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Research Article

Pancreatic Stone Protein/ regenerating Protein (PSP/reg) as a Biochemical Marker for prediction of Microvascular Complications of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) characterized by insulin resistance (IR) and progressive decline in functional beta (β) cell mass partially due to increased β cell apoptosis rate. Pancreatic stone protein /regenerating protein (PSP/reg) is produced mainly by the pancreas and elevated drastically during pancreatic disorder. Beta cells are experiencing apoptosis that stimulate the expression of PSP/reg gene in surviving neighboring cells, and that PSP/reg protein is subsequently secreted from these cells which could play a role in their regeneration.

Objectives: To analyze serum levels of PSP/reg protein in T2DM patients and evaluate its correlation with the microvascular complications of the disease.

Subjects and Methods: One hundred fifty participants (64 males, 86 females; aged 40–70 years) include T2DM patients with and without microvascular complications as well as healthy controls were enrolled in this study. Biochemical parameters like random blood glucose (RBG), glycated hemoglobin (HbA1c), lipid profile, urea and creatinine (Cr) were measured. Serum values of PSP/reg protein were measured by enzyme- linked immunosorbent assay (ELISA).

Results: Serum levels of PSP/reg protein were found significantly elevated in T2DM patients with microvascular complications compared with those of controls ($p<0.001$) and T2DM patients without microvascular complications ($p< 0.001$).PSP/reg protein is correlated with type 2 DM duration ($p<0.001$), RBG ($p<0.001$), and HbA1c ($p<0.001$). The area under the curve (AUC) for the presence of microvascular complications was 0.973.

Conclusion: PSP/reg protein may be used as biochemical marker to predict microvascular complications of T2DM.

Introduction

Diabetes mellitus (DM) is a complex metabolic disease characterized by hyperglycemia resulting from impairment of carbohydrate, fat, and protein metabolism as a result of impaired insulin secretion, action or both (1) . In 2021, there were 537 million diabetics worldwide, and this number is expected to rise to 700 million by 2045 (2). Human vascular system is directly and indirectly affected by diabetes, resulting in macrovascular and microvascular complications (3).

The root cause of type 2 DM is peripheral insulin resistance, which causes an initial compensatory increase in insulin production

by beta (β) cells (4-7). Later, these cells begin to decline in function and mass and can no longer compensate (8), resulting in the development of T2DM (9).

The impairment of β-cell function exhibits a marked progression over time (10). By the time a patient is diagnosed with diabetes there is a significant reduction, not only in beta cell function (80%) but also in mass (30% - 40%) (11-13). Patients with T2DM experience increased β-cell apoptosis, while neither replication nor neogenesis of beta cells is affected, indicating that increased beta cell loss is mainly responsible for its decline in mass (14).

Pancreatic stone protein /regenerating protein (PSP/reg) is a 16-kDa lectin binding protein (15,16). It is secreted into pancreatic juice by pancreatic acinar cells (17), and it is highly upregulated during acute or chronic pancreatitis (18). In addition, PSP/reg protein was found to have a regenerative capacity. In previous studies, it was reported that β-cells undergoing apoptosis induce neighboring cells to express the PSP/reg gene, resulting in PSP/reg protein secretion, thereby providing a cue to the microenvironment to regenerate (19).

A number of diseases other than pancreatic dysfunction are associated with PSP/reg, and it has been shown to be elevated in sepsis (20,21), ventilator-associated pneumonia (VAP)(22) and exacerbation of chronic obstructive pulmonary disease (COPD) (23) . PSP/reg and diabetes have recently been linked. PSP/reg levels were increased in type 1 and type 2 DM and in maturity onset diabetes of the young (MODY 3) (24,25).

This study aims to analyze serum levels of PSP/reg protein in patients with T2DM, and to determine their association with the biochemical parameters and microvascular complications of T2DM.

Subjects and Methods

Study population

One hundred fifty participants (64 males, 86 females; age range 40–70 years) participated in this case control study.

The participants were divided into three groups including T2DM patients without microvascular complications (n = 50) and with microvascular complications (n= 50), as well as healthy sex and age matched controls (n = 50).

