Research Article

Association of Serum PSP/REG Iα with Renal Function in Type 2 Diabetes Mellitus

Huimin Zhu,1,2 Xiangyun Zhu,1,2 Hao Lin,2,3 Dechen Liu,2,3 Yu Dai,4 Xianghui Su,5 and Ling Li1,2

1Department of Endocrinology, Zhongda Hospital, School of Medicine, Southeast University, No. 87 Dingjiaqiao, Nanjing, Jiangsu 210009, China
2Pancreatic Research Institute, Southeast University, China
3Department of Clinical Science and Research, Zhongda Hospital, School of Medicine, Southeast University, No. 87 Dingjiaqiao, Nanjing, Jiangsu 210009, China
4Nanjing Foreign Language School, Nanjing, Jiangsu 210009, China
5Department of Endocrinology, Changji Branch, First Affiliated Hospital of Xinjiang Medical University, Xinjiang 831100, China

Correspondence should be addressed to Xianghui Su; sxh-wjf@163.com and Ling Li; dr_liling@126.com

Received 2 January 2020; Accepted 7 March 2020; Published 23 March 2020

Academic Editor: Hiroshi Okamoto

Copyright © 2020 Huimin Zhu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. Pancreatic stone protein/regenerating protein I (PSP/REG Iα) is a secretory protein mainly detected in the pancreas. Recent studies revealed increased serum PSP/REG Iα levels may reflect renal dysfunction. The purpose of this study was to detect the relationship between PSP/REG Iα and renal function in subjects with and without type 2 diabetes mellitus (T2DM).

Methods. This cross-sectional study was conducted at Zhongda Hospital, affiliated with Southeast University in China. Serum PSP/REG Iα levels were measured using a method of enzyme-linked immunosorbent assay. Baseline characteristics and biochemical parameters, such as blood urea nitrogen (BUN), serum creatinine (SCr), and uric acid (UA), were collected. The estimated glomerular filtration rate (eGFR) of each individual was calculated using the diagnostic criteria for renal function. Correlations between PSP/REG Iα and renal function parameters were analyzed by Spearman’s rank correlation coefficient using SPSS 20.0 software. Results. Serum PSP/REG Iα levels were significantly higher in T2DM patients than those without T2DM (P < 0.05). The level of PSP/REG Iα was positively correlated with age, SCr, and BUN and negatively correlated with eGFR. The ordinal multiple logistic regression analysis further illustrated that PSP/REG Iα levels were negatively related with eGFR in both groups after adjusting for other parameters. Conclusions. Serum PSP/REG Iα level is significantly upregulated in T2DM patients and reflects renal function in both T2DM and nondiabetic control groups. The relationship between PSP/REG Iα and eGFR suggested that PSP/REG Iα might be a potential indicator of renal dysfunction.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease that affects patients and relates with increased cancer incidence and poor prognosis [1, 2]. As a chronic disease, it is generally accepted that diabetes mellitus causes a variety of macrovascular and microvascular complications during the progression of the disease. Approximately 30–40% of diabetic patients develop nephropathy, and renal injury occurs in about a third of patients [3, 4]. Due to the growing incidence of T2DM, diabetic nephropathy has become the leading cause of end-stage renal disease (ESRD) worldwide. Accumulating evidence from experimental and clinical studies has demonstrated that renal inflammation plays a critical role in the development of diabetic nephropathy [5, 6]. Mou et al. reported that inflammatory stress may be caused by metabolic and hemodynamic disorders in diabetic nephropathy [7]. Inflammatory markers such as interleukin-1β and tumor necrosis factor-α upregulated in the patients with diabetic nephropathy [8].

Pancreatic stone protein/regenerating protein (PSP/REG Iα) was originally a 16 kDa polypeptide found in pancreatic
stones belonging to the superfamily of calcium-dependent lectin genes [9, 10]. It was initially discovered independently in the fields of pancreatitis, which is prominently upregulated when acute or chronic pancreatitis occurs [11]. It has subsequently been found to have a high degree of diagnostic accuracy in determining the seriousness of inflammation and predicting organ failure. In addition, PSP/REG I has been demonstrated to increase β cell growth and regeneration by inducing cellular proliferation. PSP/REG I messenger ribonucleic acid (mRNA) is mainly found in the pancreas, but its expression has also been detected in the gastric mucosa and the kidneys [9, 12]. It has been found in the urine and renal calculi of healthy individuals [13], which suggested a physiological role of PSP/REG Iα in the kidney. Sobajima et al. reported that urinary PSP/REG Iα was increased significantly in patients with various renal diseases, including diabetic nephropathy [14, 15]. Moreover, a previous study by the present researchers has found increased serum levels of PSP/REG Iα in patients with diabetic nephropathy [16].

