



Original Article

Pancreatic stone protein as a novel biomarker of microvascular complications in type II diabetes mellitus: A systematic review and meta-analysis

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Submission : 22-Aug-2024
Revision : 18-Oct-2024
Acceptance : 04-Nov-2024
Web Publication : 05-Mar-2025

ABSTRACT

Objectives: Pancreatic stone protein (PSP) has been identified as an indicator of systemic stress and is elevated in individuals diagnosed with type 2 diabetes mellitus (T2DM), potentially serving as a prognostic marker for both the onset and progression of the disease. **Materials and Methods:** This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guidelines. Articles were sourced from MEDLINE, ProQuest, Science Direct, Google Scholar, and Cochrane Library electronic databases. Studies included are all observational studies examining PSP/Reg1 α serum levels in patients with T2DM. The quality of the study was evaluated using the Newcastle–Ottawa Scale, as well as Review Manager 5.4 to perform the meta-analysis. **Results:** Seven studies met the criteria for inclusion. Pooled analysis revealed significant differences in PSP values between T2DM individuals and healthy controls (standardized mean difference [SMD] = 2.14, 95% confidence interval CI: 1.05–1.92, $P < 0.00001$). Further subgroup analysis showed PSP was substantially higher in T2DM with complications (SMD = -1.57, 95% CI: -2.12 to -1.02, $P < 0.00001$) compared to T2DM without complications (SMD = -1.39, 95% CI: -2.17 to -0.61) and newly diagnosed T2DM (SMD = -1.85, 95% CI: -2.96 to -0.74). Grading of Recommendations, Assessment, Development, and Evaluations demonstrated moderate quality of evidence. **Conclusion:** Our analysis revealed a progressive elevation in PSP values concomitant with the worsening T2DM disease state across the entire spectrum. PSP exhibits promising potential as a biomarker for predicting both disease initiation and subsequent clinical course.

KEYWORDS: Pancreatic stone protein, Regenerating protein, Type 2 diabetes mellitus

INTRODUCTION

Chronic and multifaceted metabolic disorder with complex origins, diabetes mellitus (DM) is characterized by hyperglycemia, a condition of elevated blood glucose resulting from abnormalities in insulin secretion, utilization, or both [1,2]. Type 2 DM (T2DM) accounts for up to 96% of all diabetes [3]. Global Burden of Diseases, Injuries, and Risk Factors Study 2019 revealed diabetes to be the eighth leading cause of death and disability, afflicting approximately 460 million people [4]. Diabetes gives rise to complications involving multiple organs, including renal disease, ischemic heart disease, and stroke, resulting in an increased mortality

rate and higher medical costs [5]. The medical costs for people with diabetes are 2.3 times higher than for those without diabetes, and the mortality rate of diabetes increased by 3% from 2000 to 2019, emerging as a leading cause of death for 1.5 million people in 2019 [3].

The discovery of pancreatic stone protein (PSP) traces back to 1979 when its initial identification implicated its

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How to cite this article: Widjanarko ND, Soetedjo NN, Iryaningrum MR, Arifin ES, Alvianto S, Lionardi SK, et al. Pancreatic stone protein as a novel biomarker of microvascular complications in type II diabetes mellitus: A systematic review and meta-analysis. Tzu Chi Med J 2025;37(3):328-38.

Supplementary material available online

Access this article online

Quick Response Code:



Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_211_24

involvement in stone formation in chronic pancreatitis [6]. In addition, it has also been known as lithostathine in consideration of its functions [7]. Subsequent investigations during the 1980s revealed the presence of this protein in β -cells within islet preparations, leading to its designation as regenerating protein 1 (REG1) [8]. Its biological and functional role is found to be an indicator of systemic stress, originating from the pancreas that could detect remote organ damage even though there is an absence of pancreatic tissue damage [9].

As of today, PSP in a clinical setting has been evaluated to perform well as a biomarker in detecting inflammation caused by infection [10]. It is utilized to aid in early detection, severity characterization, and even assist in understanding prognosis, ranging from pediatric [11] to adult patients within the emergency [12] to intensive care unit setting [13,14], thereby enabling timely initiation of treatment with reduced mortality and decreased costly measures [15]. Currently, PSP cannot serve as a standalone test to define sepsis, particularly within the context of infection associated with diabetes [16]. However, it exhibits a promising future with high diagnostic accuracy and has demonstrated similar results, as well as the potential to assist, or even surpass, established biomarkers such as procalcitonin or high-sensitivity C-reactive protein for risk stratification [13,17,18].

