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Gene Expression and Correlation of *Pten* and *Fabp4* in Liver, Muscle, and Adipose Tissues of Type 2 Diabetes Rats

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Background: The aim of this work was to study the *Fabp4* and *Pten* gene expression and correlation in the liver, muscle, and adipose tissues of type 2 diabetes mellitus (T2DM) rats.


Material/Methods: Male Wistar rats (8 weeks old) were randomly divided into 2 groups (n=12/group): a control group fed a normal diet for 8 weeks and an experimental group fed a high-fat, high-sugar diet for 8 weeks and that received 25 mg/kg streptozotocin by intraperitoneal injection to induce T2DM. The random blood glucose, fasting blood glucose, and fasting insulin levels were measured. The expression of *Pten* and *Fabp4* in the liver, muscle, and epididymal adipose tissues was estimated by real-time quantitative PCR. Pearson correlation coefficient analysis was used to investigate the expression correlation between *Pten* and *Fabp4* in T2DM rats.

Results: The gene expressions of *Pten* and *Fabp4* in the liver, muscle, and adipose tissues of T2DM rats were all significantly higher than those in the control group ($P<0.05$). *Pten* was highly expressed in the muscles and *Fabp4* was highly expressed in muscle and adipose tissues. Furthermore, expressions of *Fabp4* and *Pten* in the muscle and adipose tissues of T2DM rats were positively correlated ($P<0.05$), but not in the liver.

Conclusions: The increased expression of *PTEN* and *FABP4* in the adipose and muscles of T2DM rats may play an important role in the insulin resistance of T2DM. However, the mechanism by which these 2 genes function in T2DM needs further study.

MeSH Keywords: **Diabetes Mellitus, Type 2 • Fatty Acid-Binding Proteins • PTEN Phosphohydrolase**

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Background

Type 2 diabetes mellitus (T2DM) is a pervasive metabolic syndrome and its pathogenesis remains unclear. The main characteristic of T2DM is considered to be insulin resistance (IR). To our knowledge, liver, adipose and muscle are major insulin responsive tissues. Under normal conditions, insulin stimulates the uptake of glucose and potentially inhibits lipolysis in adipocytes. Under insulin-stimulated conditions, adipose and liver account for about 10% and 30% of the whole body glucose uptake, respectively [1]. The skeletal muscle accounts for about 75% of glucose disposal after glucose infusion [1]. In addition, the insulin-stimulated glucose uptake in adipose and muscle occurs via the intracellular PI3K/Akt pathway which is required for translocation of glucose transporter GLUT4 to the plasma membrane [1].

Phosphatase and tensin homolog deleted on chromosome ten (PTEN) was identified as a tumor suppressor with dual lipid and protein tyrosine phosphatase activity and frequently mutated/deleted in many human cancers [2]. It was also widely known as the negative regulator of insulin/phosphoinositide 3-kinase (PI3K) signaling pathway in which PTEN hydrolyzes PI(3,4,5)P₃ to PI(4,5)P₂, and suppresses cell growth and other PI3K/Akt-dependent processes [3]. Therefore, PTEN was considered as a promising target in T2DM and obesity treatment because of its negative effects on insulin resistance [4–6]. However, the specific role of PTEN in insulin target tissues and insulin resistance is not yet known.

Fatty acid-binding protein 4 (FABP4), known as adipocyte FABP (A-FABP) or aP2, is abundantly expressed in adipocytes and plays important roles in adipocyte differentiation and lipid metabolism [7]. Multiple studies have been showed that Fabp4 functions in the free fatty acid transport, regulation whole body insulin sensitivity and development of atherosclerosis [8–10].

Recently PTEN was found to be interacted with FABP4 [11], suggesting that PTEN may function in the regulation of lipid metabolism and adipocyte differentiation. Our previous study found that the plasma levels of FABP4 and PTEN were increased with more severe IR in women with gestational diabetes mellitus [12], indicating that both genes were important in the development of IR. Therefore, here we investigated the gene expression of *Pten* and *Fabp4* in the liver, muscle and adipose tissues of T2DM rats to explore the expression and correlation between *Pten* and *Fabp4* in T2DM.

Material and Methods

Ethics statement

All experimental protocols were performed in accordance with the approved national and international guidelines. All animal studies have been performed with the approval of the ethics committee of Inner Mongolia Medical University.