In this study, we measured serum PSP/REG Iα levels in participants with and without diabetes to investigate whether PSP/REG Iα is associated with renal function and further to evaluate its predictive value of kidney disease.

2. Methods

2.1. Study Subjects. Participants in this study were recruited from December 2018 to January 2019 in the Department of Endocrinology at Zhongda Hospital. The study was approved by the ethics committee of the hospital (2018ZDSYLL143-P01), and experimental methods were performed strictly in accordance with the approved guidelines. Informed consent was acquired from all participants. All patients in the T2DM group met the following inclusion criteria: a patient age > 10 years and a diagnosis of T2DM based on the 2012 criteria of the American Diabetes Association (ADA). Exclusion criteria were (1) enrolled in another trial, (2) pregnancy, (3) renal disease other than diabetic nephropathy, (4) acute complication of diabetes, (5) blood pressure ≥ 200/100 mmHg, (6) active infection, and (7) with tumor and take radiotherapy or chemotherapy within six months. 80 participants with T2DM and eGFR > 30 ml/min/1.73 m² were randomly chosen and compared with an age-matched nondiabetic control group who underwent a regular health examination recruited from the hospital.

We collected demographic information including age, sex, height, weight, smoking status, and hypertension. From each patient, 5 ml of peripheral blood was collected and centrifuged directly for 6 min at a rotating speed of 3,000. The obtained serum was immediately frozen in sterile tubes at −80°C. Other clinical biochemical parameters, such as serum creatinine (SCR), blood urea nitrogen (BUN), uric acid (UA), total cholesterol (TC), and triglyceride (TG), were measured based on the standard methods. The center of Clinical Laboratory of Zhongda Hospital implements internal and external quality control procedures directed by a Chinese Quality Control Laboratory. Body mass index (BMI) was calculated using the following formula: BMI = body weight (kg)/body height (m²). The eGFR level was calculated using the modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for Asians. The following formula was used: GFR (ml/min/1.73 m²) = 141 × min (SCR/0.7, 1)⁻¹⁰⁻³⁸ × max (SCR/0.7, 1)⁻¹²⁰⁹ × 0.993985 × 1.018 (*0.739 if female). Kidney function was classified using the method proposed by the U.S. National Kidney Foundation into three groups: normal (eGFR ≥ 90 ml/min/1.73 m²), mildly reduced (eGFR, 60 ml/min/1.73 m² to 89 ml/min/1.73 m³), and moderately or severely reduced (eGFR < 60 ml/min/1.73 m²) [17, 18].

2.2. PSP/REG Iα Enzyme-Linked Immunosorbent Assay (ELISA). The enzyme-linked immunosorbent assay (ELISA) to measure human PSP/REG Iα was performed as described previously [16], with guinea pig anti-human recombinant PSP/REG Iα antibodies. The serum collected from the patients was prepared by centrifugation, and a sandwich method of ELISA was performed on 96-well plates. The plates were then blocked with 1% bovine serum albumin (BSA) for one hour. After that, guinea pig anti-PSP/REG Iα antibody was coated on the bottom. The diluted recombinant human PSP/REG Iα protein and serum were then used as supplements to the culture dish. After washing, rabbit anti-PSP/REG Iα and then phosphatase-coupled rabbit anti-human PSP/REG Iα were incubated. The reaction of the phosphatase with a substrate was determined at the absorbance of 405 nm on a microplate reader.

2.3. Statistical Analysis. Statistical analyses were conducted using SPSS 20.0 software. Descriptive analyses were presented as follows: (1) means ± SDs for normally distributed variables, (2) the medians (interquartile range (IQR)) for abnormally distributed variables, and (3) frequencies and percentages for count data. For the normally distributed variable, a t-test was performed to assess significant differences between the groups based on a test for homogeneity of variance. If the variable was nonnormally distributed, a Wilcoxon–Mann–Whitney test was used. A chi-squared test was performed for the count data to assess significant differences between the groups. The correlation between variables was presented using Spearman’s rank correlation coefficient analyses. Ordinal logistic regression models were conducted in this study. As the dependent variable, eGFR was divided into three levels according to the National Kidney Foundation. All hypothesis tests used two-sided tests and set alpha at 0.05.