The study took place at Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in AL-Faiha Hospital, Basrah, Iraq, from January 2018 to December 2018, and was approved by the research Ethical Committee of Basrah College of medicine. Type 2 diabetics were evaluated according to the American Diabetes Association (ADA) criteria (26) .

The chronic microvascular complications of DM were evaluated, diabetic patients were checked for:

1. Nephropathy: It was defined by urinary albumin excretion rate (UAE) of at least two specimens > 30 mg/24 hours or low glomerular filtration rate.
2. Retinopathy: was evaluated and diagnosed using a standard fundus eye examination. [3] Neuropathy: It was diagnosed on the basis of clinical examination, electromyography (EMG) and nerve conduction studies (NCS) (27).

Exclusion criteria were: (1) T1DM; (2) Active infection, tumor, inflammatory disorder, hepatic disorder;(3) Pregnancy.

Measurements of Anthropometric and Biochemical Parameters

Standardized questionnaire was used to obtain a comprehensive clinical assessment. Anthropometric measurements including height, weight and body mass index (BMI) were collected. Data on age, gender, smoking and drinking habits, hypertension, diabetes duration, medical history, and drug history was also collected.

Venous blood samples were taken and placed in EDTA tubes for the measurement of HbA1c and in clot activator tubes, centrifuged then serum aliquoted and some of it used for the measurement of random serum glucose, random lipid profile, urea and creatinine and the rest stored at -20 until PSP/reg analysis.

The random serum glucose, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) concentrations, urea and creatinine (Cr) were measured by COPAS INTEGRA 400 plus (Roche Diagnostics, Mannheim, Germany). HbA1c was measured using an ion-exchange high performance liquid chromatography (HPLC) (Bio-Rad Variant™ II Turbo analyzer).

The serum PSP/reg protein level was determined using enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology Co.,Ltd) in accordance with manufacturer's instructions.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), version 23 (IBM). The results are displayed as means ± standard deviation (SD) or as percentages. Spearman's correlation coefficient was used to assess the correlation between PSP/reg and clinical parameters. Continuous variables were analyzed between two groups only using 2-tailed t-testing and between more than two groups using Analysis of variance (ANOVA) followed by Tukey post-hoc test. Categorical variables were analyzed with chi-square test. Area under the curve (AUC) values were reported with 95 % confidence intervals (95% CI). A P Value < 0.05 considered statistically significant.

Results

Baseline and biochemical characteristics

The baseline and biochemical characteristics of the study groups are shown in (Table 1) and (Table 2) respectively. Diabetic patients had higher mean BMI, systolic blood pressure (BP), RBG, HbA1c, TG levels and lower HDL levels than controls.

PSP/reg levels in different study groups

Serum levels of PSP/reg from controls and diabetics are shown in (Figure 1). Elevated levels of PSP/reg were observed in T2DM patients compared to controls (P<0.001). PSP/reg levels were notably higher in T2DM patients with microvascular complications (202.2 ng/ml ±143.47) than in those of controls (17 ng/ml ±7.07, p < 0.001), and T2DM patients without microvascular complications (30.4 ng/ml ±15.38, p < 0.001).

Table 1: Baseline characteristics of subjects

Group	Control N=50	T2DM without microvascular complications N=50	T2DM with microvascular complications N=50	P-value
Age (years)[a]	51.8±8.1	51.1±8.6	52.5±6.1	**0.664**
Gender male (%)£	44 %	46%	38 %	**0.702**
Duration (years)♣	-----	4.86±3.123	7.78±5.625	**<0.001**
BMI (kg/m2)[a]	28.142±5.61	32.34±6.45*	31.11±4.98*	**0.001**
Systolic BP (mmHg)[a]	122.2±8.154	130.8±18.9*	142±21.38*†	**<0.001**
Diastolic BP (mmHg)[a]	79 ± 6.468	79.8±10.9	84±12.77*†	**0.039**

***significant as compared to controls, † significant as compared to T2DM without microvascular complications. [a] 1-way ANOVA and Tukey`s post-hoc test, £ chi -square test, ♣ Student t-test**