Animals, diets and sample preparation

Briefly, 24 male Wistar rats, 8 weeks old (weight, 200–220 grams) were purchased from the Experimental Animal Center of Inner Mongolia University and housed (3 animals per cage) under standard conditions. All animals were initially fed the normal diet for 1 week. Subsequently, all rats were randomly divided into 2 groups (n=12/group) fed 2 different diets: a control group fed normal diet (low-fat diet, LFD) containing 5% fat, 53% carbohydrate, and 23% protein, with total calorific value 25 kJ/kg, and the T2DM experimental group fed a high-fat, high-sugar diet (HFHSD) containing 22% fat, 48% carbohydrate, and 20% protein with total calorific value 44.3 kJ/kg. After 8 weeks, the experimental group rats received intraperitoneal (IP) injection of streptozotocin (STZ; Sigma-Aldrich, St. Louis, MO, USA) 25 mg/kg of body weight, and the control rats were given vehicle citrate buffer (pH 4.4) 0.25 mL/kg IP. After 1 week, all the rats were fasted for 12 hours; blood glucose was measured from a tail vein using a glucometer (Roche Diagnostics GmbH, Germany). The rats with blood glucose <16.7 mmol/L were injected with STZ again (25 mg/kg). After 4 weeks, rats with blood glucose levels of ≥16.7 mmol/L were considered diabetic [13,14]. The insulin resistance index was calculated by the homeostasis model assessment (HOMA) (HOMA-IR=Fasting blood glucose levels (FBG, mmol/L) × Fasting insulin (FINS, mU/L)/22.5) [13,14]. The blood glucose level and body weight were measured every week. All rats were fasted for 12–16 hours and blood was obtained from the heart and separated by centrifugation (1500 rpm, 20 min) for serum. All the rats were killed and all the tissues were collected, flash frozen, and subsequently stored at –70°C.

Total RNA extraction and cDNA synthesis

The total RNA from muscle, liver, and epididymal adipose tissues were obtained with TRIzol reagent (Invitrogen Life Technologies, Carlsbad, CA, USA) following the manufacturer's instructions. The total RNA concentration and purity were determined using a NanoDrop™ 2000c Spectrophotometer (Thermo Scientific, USA). The 1.5% agarose gel electrophoresis was performed to check the RNA integrity. One µg of total RNA was used for cDNA synthesis with a final volume of 20 µL, using PrimeScript™ RT reagent Kit (TaKaRa, Japan) following the manufacturer's instructions.

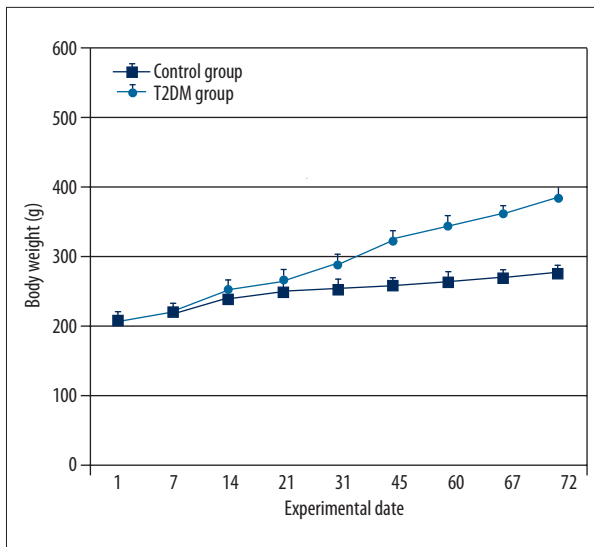


Figure 1. The body weight of rats. High-fat, high-sugar feeding resulted in greater increases in body weight in T2DM rats than in controls. Values are means \pm SD. $n=12$ /group.

Real-time quantitative PCR

To measure the relative mRNA expression, real-time qPCR was performed with an ABI 7500fast System (Applied Biosystems, Foster City, CA) with SYBR Premix Ex Taq™ reagent (TaKaRa, Japan). The housekeeping gene *Gapdh* was used as a reference gene for normalization. The primers sequences were as follows: *Pten* (NM_031606.1): 5'-CCCAGTTTGTGGTCTGCCAGC-3' and 5'-ATGAGCTTGTCTCCCGCCG-3'; *Fabp4* (NM_053365.1): 5'-GTCTGGTACATGTGCAGAA-3' and 5'-CTCTGTAGAAGTCACGCCT-3'; *Gapdh* (NM_017008.4): 5'-GGTGAAGTCTGGTGAACG-3' and 5'-CTCGCTCTGGAAGATGGTG-3'. The qPCR was performed with 12.5 μ l 2X SYBR /ROX qPCR Mix and 10 pmol forward and reverse primers specific for the respective genes, in a total volume of 25 μ l. The following reaction conditions were applied: 2 min at 95°C, 40 cycles of 15 s at 95°C and 30 s at 60°C, and a melting curve protocol (plates read when increased 0.5°C every 5 s from 65°C to 95°C) for amplicon specificity verification. All amplifications were run in triplicate, and any doubtful