3. Results

3.1. Participants and Baseline Characteristics. A total of 183 subjects aged 14-82 participated in the study. The participants were divided into two groups, including 80 patients with T2DM and 103 subjects without T2DM enrolled as a control group. In the T2DM group, 7 patients were clinically diagnosed with diabetic nephropathy. The baseline characteristics of the participants are shown in Table 1. The proportion of males to females was significantly different between the T2DM and nondiabetic control group (P = 0.008).
Among the two groups, no significant differences were observed in terms of age, BMI, TC, SCr, eGFR, and UA. The proportion of smoking was higher in the T2DM group (18.75%) than that in the non-diabetic control group (10.68%), but there was no significant difference in the value between the two groups ($P = 0.121$). The PSP/REG Ia levels and the incidence of hypertension were significantly higher in individuals with T2DM compared to those in the control group ($P = 0.025$ and $P < 0.001$). Additionally, this is in accordance with our previous study showing that individuals with diabetic nephropathy had elevated PSP/REG Ia levels.

3.2. The Correlation Analyses between Serum PSP/REG Ia Levels and Renal Function. Considering that there may be some correlations between PSP/REG Ia and renal function indicators, the researchers analyzed their correlations using Spearman’s correlation coefficient analysis as the statistics in nonnormal distribution. It was observed that serum PSP/REG Ia levels were negatively correlated with eGFR ($r = -0.500$, $P < 0.001$) and positively associated with age ($r = 0.331$, $P < 0.001$), SCr ($r = 0.398$, $P < 0.001$), and BUN ($r = 0.351$, $P < 0.001$).

To further investigate the correlations between PSP/REG Ia and renal function indicators, analysis was performed on subjects according to whether they had T2DM. Spearman’s correlation analysis indicated that serum PSP/REG Ia levels were negatively correlated with eGFR ($r = -0.519$, $P < 0.001$) and positively associated with SCr ($r = 0.440$, $P < 0.001$), BUN ($r = 0.348$, $P = 0.003$), age ($r = 0.259$, $P = 0.031$), and UA ($r = 0.314$, $P = 0.009$) in patients with T2DM. Meanwhile, serum PSP/REG Ia levels negatively correlated with eGFR ($r = -0.474$, $P < 0.001$) and associated significantly with age ($r = 0.335$, $P = 0.001$), serum Cr ($r = 0.366$, $P < 0.001$), and BUN ($r = 0.346$, $P < 0.001$) in subjects without T2DM (Table 2).

### Table 1: Baseline characteristics of metabolic and laboratory parameters in patients.

|                         | Control ($N = 103$) | T2DM ($N = 80$) | $\chi^2/t/z$ | $P$  |
|-------------------------|---------------------|-----------------|--------------|------|
| Sex (male/female)       | 44/59               | 50/30           | 7.050        | 0.008|
| Age (years)             | 58.08 ± 14.29       | 61.58 ± 12.11   | 1.680        | 0.095|
| BMI (kg/m²)             | 23.64 ± 3.19        | 24.44 ± 3.12    | 1.617        | 0.108|
| Smoking (%)             | 11 (10.68)          | 15 (18.75)      | 2.406        | 0.121|
| Hypertension (%)        | 41 (39.81)          | 54 (67.5)       | 13.840       | <0.001|
| TC (mmol/l)             | 4.59 ± 1.11         | 4.55 ± 1.30     | -0.308       | 0.759|
| TG (mmol/l)             | 1.41 ± 0.91         | 2.19 ± 1.98     | 3.208        | 0.002|
| SCr (μmol/l)            | 76 (50, 145)        | 75 (45, 137)    | -0.502       | 0.615|
| eGFR (ml/min/1.73 m²)   | 88.93 ± 17.83       | 85.22 ± 26.58   | -0.965       | 0.336|
| UA (μmol/l)             | 320.90 ± 78.02      | 309.58 ± 86.43  | -1.090       | 0.277|
| BUN (mmol/l)            | 5.24 ± 1.53         | 6.26 ± 3.74     | 2.209        | 0.029|
| PSP/REG Ia (ng/ml)      | 36.81 (13, 140.93)  | 47.01 (13, 694) | -2.248       | 0.025|

T2DM = type 2 diabetes mellitus; control = without diabetes mellitus. Data are presented as n (%), mean ± SD, or median (interquartile range) as appropriate. BMI = body mass index; TC = total cholesterol; TG = triglyceride; SCr = serum creatinine; eGFR = estimated glomerular filtrations rate; UA = uric acid; BUN = blood urea nitrogen. Significance: $P < 0.05$ compared with control.