Table 2: Biochemical characteristics of subjects

Group	Control N=50	T2DM without microvascular complications N=50	T2DM with microvascular complications N=50	P-value
Human PSP/reg (ng/ml)[a]	17±7.07	30.4±15.38	202.2±143.47*†	**<0.001**
RBG(mg/dL)[a]	94.78±20.229	198.04±89.91*	237.12±116.9*	**<0.001**
HbA1c (%)[a]	5.09±0.4	8.78±1.56*	9.13±1.92*	**<0.001**
TC (mg/dL)[a]	172.92±44.525	170.6±43.6	172.48±44.33	**0.962**
TG(mg/dL)[a]	113.46±57.902	181.54±114.176*	182.26±84.65*	**<0.001**
HDL-cholesterol (mg/dL)[a]	50.72±16.827	39.9±10.8*	41.48±12.97*	**<0.001**
LDL-cholesterol (mg/dL)[a]	115.48±39	118.56±42.502	120.26±43.364	**0.845**

*Significant as compared to controls, † significant as compared to T2DM without microvascular complications, [a] 1-way ANOVA and Tukey`s post-hoc test.

Metabolic and risk factors correlation

This study demonstrates a significant statistical correlation of PSP/reg protein with T2DM duration (Spearman's rank correlation coefficient 0.590, p<0.001, Figure 2) likewise, a significant statistical correlation was also noticed with the glycemic control, PSP/reg correlated positively with HbA1c (Spearman's rank correlation coefficient 0.572, p<0.001, Figure 3) and RBG (Spearman's rank correlation coefficient 0.577, p <0.001). BMI significantly correlated with PSP/reg (Spearman's rank correlation coefficient 0.254, p <0.05).

Other factors like age, gender and family history have no significant correlation with PSP/reg protein, apart from these, although smoking showed no significant correlation with PSP/reg protein; smokers, however, have higher PSP/reg than nonsmokers

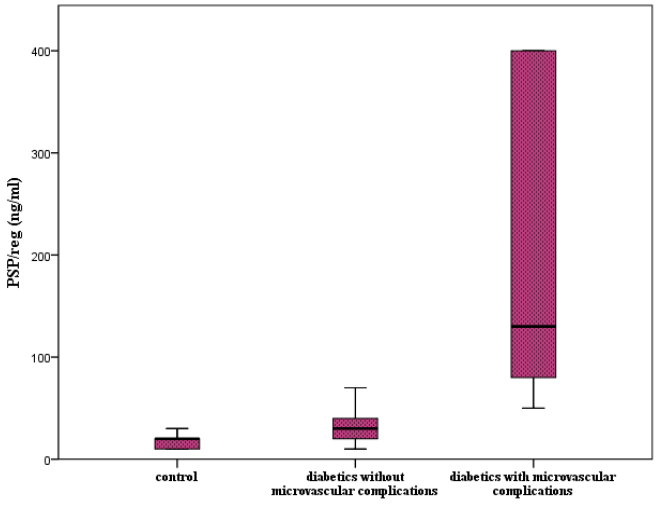

Figure 1: PSP/reg levels in different study groups

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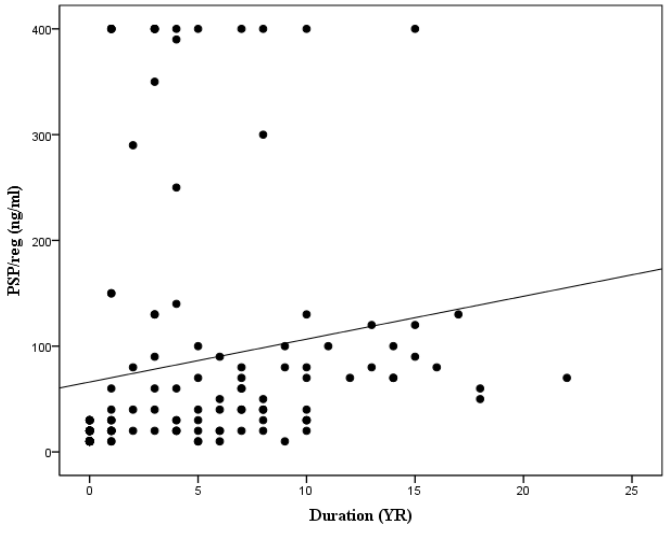