curves were excluded. The amplification efficiency for *Pten*, *Fabp4* and *Gapdh* was estimated by real-time qPCR with different diluted cDNA template. The threshold cycle (Ct) values from all amplifications were measured.

Statistical analysis

The comparative $2^{-\Delta\Delta CT}$ method for relative quantitative analysis was used, and the results are expressed as a fold change of expression levels. The mean value of triplicates was applied for all calculations. Results are expressed as mean \pm SD. All statistical calculations were performed with the SPSS 13.0 software package (SPSS Inc.). The *t* test was used for comparisons between 2 groups. Correlation between parameters was determined by Pearson's correlation coefficient (*r*). A *P* value less than 0.05 was considered statistically significant.

Results

Animal model

The body weight of rats throughout the study is shown in Figure 1. At the beginning of the study, there were no significant differences in body weight between the groups. After high-fat diet feeding, the body weight of rats increased faster than in the control group with normal diet ($P<0.01$). The rats in the experimental group with blood glucose levels ≥ 16.7 mmol/L and HOMA-IR ≥ 2.69 (Table 1) were considered as diabetic and were used as the T2DM model for study. Insulin resistance was induced in the T2DM group as shown by hyperinsulinemia and increased HOMA-IR as compared with the control group (Table 1). Not surprisingly, the fasting blood glucose (FBG) in the T2DM group was significantly higher than that of the control group (all $P<0.01$), and the glucose level in the T2DM group was increased obviously compared to that of the control group ($P<0.01$) (Table 1), which indicated that the insulin sensitivity was remarkably decreased in the T2DM group compared to the control group. Phenotypically, T2DM rats appeared drowsy, with slow reaction, depression, loss of hair, and water intake and urine volume increased compared with the control group rats. Some diabetic rats' tails were festered.

Table 1. Serum metabolic parameters in the 2 groups of rats ($\bar{x}\pm s$).

	Random blood glucose (mmol/L)	FPG (mmol/L)	FINS (mU/L)	HOMA-IR
Experimental group (n=12)	21.28 \pm 3.33	9.01 \pm 1.20	9.78 \pm 1.68	3.92 \pm 0.92
Control group (n=12)	6.93 \pm 0.46	5.59 \pm 0.81	7.49 \pm 1.31	1.87 \pm 0.47
t	-14.753	-8.161	-3.715	-6.857
P	0.000*	0.000*	0.001*	0.000*

* $p<0.01$.

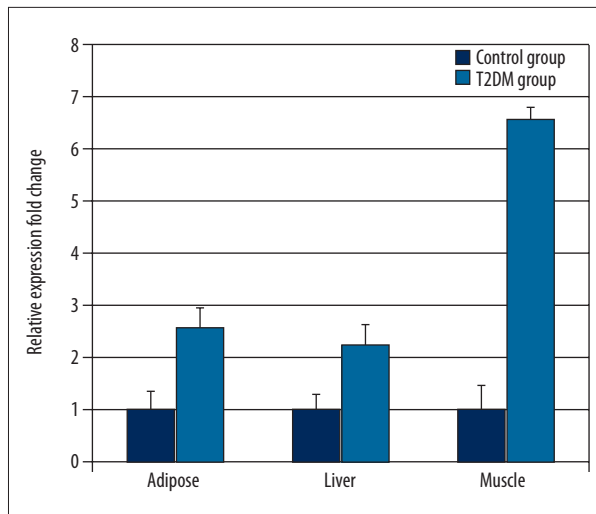


Figure 2. Pten mRNA expressions in the liver, muscle, and adipose tissues of the T2DM rats was determined by real-time PCR (n=12). Values were normalized to Gapdh mRNA expression. The mean change in liver, muscle, and adipose tissues was 2.25-, 6.59-, and 2.6-fold, respectively.