### Table 2: Relationship of metabolic and laboratory parameters with PSP/REG Ia.

|                         | Control ($N = 103$) | T2DM ($N = 80$) | $r$ | $P$  | $r$ | $P$  |
|-------------------------|---------------------|-----------------|-----|------|-----|------|
| Age (years)             | 0.335               | 0.001           | 0.259| 0.031|
| BMI (kg/m²)             | 0.074               | 0.457           | -0.041| 0.739|
| BUN (mmol/l)            | 0.346               | <0.001          | 0.348| 0.003|
| SCr (μmol/l)            | 0.366               | <0.001          | 0.440| <0.001|
| eGFR (ml/min/1.73 m²)   | -0.474              | <0.001          | -0.519| <0.001|
| UA (μmol/l)             | 0.106               | 0.287           | 0.314| 0.009|
| TC (mmol/l)             | -0.104              | 0.308           | 0.001| 0.993|
| TG (mmol/l)             | -0.088              | 0.389           | 0.093| 0.448|

Significance: $P < 0.05$. Spearman’s rank correlation coefficient: $r$. BMI = body mass index; BUN = blood urea nitrogen; SCr = serum creatinine; eGFR = estimated glomerular filtrations rate; UA = uric acid; TC = total cholesterol; TG = triglyceride.

3.3. The Ordinal Multiple Logistic Regression Analysis Correlated with eGFR. In ordinal multiple logistic regression analysis, eGFRs were used as a grade-dependent variable in the model, which was classified into three levels by the National Kidney Foundation: normal (eGFR ≥ 90 ml/min/1.73 m²), mildly reduced (eGFR, 60 ml/min/1.73 m² to 89 ml/min/1.73 m²), and moderately or severely reduced (eGFR < 60 ml/min/1.73 m²) [17, 18]. BUN, UA, hypertension, smoking, and PSP/REG Ia levels were used as independent variables. The results illustrated that eGFRs showed association with PSP/REG Ia levels in subjects of the nondiabetic control group (OR = 1.06, 95% CI: 1.04-1.09, $P < 0.001$) and the T2DM group (OR = 1.02, 95% CI: 1.01-1.03, $P = 0.006$) (Table 3).
There are three possible mechanisms to explain the correlation between PSP/REG Iα and renal function. First, PSP/REG Iα is upregulated in T2DM patients. Initially, PSP and regenerating gene Iα (REG Iα) are found in the fields of pancreatitis and diabetes, respectively [10]. Sequence analysis later revealed that PSP and REG Iα are indeed identical [11], and Graf et al. suggested that the combined term of PSP/REG Iα could be used in the future. The regenerative capabilities of PSP/REG Iα were identified in a screening study of genes related to beta cell regeneration firstly [19]. Subsequently, in diabetic rodent models, PSP/REG Iα has been shown to increase the number of beta cells and stimulate beta cell proliferation under physiological conditions [9, 10]. Recently, strong evidence has shown that PSP/REG Iα is associated with diabetes. Elevated PSP/REG Iα levels have been observed in HNF1A-maturity onset diabetes of the young and the type 1 diabetes mellitus reported by Bacon et al. [20]. The present researchers have previously reported increased serum PSP/REG Iα levels in T2DM patients, and these levels positively correlated with the duration of T2DM. With high levels of PSP/REG Iα, the incidence of chronic complications is also increased [16]. In the present study, it was also confirmed that PSP/REG Iα levels were higher in subjects in the T2DM group than those in the nondiabetic control group.

Another interesting observation in this study was that PSP/REG Iα is more likely to reflect reduced glomerular filtration capacity rather than reabsorption from damaged renal tubules. In addition, PSP/REG Iα may be participated in diabetic kidney hypertrophy as a kidney growth factor [24, 25]. As epidermal growth factor in the fluid of accumulating duct cysts has been shown to stimulate cyst growth, a similar role of PSP/REG Iα in proximal tubule cysts is anticipated. Finally, many researchers have made suggestions that inflammation plays a crucial role in the development of diabetic nephropathy, and many studies have proved that higher levels of inflammatory biomarkers are associated with chronic kidney disease [26–29]. PSP/REG Iα serves as an inflammatory factor that may be involved in renal disease.

