*\*\* A multiple stepwise regression analysis was performed. Variables included in the original model are age, gender, BMI, SBP, HDL-c, FPG, fasting insulin, HOMA-IR, AIR, and A-FABP.

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positively associated with each other after adjusting for confounding factors \((\beta = 0.320, P = 0.007)\). In addition, changes in A-FABP and NT-proBNP were independently associated with changes in waist circumference and BMI, respectively \((P < 0.05)\).

**Discussion**

In the present study, we have shown that serum levels of both A-FABP and NT-proBNP were increased progressively and significantly after the treatment with rosiglitazone in a cohort of newly diagnosed type 2 diabetic patients, and have demonstrated for the first time that changes in serum levels of A-FABP were independently and positively associated with changes in NT-proBNP.

*In vitro* studies suggest that A-FABP is regulated by PPAR\(\gamma\) agonists such as rosiglitazone not only in human adipocytes but also in macrophages [14,23]. A-FABP expression is activated by PPAR\(\gamma\)-signaling through the PPRE element present in the A-FABP gene promoter [24]. Rosiglitazone treatment not only caused an increase in A-FABP mRNA and protein levels in human adipocytes but also in A-FABP secretion from adipocytes [25]. However, few clinical studies have reported the effect of rosiglitazone on serum levels of A-FABP. In this study, in accordance with these cell-based observations, we found serum levels of A-FABP increased progressively with rosiglitazone therapy in diabetic patients. An approximately 6-fold increase in serum A-FABP levels was observed after the 48-week treatment. Likewise, a cross-sectional study demonstrated that serum A-FABP levels were significantly higher in TZD-treated type 2 diabetic patients than that in control subjects. In addition, they also reported in their subgroup analysis on 6 patients that another PPAR\(\gamma\) agonist pioglitazone increased serum A-FABP levels significantly after a 12-week treatment [25]. Therefore, our study provides the clinical evidence that rosiglitazone act as an important regulator in A-FABP production in humans.

Another novel observation of this study is the independent and positive relationship between changes in serum levels of A-FABP and NT-proBNP. It has been reported previously that plasma BNP levels are increased with impaired ventricular function in the treatment of diabetic patients with TZD [15,26]. In the present study we found a significant increase in serum NT-proBNP levels associated with rosiglitazone treatment. The precise mechanisms responsible for the increase in NT-proBNP levels associated with rosiglitazone treatment remain unclear. One probable explanation is the result of increased cardiac wall stretch caused by volume retention which is considered as the main adverse event of TZD therapy. Christos Sambanis *et al.* reported that pioglitazone does not alter echocardiographic parameters even though it increases NT-proBNP after a 3 month treatment period in 44 patients with T2DM, and speculated that it may represent a reaction to volume overload [27]. It has been suggested that serial monitoring changes in BNP levels over time is beneficial to potentially enable the

| \(\Delta\) A-FABP | \(\Delta\) NT-proBNP |
|-----------------|------------------|
| **Univariate** | **Multivariate** | **Univariate** | **Multivariate** |
| \(r\) | \(P\) | \(\beta\) | \(P\) | \(r\) | \(P\) | \(\beta\) | \(P\) |
| Age | 0.372 | 0.001 | 0.289 | 0.014 | 0.403 | <0.001 | 0.200 | 0.044 |
| Gender (women) | 0.237 | 0.030 | -0.099 | 0.403 |
| \(\Delta\) Waist circumference | 0.242 | 0.028 | 0.309 | 0.004 | 0.017 | 0.138 |
| \(\Delta\) BMI | 0.081 | 0.468 | 0.208 | 0.076 | 0.097 | 0.138 |
| \(\Delta\) SBP | 0.120 | 0.027 | -0.099 | 0.109 |
| \(\Delta\) DBP | 0.217 | 0.047 | -0.099 | 0.109 |
| \(\Delta\) HOMA-B% | 0.239 | 0.039 | 0.289 | 0.014 | 0.239 | 0.039 | 0.320 | 0.007 |

\(\Delta\), differences between after and before treatment.
\(\beta\), Standardized regression coefficients.
Pearson correlation analyses were performed.
*A multiple stepwise regression analysis was performed. Variables included in the original model are age, gender, \(\Delta\) waist circumference, \(\Delta\) TG, \(\Delta\) HDL-c, and \(\Delta\) NT-proBNP.
*\(\Delta\) A-FABP.

Elevation of A-FABP and NT-proBNP by Rosiglitazone

**Table 4.** Changes in anthropometric and biochemical parameters showing significant correlations with changes in serum A-FABP and NT-proBNP during the 48-week rosiglitazone treatment.
Interestingly, our study also demonstrated an independent and FABP as a key player of obesity-related metabolic disorders. In waist circumference was also observed. It is known that A-FABP especially after the 48-week rosiglitazone treatment. An independent association between A-FABP and NT-proBNP requires [31]. However, the precise mechanism underlying the independent association between A-FABP and NT-proBNP requires further investigation.

Consistent with previous studies [4,5], serum levels of A-FABP in our type 2 diabetic patients were independently associated with lipid and parameters of adiposity such as TG, LDL-c and BMI, especially after the 48-week rosiglitazone treatment. An independent relationship between changes in serum A-FABP and changes in waist circumference was also observed. It is known that A-FABP binds fatty acids with high affinity and mediates intracellular lipid trafficking [32]. Therefore, our findings support the role of A-FABP as a key player of obesity-related metabolic disorders. Interestingly, our study also demonstrated an independent and negative relationship of serum NT-proBNP with HOMA-IR both at baseline and the end of the study. Recently, several studies reported the link between obesity and natriuretic peptide levels, demonstrating an inverse relationship of BMI with BNP and NT-proBNP concentration in subjects with and without heart failure [33,34]. Multiple mechanisms may contribute to these inverse associations. On the one hand, impaired synthesis and diminished release of NT-proBNP from the heart with increasing BMI are likely to play a role [34]. On the other hand, natriuretic peptides also exert impact on fat cells. BNP was found to be able to stimulate lipolysis in human fat cells through a cGMP-dependent protein kinase signaling pathway [35]. Therefore, the negative relationship between NT-proBNP and cardiovascular risk factors in our study also suggests a reciprocal regulation between heart and fat metabolism.

This study is limited by the lacking of data on echocardiography. Therefore, we could not provide solid evidence on the change of cardiac structure and systolic or diastolic function, as well as their relationship with the increment of serum A-FABP. Further prospective studies including echocardiographic evidence are warranted to clarify whether the association between A-FABP and NT-proBNP following rosiglitazone therapy is dependent on the cardiovascular function.

In summary, our study provide the first evidence that changes in serum levels of A-FABP are independently associated with changes in serum NT-proBNP following rosiglitazone treatment. The findings of our study suggest A-FABP may play an important role in early cardiac dysfunction and imply that A-FABP may mediate the cross talk between the heart and adipose tissue.

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Author Contributions
Conceived and designed the experiments: MZ. WJ. Performed the experiments: JL, JZ. Analyzed the data: MZ. YB. Contributed reagents/materials/analysis tools: YB. JL, JZ. Wrote the paper: MZ.

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