Pten and Fabp4 mRNA expression in liver, muscle, and adipose tissues of T2DM rats

The liver, muscle and adipose tissues were taken from T2DM and control rats and the relative expression of *Pten* mRNA was measured by real-time qPCR. The $2^{-\Delta\Delta CT}$ method for relative quantitative analysis was used since the amplification efficiency (in the range of 0.9–1.2) in *Pten*, *Fabp4*, and *Gapdh* genes is the same. The qPCR results showed that the *Pten* expression levels in liver, muscle, and adipose tissues of the T2DM group were significantly higher than those of the control group (2.25-, 6.59-, and 2.6-fold higher in liver, muscle, and adipose tissues, respectively $p < 0.05$) (Figure 2, Supplementary Table 1). *Pten* was

highly expressed in muscles of T2DM rats (Figure 2). Compared to the control group, *Fabp4* mRNA relative expression in the T2DM group was also increased by 1.43-, 4.35-, and 5.17-fold in the liver, muscle, and adipose tissues of T2DM rats, respectively ($P < 0.01$) (Figure 3, Supplementary Table 2). Interestingly, *Fabp4* was also highly expressed in adipose tissues and muscles. The results indicate *Pten* and *Fabp4* may be correlated and function in muscle and adipose tissues of T2DM rats.

The gene expression correlation between Pten and Fabp4 in liver, muscle, and adipose tissues of T2DM rats

Since PTEN and FABP4 interacted each other, we analyzed the expression correlation in liver, muscle, and adipose tissues of T2DM rats by Pearson correlation coefficient, finding that the expression levels of *Pten* and *Fabp4* in muscle and adipose tissues of T2DM rats were positively correlated ($P < 0.05$) (Table 2), but in the liver tissue of T2DM rats no significant correlation was found ($r = 0.095$, $P = 0.839$). The correlation study verified the result from qPCR by which *Pten* and *Fabp4* were found to be highly expressed in adipose and muscles of T2DM rats.

Discussion

Type 2 diabetes is a complex and heterogeneous disease resulting from a combination of genetic and environmental factors. Many investigators developed the rat model by high-fat diet following low-dose STZ injection, closely mimicking the natural characteristics of T2DM [13–15]. Therefore, we used the T2DM rat model previously established to study the gene expression and correlation of *Pten* and *Fabp4* in the liver, muscle, and adipose tissues. In the present paper, we intended, for the first time, to study the expression and correlation between *Pten* and *Fabp4* in the liver, muscle, and adipose tissues of T2DM rats.

Supplementary Table 1. PTEN expression value in adipose, liver, and muscle tissues by real-time PCR.

	PTEN CT	GAPDH CT	ΔCT	$\Delta\Delta CT$	$2^{-\Delta\Delta CT}$	std
Adiposae						
Control group	23.12±0.4	17.41±0.21	5.71±0.35	0	1	0.35
T2DM group	23.1±0.42	18.77±0.15	4.33±0.36	-1.38	2.6	0.36
Liver						
Control group	25.11±0.28	18.26±0.3	6.85±0.29	0	1	0.29
T2DM group	23.43±0.35	17.75±0.41	5.68±0.38	-1.17	2.25	0.38
Muscle						
Control group	29.39±0.52	26.23±0.34	3.16±0.46	0	1	0.46
T2DM group	27.79±0.2	27.35±0.25	0.44±0.23	-2.72	6.59	0.23

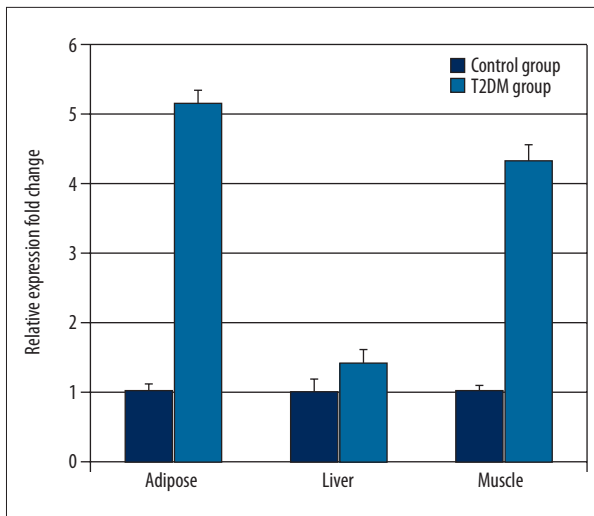


Figure 3. Fabb4 mRNA expressions in the liver, muscle and adipose tissues of the T2DM rats was determined by real-time PCR (n=12). Values were normalized to Gapdh mRNA expression. The mean change in liver, muscle, and adipose tissues was 1.43-, 4.35-, and 5.17-fold, respectively.

