Assessment of Thrombospondin-1 Level in Type II Diabetic Patients

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Abstract:

The study is intended to asses serum levels of Thrombospondin-1, fasting blood glucose in type 2 diabetic patients, also correlation between Thrombospondin-1 in both males and females.

The study was conducted on randomly selected 65 type 2 diabetic patients (34 males and 31 females) attending the diabetes mellitus center in Al-Sadder Teaching City in Al- Najaf province , Iraqi and a group of 24 apparently healthy subjects (12 Males and 12 Females) were included as a control group . The Study was carried out from August 2013 to February 2014.The patients' age was ranging from 35 to 64 years old.

The results indicated a significant increase ($p<0.05$) in serum FBG and TSP-1 levels in diabetic patients in comparing with healthy groups.

The results also revealed no significant differences ($p> 0.05$) in serum TSP-1 levels between males and females in both patients and healthy groups, while the results of FBG levels significantly ($p<0.05$) increase in females than males in both patients and healthy groups.

The results have been shown significant positive correlation ($P<0.05$) between TSP-1 and FBG in (males and females), males, females DM patients.

The present study concluded that Thrombospondin-1 were marker for detection and diagnosis of diabetic patients type 2.

Key word: Fasting blood glucose ,Thrombospondin-1, Type II diabetic patients.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders of carbohydrates metabolism, this condition occurs when inadequate uptake of glucose by the cells of the body causes high levels of glucose in the blood (hyperglycemia) [1].The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic ß-cell damage (type 1 DM), and those that are a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of ß-cell impairment (type 2 DM)   [2]**.**

Type II diabetes is most commonly associated with the obesity in middle-aged individuals, it is due to reduction in the number or affinity of insulin receptors on the plasma membrane of cells in target tissues, or an abnormal binding of insulin to the receptors [3]. Patients with type I diabetes mellitus depend on external insulin (most

commonly injected subcutaneously) for their survival because this hormone is no longer produced internally .

Patients with type II diabetes mellitus are insulin resistant, have relatively low insulin production, or both, some patients with type II diabetes may eventually require insulin when other medications fail to control blood glucose levels adequately [4].

Thrombospondin-1 (TSP-1) is a well-studied glycoprotein that has four motifs (*i.e.*, adhesive domains; *N*-terminal domain, type I repeats, type III repeat and a *C*-terminal domain) [5] . TSP-1 suppresses endothelial cell proliferation, migration, and tube-formation and induces endothelial apoptosis [6;7;8] .Thus, TSP-1 is an endogenous inhibitor of angiogenesis under physiological and pathological conditions , including in the context of malignancy [9;10;11]. TSP-1 also modulates the extracellular matrix and leads to degradation and remodeling of connective tissues [12].

TSP-1 controls tissue perfusion and homeostasis by regulation of nitric oxide (NO) signaling [13]. Thus, the roles of TSP-1 in the regulation of angiogenesis are extremely complex and involve direct and indirect effects on stromal cells and the extracellular matrix. Regulation of angiogenesis and degradation of the extracellular matrix are also crucial steps for tumor growth, cancer cell invasion, and metastasis in nearly all solid tumors, and TSP-1 plays important roles for cancer cell invasion and dissemination in malignancies. In fact, the regulation of tumor growth and progression by TSP-1 [9]. TSP-1 plays an important role in the regulation of various biological activities, including vascular homeostasis, immunity, and wound healing [14;15;16].

- **Materials and Methods**

1- Patients and healthy groups

The study was performed on randomly selected 65 type 2 diabetic patients (34 males and 31 females) attending the diabetes mellitus center in Al-Sadder Teaching City Al- Najaf province , Iraqi . The patients' age was ranging from 35 to 64 years old. The study was carried out from the period August 2013 to February 2014.

Diabetes mellitus was diagnosed by consultant doctors. The information of patients were obtained through a questionnaire consisted of the name, sex, age, weight, height . Patients with renal dysfunction, heart diseases, who were on drugs affect oxidative stress, i.e., antioxidants, antihyperlipidemic agents were excluded from the current investigation.

A group of 24 apparently healthy subjects (12 Males and 12 Females) were included as a control group. Type 2 diabetic Patients are divided into subgroups according to the gender, ages, duration of disease and body mass index .

2- Collection of blood samples

Five milliliters of venous blood samples were drown using a disposable needle and plastic syringes from each patients and controls subject. Blood was left at room temperature for 10 minutes to clot, centrifuged 6000 rpm for 10 minutes, and then serum was separated and transported into new disposable tubes.