The present researchers also found that smoking is a risk factor for the decline of eGFR in the nondiabetic control group, while it did not matter in the T2DM group. Researchers have reported that cigarette smoking has been identified as a modifiable risk factor for diseases because of its contrary effects. The amount of smoking and smoking habit may also have effects on the results; this is called a dose-response relationship [30]. In general conditions, T2DM patients with renal impairment could realize the damage caused by cigarettes. As a result, they may quit smoking so that the dose of smoking might be smaller than those in the nondiabetic control group. To sum up, more studies should certify the associations of smoking and eGFR in T2DM, and the mechanism needs to be further verified.

Circulating serum PSP/REG Iα levels correlate with age, which implies that there is a positive correlation in the present study. This was identified by an age-dependent increase of PSP/REG Iα levels in subjects in both groups. Schlapbach et al. [31] reported that age categories determined PSP/REG Iα concentrations in healthy subjects. The lowest levels were seen in extremely preterm babies, while the highest levels were observed in children. This study provided normal values for specific ages that can be used to determine cutoff values for future PSP/REG Iα level trials and demonstrated that PSP/REG Iα increased from birth to childhood with an age development. However, the study did not clarify the relationship between age and PSP/REG Iα levels in adults in a sickness state. Hence, further study is needed to confirm the relationships between age categories and PSP/REG Iα levels in Asians.

To the present researchers’ knowledge, this study is the first to recognize the correlations between serum PSP/REG Iα and renal function in patients with and without T2DM. However, it also has some limitations. First, as a cross-
sectional design, the sample size of this study is relatively small, so further prospective studies with larger samples are needed. Second, researchers need to detect PSP/REG Iα levels in diabetic nephropathy even other kidney diseases to further ensure the value of PSP/REG Iα in the diagnosis of renal function. Third, it is worth investigating further the associations between other diabetic complications, such as diabetic retinopathy, diabetic peripheral neuropathy, and diabetic foot.

5. Conclusions

This study provides evidence that PSP/REG Iα is significantly upregulated in T2DM patients and reflects renal function in both T2DM and nondiabetic control subjects. Given the correlation between PSP/REG Iα and eGFR, it is suggested that increased serum PSP/REG Iα may reflect decreased glomerular filtration capacity. However, further research is needed to determine the value of PSP in the renal function of all the individuals and mechanisms involved.

Abbreviations

PSP/REG Iα: Pancreatic stone protein/regenerating protein Iα
T2DM: Type 2 diabetes mellitus
BUN: Blood urea nitrogen
Scr: Serum creatinine
UA: Uric acid
eGFR: The estimated glomerular filtration rate
ESRD: End-stage renal disease
mRNA: Messenger ribonucleic acid
ADA: American Diabetes Association
BMI: Body mass index
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
ELISA: Enzyme-linked immunosorbent assay
BSA: Bovine serum albumin
CI: Confidence interval
OR: Odds ratio.

Data Availability

The datasets generated and/or analyzed during this study are not publicly available, owing to currently ongoing research studies, but the data are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors’ Contributions

Huimin Zhu and Xiangyun Zhu have contributed equally to this work.

Acknowledgments

This study was supported a fundamental research grant by Professor Ling Li in the Department of Endocrinology, Zhongda Hospital, School of Medicine, Southeast University from the National Natural Science Foundation of China (Nos. 81570739 and 81970717), the Key Research and Development Program of Jiangsu Province (No. BE2018742), and the Joint Key Project funded by the Southeast University and Nanjing Medical University (No. 2242019K3DN07) and has received an external research grant from Hao Lin by the National Natural Science Foundation of China (No. 81800571). All funders have role in the design of the study, analysis, interpretation of data, and in writing the manuscript. The authors would like to thank Professor Rolf Graf for providing us the technique to measure PSP/REG Iα.