Adipose tissue, liver, and muscle are the principal responsive tissues in whole-body glucose homeostasis and their defects lead to insulin resistance and T2DM. A previous study

demonstrated that Pten liver-specific deletion in mice could increase fatty acid synthesis, enhance liver insulin action, and improve systemic glucose tolerance [16]. Similarly, muscle- and adipose-specific PTEN deletions prevented the development of IR and diabetes induced by a high-fat diet in mice [17,18]. Overexpression Of PTEN in 3T3-L1 adipocytes significantly inhibits insulin-stimulated GLUT4 translocation, glucose uptake, and membrane ruffling, all of which are dependent on PI3K activity [19]. Few attempts have been made to fully investigate the changes of *Pten* in adipose tissue under insulin resistance conditions. Our results show that *Pten* was highly expressed in adipose, liver, and muscle tissues of T2DM rats, indicating that PTEN plays an important role in IR of T2DM rats. The increased expression of *Pten* was also observed in a diabetic mouse [20]. The result was consistent with our finding from T2DM rats, indicating that PTEN might suppress the PI3K activity, which induced IR in diabetic rats. It is necessary to further investigate the insulin signaling PI3K/Akt pathway in *Pten* highly expressed tissues of T2DM rats to define the mechanism of IR.

Fabp4 encodes the fatty acid binding protein found in adipocytes [21]. It is reported to function in fatty acid uptake, transport, and metabolism and plays a key role in obesity-induced insulin resistance [10]. A *Fabp4* knockout mouse study showed that *Fabp4* plays a key role in diabetes and atherosclerosis.

Supplementary Table 2. FABP4 expression value in adipose, liver, and muscle tissues by real-time PCR.

	PTEN CT	GAPDH CT	Δ CT	$\Delta\Delta$ CT	$2^{-\Delta\Delta$ CT	std
Adiposae						
Control group	16.49±0.1	17.41±0.07	-0.92	0	1	0.09
T2DM group	15.49±0.21	18.78±0.13	-3.29	-2.37	5.17	0.18
Liver						
Control group	27.38±0.15	18.03±0.19	9.35	0	1	0.17
T2DM group	26.6±0.07	17.77±0.18	8.83	-0.52	1.43	0.16
Muscle						
Control group	26.5±0.11	22.08±0.07	4.42	0	1	0.1
T2DM group	30.47±0.25	28.17±0.16	2.3	-2.12	4.35	0.22

Table 2. The correlation between the expression of Pten and Fabp4 genes in T2DM rats.

Tissue	Pearson correlation coefficient (r)	P value
Liver	0.095	0.839
Muscle	0.667	0.018*
Adipose	0.662	0.026*

* P<0.05.

Therefore, *Fabp4* has been suggested as a potential therapeutic target for intervention in metabolic syndrome [22]. A previous study found that the serum FABP4 level was significantly increased in obese patients, and had a significant positive correlation with BMI and blood pressure. This observation suggests that FABP4 is involved in the development of metabolic syndrome and obesity [23]. Our previous study also found that the plasma level of FABP4 was also increased in women with gestational diabetes mellitus showing severe insulin resistance [12]. The deletion of *Fabp4* in macrophages can lead to elevated glucose uptake in adipocytes and insulin signal conduction enhancement [24]. On the other hand, the loss of *Fabp4* can improve peripheral insulin resistance and protect β cell function and thus glucose and lipid metabolism [24].

A recent study found that PTEN can interact with FABP4 using yeast 2-hybrid assay, and the interaction was confirmed by co-immunoprecipitation and gel-filtration assays [11]. The gene expression profile of PTEN-null keratinocytes analysis showed higher expression of FABP4, suggesting the importance of PTEN in the regulation of FABP4 expression at transcription level [25].

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Conclusions

The present study shows that the expression of *Pten* and *Fabp4* was increased and was correlated in adipose and muscles of T2DM rats. Our study suggests a possible link between PTEN/FABP4 co-expression and pathogenesis of T2DM. The specific mechanism should be investigated further.

Conflicts of Interest

The authors declare no conflict of interest.