- **Biochemical measurement**

1-Determination of serum Thrombospondin-1 level

Thrombospondin ELISA Kit For the quantitative determination of human thrombospondin-1 (TSP-1) concentrations in serum was supplied by CUSABIO, USA.

2-Determination of fasting blood glucose concentration:

Glucose kit for quantitative determination of Glucose in human serum was supplied by Bio Merieux, France.

- **Statistical Analysis**

Analysis of data was performed by using megastat (Version 10.12) for excel 2007 in the home computer. The results were expressed as (mean ± standard deviation) . P-value < 0.05 was used as a level of statistically significant [17].

- **Results**:

1- Comparison between diabetics mellitus patients and healthy groups

A. Thrombospondin-1 level

The results showed in figure (1) were indicated a significant increase (P<0.05) in serum Thrombospondin-1 (TSP-1) level in diabetic patients 10.942 ± 0.043 ng/ml in comparing the with control group 1.181 ± 0.226 ng/ml.
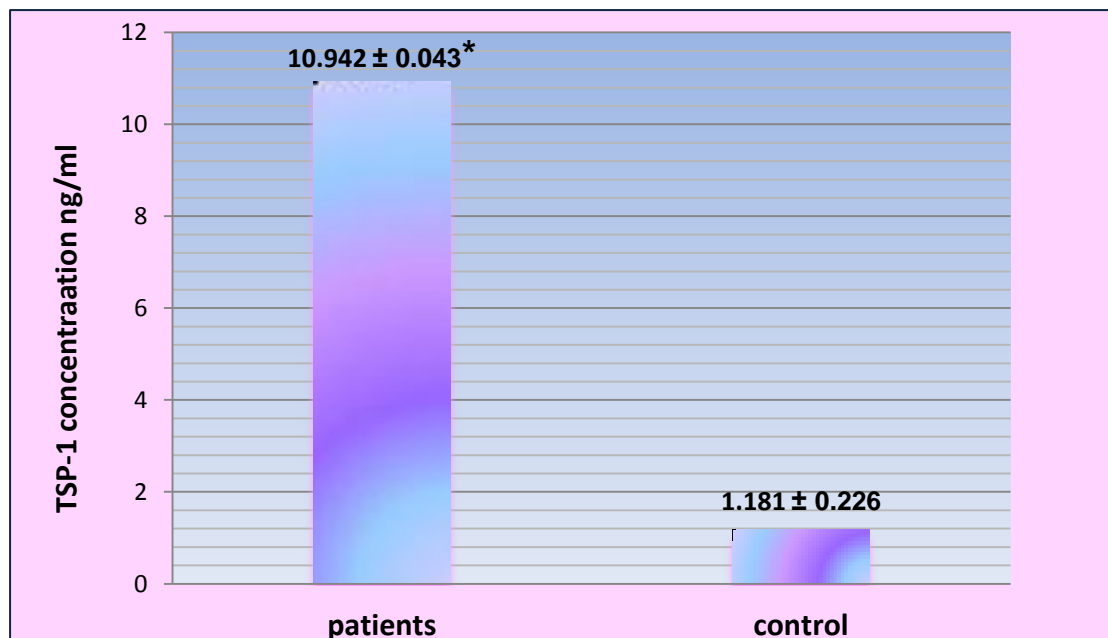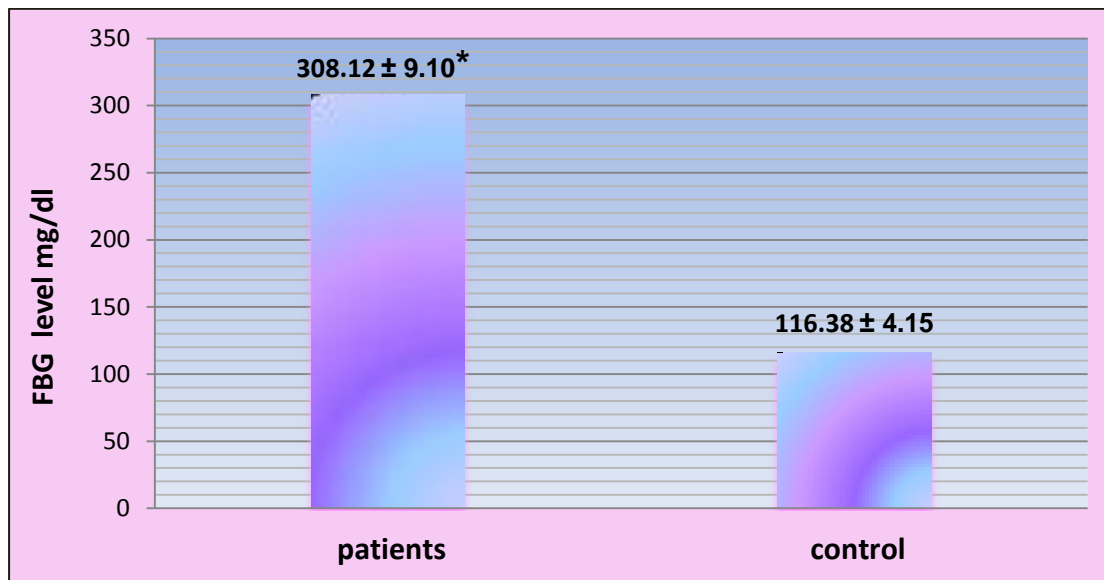