References

[1] J. Hu, J. B. Chen, Y. Cui et al., "Association of metformin intake with bladder cancer risk and oncologic outcomes in type 2 diabetes mellitus patients: a systematic review and meta-analysis," Medicine, vol. 97, no. 30, article e11596, 2018.
[2] L. Tap, N. D. A. Boye, K. A. Hartholt, T. J. M. van der Cammen, and F. U. S. Mattace-Raso, "Association of estimated glomerular filtration rate with muscle function in older persons who have fallen," Age and Ageing, vol. 47, no. 2, pp. 269–274, 2018.
[3] C. Toppe, A. Möllsten, I. Waernbaum et al., "Decreasing cumulative incidence of end-stage renal disease in young patients with type 1 diabetes in Sweden: a 38-year prospective nationwide study," Diabetes Care, vol. 42, no. 1, pp. 27–31, 2019.
[4] Centers for Disease Control and Prevention (CDC), "Incidence of end-stage renal disease attributed to diabetes among persons with diagnosed diabetes — United States and Puerto Rico, 1996–2007," Morbidity and Mortality Weekly Report, vol. 59, no. 42, pp. 1361–1366, 2010.
[5] S. Dronavalli, I. Duka, and G. L. Bakris, "The pathogenesis of diabetic nephropathy," Nature Clinical Practice Endocrinology & Metabolism, vol. 4, no. 8, pp. 444–452, 2008.
[6] K. Ichinose, E. Kawasaki, and K. Eguchi, "Recent advancement of understanding pathogenesis of type 1 diabetes and potential relevance to diabetic nephropathy," American Journal of Nephrology, vol. 27, no. 6, pp. 554–564, 2007.
[7] Z. Mou, Z. Feng, Z. Xu et al., "Schisandrin B alleviates diabetic nephropathy through suppressing excessive inflammation and oxidative stress," Biomedical and Biophysical Research Communications, vol. 508, no. 1, pp. 243–249, 2019.
[8] S. Ogawa, T. Mori, K. Nako, and S. Ito, "Combination therapy with renin-angiotensin system inhibitors and the calcium channel blocker azelnidipine decreases plasma inflammatory markers and urinary oxidative stress markers in patients with diabetic nephropathy," Hypertension Research, vol. 31, no. 6, pp. 1147–1155, 2008.
[9] T. Watanabe, H. Yonekura, K. Terazono, H. Yamamoto, and H. Okamoto, "Complete nucleotide sequence of human reg gene and its expression in normal and tumoral tissues. The reg protein, pancreatic stone protein, and pancreatic thread protein are one and the same product of the gene," The Journal of Biological Chemistry, vol. 265, no. 13, pp. 7432–7439, 1990.
K. Terazono, H. Yamamoto, S. Takasawa et al., “A novel gene activated in regenerating islets,” The Journal of Biological Chemistry, vol. 263, no. 5, pp. 2111–2114, 1988.

R. Graf, M. Schiesser, T. Reding et al., “Exocrine meets endocrine: pancreatic stone protein and regenerating protein—two sides of the same coin,” The Journal of Surgical Research, vol. 133, no. 2, pp. 113–120, 2006.

T. Saito, Y. Tanaka, Y. Morishita, and K. Ishibashi, “Proteomic analysis of AQP11-null kidney: proximal tubular type polycystic kidney disease,” Biochemistry and Biophysics Reports, vol. 13, pp. 17–21, 2018.

J. M. Verdier, B. Dussol, P. Casanova et al., “Evidence that human kidney produces a protein similar to lithostathine, the pancreatic inhibitor of CaCO3 crystal growth,” European Journal of Clinical Investigation, vol. 22, no. 7, pp. 469–474, 1992.

T. Watanabe, Y. Yonemura, H. Yonekura et al., “Pancreatic beta-cell replication and amelioration of surgical diabetes by Reg protein,” Proceedings of the National Academy of Sciences of the United States of America, vol. 91, no. 9, pp. 3589–3592, 1994.

S. Bacon, M. P. Kyithar, J. Schmid et al., “Serum levels of pancreatic stone protein (PSP)/reg1A as an indicator of beta-cell apoptosis suggest an increased apoptosis rate in hepatocyte nuclear factor 1 alpha (HNF1A-MODY) carriers from the third decade of life onward,” BMC Endocrine Disorders, vol. 12, no. 1, 2012.

N. Tatemichi, M. Kato, S. Hayakawa et al., “Immunological characterization of pancreatic stone protein in human urine,” Journal of Clinical Laboratory Analysis, vol. 8, no. 2, pp. 76–80, 1994.

A. Piwowar, M. Knapik-Kordecka, I. Fus, and M. Warwas, “Urinary activities of cathepsin B, N-acetyl-beta-D-glucosaminidase, and albuminuria in patients with type 2 diabetes mellitus,” Medical Science Monitor, vol. 12, no. 5, pp. CR210–CR214, 2006.

P. A. Peterson, P. E. Evrin, and I. Berggard, “Differentiation of glomerular, tubular, and normal proteinuria: determinations of urinary excretion of beta-2-macroglobulin, albumin, and total protein,” The Journal of Clinical Investigation, vol. 48, no. 7, pp. 1189–1198, 1969.