Figure 2: Correlation of PSP/reg with T2DM duration (Spearman r =0.590, p<0.001)

The association between PSP/reg and microvascular complications of T2DM

In addition to the role of HbA1c as predictor of diabetic complications, this study showed that PSP/reg protein have higher and better prediction value with higher specificity for microvascular complications in Type2 diabetes mellitus with AUC of PSP/reg protein for presence of microvascular complications was 0.973 (Figure 4). Additionally, the optimal cutoff point of PSP/reg for detecting microvascular complications based on receiver operating characteristic (ROC) curve analysis was 65 ng/ml (95 % sensitivity, 94 % specificity).

While the AUC of HbA1c for the presence of microvascular complications was 0.78, and the optimal HbA1c cutoff for detecting

microvascular complications was 6.9 % (93 % sensitivity, 54 % specificity).

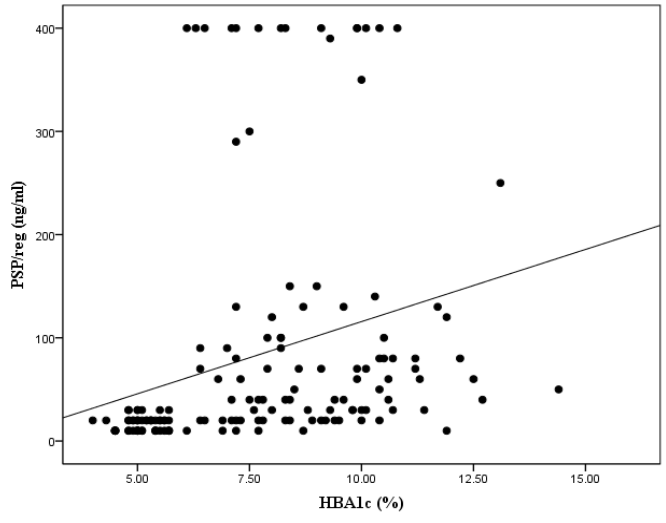

Figure 3: Correlation of PSP/reg with HbA1c (Spearman r =0.572, p<0.001)

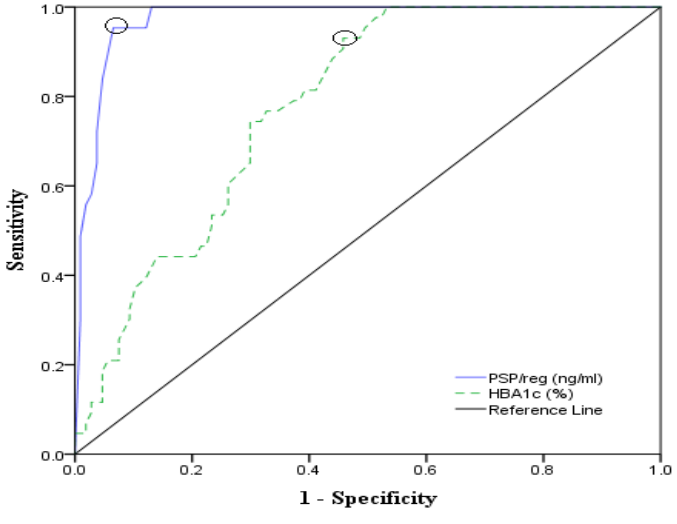

Figure 4: ROC curve for PSP/reg and HbA1c

Discussion

PSP/reg protein in type 2 diabetes is attracting considerable interest worldwide, but despite this, in the developing countries few studies concentrate on its role (28, 29).

Three noteworthy findings were observed in this study. First, Type 2 diabetics have raised PSP/reg. Second, PSP/reg levels increase in subjects with diabetes in a time-dependent manner as evidenced by a positive correlation between PSP/reg and diabetes duration. Third, PSP/reg may reflect microvascular complications in diabetics and may help stratify the patient's outcome.

It has been suggested that there are two scenarios for the pathophysiology of type 2 DM , loss of β-cell function and loss of β-cell mass (9, 14, 30,31) and that when beta cells are damaged, their regeneration is influenced by PSP/reg gene expression (19).