(*):Statistically significant differences (p<0.05) between patients and control groups.

Figure (1): Thrombospondin-1 level at diabetic mellitus patients and control groups.

B. Fasting blood glucose level

The results showed in figure (2) indicate a significant increase (P<0.05) in fasting blood glucose (FBG) level at diabetic patients 308.12 ± 9.10 mg/dl in comparing with healthy control group 116.38 ± 4.15mg/dl.

(*****):Statistically significant differences at (p<0.05) between patients and control groups.

Figure (2): Fasting blood glucose level at diabetic mellitus patients and control groups.

2-Comparison between diabetic mellitus patients and healthy group according to gender

A. Thrombospondin-1 level

The results of table (1) reveal significant increase (p< 0.05) in serum thrombospondin-1 (TSP-1) level in both males and females patients groups in comparing with males and females of healthy groups respectively, while the table shows no significant differences (p>0.05) in serum TSP-1 level between males and females at both patients and healthy groups.

Table (1): Thrombospondin-1 level in both gender of diabetic mellitus patients and control groups.

Groups	Mean ±S.E.			
	Control		Patients	
	n =24		n =65	
	Male	Female	Male	Female

Criteria	n = 12	n =12	n =34	n =31
TSP-1ng/ml	1.286 ± 0.069 [a]	1.077 ± 0.030 [a]	11.177± 0.284 [b]	10.684 ± 0.357 [b]

(The different letters refer to significant differences at level (P<0.05), same gender in different groups).(The same letters refer to no significant differences ,different gender in same groups).

B. Fasting blood glucose level

The results of table (2) reveal a significant increase (p< 0.05) in serum fasting blood glucose (FBG) level in females than males in both patients and healthy groups , while the table shows a significant increase (p<0.05) in serum FBG level at both males and females patients groups in comparing with males and females of healthy groups respectively.

Table (2): Fasting blood glucose level in both gender of diabetic mellitus patients and control groups.

Groups / Criteria	Mean ±S.E.			
	Control		Patients	
	n =24		n =65	
	Male	Female	Male	Female
	n = 12	n =12	n =34	n =31
FBG mg/dl	96.25 ± 4.11 [a]	119.50 ± 5.23 [b]	291.12 ± 11.32 [c]	326.77 ± 13.92 [d]

The different letters refer to significant differences at level (P<0.05) between groups.

3- Correlation between Thrombospondin-1 and Fasting blood glucose levels

The results of correlation and linear regression between TSP-1and FBG levels in patients are indicated:

1-The presence of a significant positive correlation at (P<0.05) between TSP-1and FBG concentrations of DM patients (males and females) , (r =0.978, TSP-1 =3.452+ 0.024 FBG) ,(figure 3).
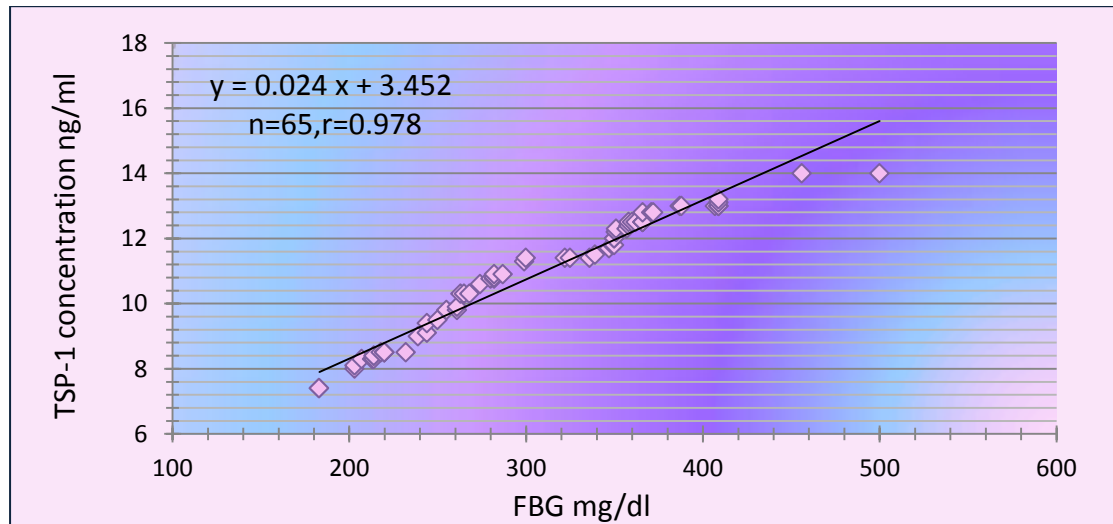
Figure (3): Correlation between Thrombospondin-1 and Fasting blood glucose in type 2 DM patients .

2- The presence of a significant positive correlation at ($P<0.05$) between TSP-1and FBG concentrations in females of DM patients, (r =0.976, TSP-1=2.504+ 0.025 FBG) , (figure 4).
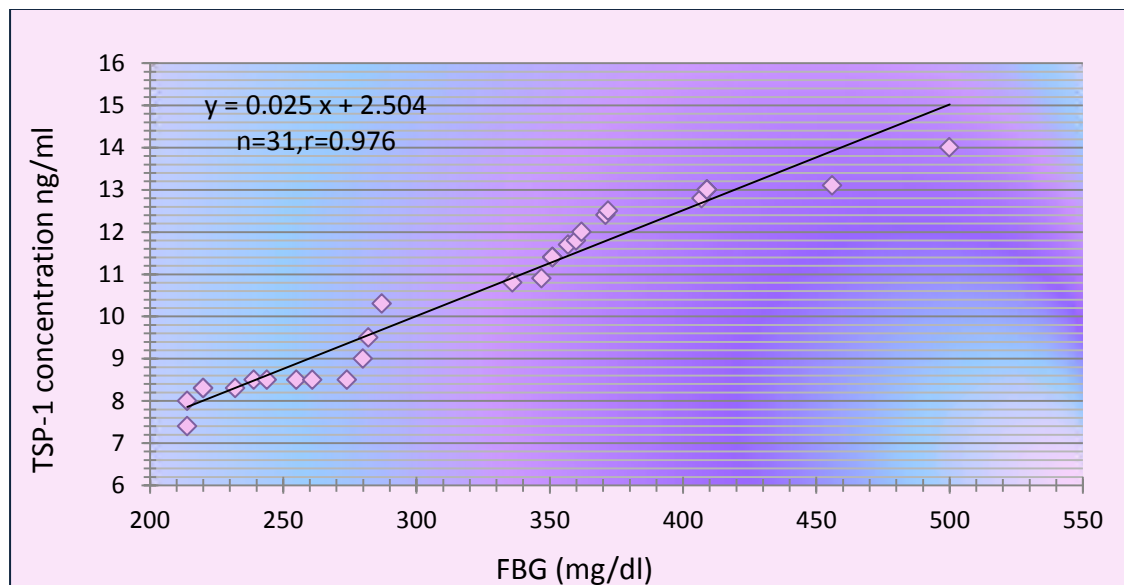

Figure (4): Correlation between Thrombospondin-1 and Fasting blood glucose in type 2 DM female patients.

3- The presence of a significant positive correlation in males DM patients between TSP-1 and FBG concentrations at ($P<0.05$) , (r =0.969,TSP-1=4.087 + 0.024 FBG) , (figure 5).
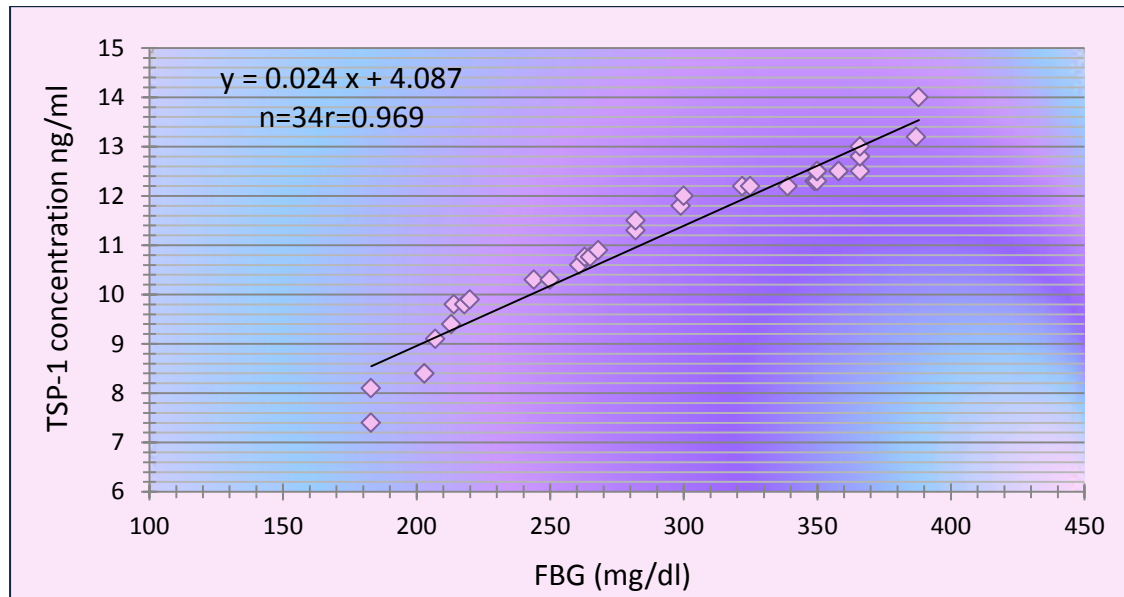
Figure (5): Correlation between Thrombospondin-1 and Fasting blood glucose in type 2 DM male patients.

- **Discussion**

A. Blood glucose level

The present results of presents study indicated significant increase (p<0.05) in serum blood glucose concentration in comparing with control group as presented in figure (2).

Most people of type 2 diabetic are still able to produce insulin at diagnosis, the insulin produced is unable to perform its primary job , which is helping the body cells used glucose for energy and this is due to a problem in the body insulin receptors also may be a problem with chemical made up of insulin itself and this conditions called insulin resistance [18;19;20].

The females patients showed significantly high levels of FBG than males as presented in table (2) , that result was agreement with other study [21]. Diabetes confers a markedly increased risk of cardiovascular events in both males and females [22]. However, women with diabetes are more susceptible to increased cardiovascular mortality [23]. Diabetic women may be subject to more adverse changes in coagulation, vascular function and cardiovascular risk factors than diabetic men [24].

B. Thrombospondin-1 level

The present study revealed a significant increase (p<0.05) in Thrombospondin-1 level in diabetic patients in comparing with control groups as presented in figure (1).

Previous study suggested that expression of Thrombospondin-1 is markedly up regulated in tissue from diabetic patients and animal models [25;26]. Other researchers suggests that hyperglycemia potentially induced TSP-1 synthesis by vascular cells through pathways that may be involved glucose mediated activation of hexosamine [27;28].

Present studies agreement with other studies that's demonstrated relation between diabetes and TSP-1 [29;30].

Elevated blood glucose concentrations increased TSP-1 synthesis which was associated with reduced cell proliferation, increased TGF- β1 bioactivity and stimulation of fibronectin synthesis [31; 32]. TSP-1 loss also improved metabolic dysfunction , reduced blood glucose level [33].

Recent studies show that TSP-1 is highly expressed in various samples from various species including human and loss of TSP-1 in various diabetic rats [34;35].Under high glucose condition demonstrated decrease TSP-1 expression and down regulation of TSP-1 [34].

Previous study suggested that TSP-1 play an important roles in insulin resistance associated with type 2 diabetic and demonstrated that deletion or reduced TSP-1 may improved glucose-insulin homeostasis is associated with reduced inflammation and macrophage accumulation and decease adipose inflammation [36].In vitro studies support the effect of TSP-1 on macrophage mobility [37].

Voros *and* Lijnen.[38] found that obese TSP-1 deficient mice have improved glucose tolerance and insulin sensitivity. study of Winzer *et al*.[39] found of an association between pro inflammatory cytokines such tumor necrosis factor-α (TNF-α) and mRNA TSP-1 expression in subcutaneous adipose tissue.