In a study by Bonner et al. (19) it was demonstrated that apoptotic beta cells secrete particles that might stimulate PSP/reg induction within neighboring cells. This means that β-cell apoptosis is linked with β-cell regeneration.

It is also have been suggested that PSP/reg is the product of acinar cells under normal situations but other tissues like regenerating islets ,stomach and intestine seems to produce PSP/reg mainly under pathological conditions(17).

Additionally, Patients with (MODY 3) and T1DM also exhibited raised PSP/reg protein, indicating a role for β-cell apoptosis and pancreatic injury in increasing PSP/reg (24).

A pilot study by Yang et al. (25) reveled that PSP/reg levels increase significantly in patients with T2DM, and they linked it to diabetes stages and complications, however, their study did not draw a distinction between macrovascular and microvascular complications.

The present study focused primarily on the microvascular complications and showed a pronounced increase in PSP/reg protein in diabetics with microvascular complications compared to the other group of patients that did not have microvascular complications, these findings provides a considerable confirmation on the close association between PSP/reg protein and T2DM and its microvascular complications , implying that PSP/reg might be used in the future as promising marker for prediction of diabetic microvascular complications.

Furthermore, the current study found a positive correlation between circulating levels of PSP/reg and diabetes duration implying that there may be an intriguing positive relationship between PSP/reg and diabetes course. This result ties well with the study done by Yang and colleagues (25) . Meanwhile, Uppal et al. (28) found that diabetics with short duration had higher PSP/reg level than those with longer duration. However, they also reported that patients with T2DM with known complications and longer disease duration were found to have higher PSP/reg levels.

PSP/reg levels correlated significantly with serum RBG and HbA1c, suggesting an association between elevated levels of PSP/reg and dysfunction of beta cells. This is in line with recent data indicating that PSP/reg gene expression is promoted by high glucose level, implying that there is a significant feedback loop for regulating β-cell mass (19) meanwhile, there was no correlation between PSP/reg and HbA1c in patients with MODY 3 and T1DM (24, 32).

Although smoking showed no significant correlation with PSP/reg protein in this study but higher levels were found in smokers and this could be attributed to the effect of nicotine and its association with β-cells apoptosis releasing PSP/reg (33). Moreover, Smoking causes an inflammatory response in the lungs and represents a risk factor for pulmonary diseases like COPD. It also elevates soluble inflammatory markers in the bloodstream (34). It has been demonstrated that various types of inflammatory conditions and organ failure are associated with a drastic increase in PSP/reg protein levels, thus the inflammation in smokers' air spaces may increase their blood levels of PSP/reg (20-22).

The positive correlation between PSP/reg protein and BMI is worth mentioning; type 2 diabetics with increased BMI had higher PSP/reg. This may be attributable to the fact that beta cell mass is increased in humans with obesity(35) . Also, obesity itself has been associated with low grade inflammation when linked to diabetes (36) and may lead to increased PSP/reg gene expression (37).

Furthermore, obesity related insulin resistance and hyperglycemia (19) may have contributed to elevated PSP/reg levels in this study.

For future risk assessment, the current study proposes a cutoff value of PSP/reg for predicting microvascular complications. A PSP/reg cutoff of 65 ng/ml provided the highest accuracy in identifying microvascular complications. A cutoff value of 22 ng/ml was suggested by Yang et al. (25) as an indication of the incidence of T2DM in non-diabetic subjects. This study investigated higher cutoff to have a better predictive value for microvascular complications.

This study also compared the AUC for PSP/reg generated by ROC curve analysis with the AUC for HbA1c, PSP/reg was superior to HbA1c for the prediction of microvascular complications.

Conclusion

This study found that PSP/reg levels are elevated in patients with T2DM, especially in those with microvascular complications. Thus, PSP/reg may be used to predict microvascular complications associated with T2DM.

Further research is needed to explore the role of PSP/reg protein in a larger cohort of type 2 DM patients after stratification according to individual microvascular complications and to better understand the role of PSP/reg in T2DM progression.

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Conflict of Interest

Authors declare no conflict of interest

Data availability

Data are available upon reasonable request

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