Study of Belmadani *et al*.[40] showed that TSP-1 expression by cardiac fibroblast was up regulated in response to high glucose and also up regulated by mRNA and protein TGF-β1.

Study of Ramis *et al*.[41] confirmed that TSP-1 gene highly expressed in VAT females than males and that finding agreement with present study as presented in table (1). TSP-1 may be stimulated a proliferation of adipocyte and also effect adipocyte fatty acid in obese females than males [42; 43].

The present studies acceptance with other studies have reported that TSP-1 over expressed in obese human and rats [44;41] .TSP-1 is an adipokines which infiltrates adipose tissues during obesity [36].

3-The correlation between thrombospondin-1 and blood glucose

The results of correlation represent a positive significant correlation ($p<0.05$) between TSP-1 and blood glucose concentrations in both males and females , (male and female) diabetic patients as presented in figures (3,4, 5).

Previous studies have shown the hyperglycemia association with increase expression of TSP-1 [27] .Further studies showed that TSP-1 is expressed in the arterial wall of animal models of diabetic type 2, also in tissues from patients with diabetes [25; 45].

Many studies proved that TSP-1 may be important in the complications of diabetes mellitus by induced vascular smooth muscles (VSMCs) proliferation, migration and atherosclerosis in type 2 diabetes [46].

Few studies have examined the relation between TSP-1 and hyperglycemia by effect on VSMC gene expression. The combination of hyperglycemia and TSP-1 for 6 hour incubation period increased a number of gene altered, also hyperglycemia alone did not cause the down regulation of any gene [47;25] .

Previous work showed a relation between hyperglycemia and induces TSP-1 mRNA in VSMCs after 24 hours, which is consistent with our data [27].

Study of Maile *et al*.[48] showed that hyperglycemia mice was a significant increase ($p<0.05$) in TSP-1 and TSP-1 binding to CD47/IAP and this associated with enhanced proliferative response to insulin growth factor-1(IGF-1).

Previous studies suggest that significant contributor to the increase in TSP-1 protein due to its protection from lysosomal degradation, In addition to stability and rapid internalization by endocytic receptor LRP-1(low density lipoprotein-related protein) that leads to degradation in type 2 diabetes patients [49;50]. Further studies proved that the level of LRP-1 receptor differ from diabetes in comparing with normal glucose and these difference that account for the change in TSP-1 uptake [51].

Conclusion: Thrombospondin-1 is a good bio marker for prediction and diagnosis for type 2 diabetes mellitus and the study also proved a positive relation between thrombospondin-1 and blood glucose.

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تقييم مستوى الثرومبوسبوندين - 1 لدى مرضى السكري النوع الثاني

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الخلاصة

تهدف هذه الدراسة إلى تقييم مستويات مصل دم كل من الثرومبوسبوندين-1(TSP-1), السكر الصيامي(FBG). وكذالك إيجاد العلاقة بين TSP-1 و FBG في كلا الذكور والإناث .

أجريت هذه الدراسة على 65 شخص مصاب بداء السكري النوع الثاني (34 ذكور و 31 اناث) وبصورة عشوائية من الوافدين لمركز الداء السكري في مدينة الصدر التعليمية في محافظة النجف الأشرف /العراق و21 شخص سوي (12 ذكور و 12 إناث كمجموعة سيطرة . وقد أجريت الدراسة للفترة من أيلول 2013 إلى شباط 2014 .وكان أعمار المرضى تتراوح من 35-64 سنه.

أشارت الدراسة إلى وجود زيادة معنوية (p<0.05) في مستويات مصل دم كل من FBG و TSP-1 لمرضى السكري مقارنة بمجموعة السيطرة.

كشفت النتائج عدم وجود فروق معنوية (p> 0.05) في مستويات مصل دم TSP-1 بين الذكور والإناث لكلا مجموعة السيطرة و المرضى ، في حين أن نتائج مستوى FBG تزداد معنويا (p> 0.05) في الإناث مقارنة مع الذكور في كلا مجموعة السيطرة والمرضى.

وقد أظهرت النتائج علاقة إيجابية معنوية (P< 0.05) بين TSP-1 وFBG في (ذكور وإناث)، ذكور، إناث المرضى.

نستنتج من الدراسة إن Thrombospondin-1 تعد دليل لكشف وتشخيص مرض الداء السكري من النوع الثاني .

مفتاح البحث: سكر الدم الصيامي , ثرومبوسبوندين -1 , داء السكر النوع الثاني.