New research findings indicate a notable increase in PSP levels among individuals diagnosed with T2DM, indicating the potential utility of PSP as a prognostic marker for both the onset and advancement of DM [19]. The elevation in PSP levels observed in diabetic patients is believed to result from the release of particles by apoptotic beta cells, which have the potential to stimulate the induction of PSP/REG in neighboring cells [20]. Albadr and Haddad, revealed a significant elevation in PSP levels among T2DM patients with complications compared to those without. These results strongly affirm the potential utility of PSP as a promising prognostic marker for predicting diabetic microvascular complications [21]. Nevertheless, there has been no systematic review or meta-analysis conducted on this topic. Therefore, this study was designed to assess the elevated levels of PSP as a novel biomarker in T2DM disease progression.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement guideline was used to design and conduct this study [22]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on December 13th, 2023 with the following registration number: CRD42023488950.

Eligibility criteria

Type of studies

This systematic review included all published and unpublished observational studies examining the PSP/Reg1 α serum levels in patients with T2DM. Conversely, studies falling under the categories of interventional studies, either RCTs, non-RCTs, quasi-experimental studies, or multiple arm studies; *in vitro* or *in silico* studies; and belong to the category of reviews, case

reports, case series, conference abstracts, book sections, and commentaries/editorial were excluded from this review.

Participants

All patients diagnosed with T2DM are included in this study. This is further classified as newly diagnosed, with and without complications. There were no limitations for gender and races. Patients who are pregnant, diagnosed with hypertensive emergency, having an active infection, unstable angina, acute complications of DM, neoplasm, liver dysfunction, renal diseases other than diabetic nephropathy (DN), and are on medications that may affect blood glucose such as hormone, antihypertensive drugs, antibiotics, and nonsteroidal anti-inflammatory drugs were excluded from the study.

Variable and outcome of interest

This study aimed to evaluate the serum level of PSP/Reg1 α across all spectrum of T2DM. The primary outcome of interest was the PSP/Reg1 α serum level in T2DM patients, which are further classified as newly diagnosed T2DM, T2DM with- and without complications. Secondary outcomes were the correlation of PSP/Reg1 α with various metabolic and anthropometric parameters.

Search strategy and study selection

A literature search was conducted including studies published up to March 2024 on several electronic databases including MEDLINE, ProQuest, Science Direct, Google Scholar, and Cochrane Library to retrieve eligible studies. This was performed by eight independent authors using PICOTS-SD criteria and a specified search strategy, as depicted in Supplementary Files 1 and 2. All studies obtained were exported into the Zotero reference manager software, and then checked for duplication, followed by titles and abstracts screening. The assessment was performed separately by the authors and studies were excluded when the title and/or abstract were not appropriate for this review. The selected papers were reviewed in full-text assessment using the aforementioned eligibility criteria. The excluded studies were listed and described in Supplementary File 3. The differences observed were settled among the review team members.

Data collection process

The included studies were analyzed and the following data were extracted: First author, publication year, country of origin, study design, sample sizes, age, gender, population, inclusion and exclusion criteria, PSP/Reg1 α detection method, type of sample taken, and outcome of interest including correlation of PSP/Reg1 α with other metabolic parameters.

Summary measures

All of the serum PSP/Reg1 α levels were measured and reported as numerical (continuous) data. The data were presented in mean \pm standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for nonnormally distributed data. The secondary outcome of PSP/Reg1 α correlation with various metabolic parameters was reported as the correlation coefficients in the systematic review table of characteristics [Table 1]. The *P* value was

Table 1: Study characteristics

Author, publication year, country	Study designs		Groups		Inclusion/exclusion criteria of participants	PSP detection method	Sample taken	Correlation of PSP with other metabolic parameters
	T2DM group	Control group	Sex, n (%)	Age (years)				
Sobajima et al., 1998, Japan [23]	Cross-sectional				Diabetic group: Not specified Control group: Adults with no abnormalities on biochemistry tests and urinalysis who underwent annual health checks	Human Reg I α ELISA assay (direct sandwich method)	Urine	Correlation of urinary PSP with urinary albumin index: $r=0.42$, $P<0.01$ Correlation of urinary PSP with NAG: $r=0.35$, $P<0.01$ Correlation of urinary PSP with α1-microglobulin: $r=0.68$, $P<0.01$ Correlation of urinary PSP with Ccr: $r=0.39$, $P<0.01$
Astorri et al., 2010, Italy [24]	Case control study				Diabetic group: Type 1 and 2 DM diagnosed with ADA criteria. All T1D patients (newly diagnosed or established) were positive for GAD or IA2 autoantibodies at diagnosis Control group: Age-matched healthy individuals with no history of diabetes or pancreatic/digestive disease	Human Reg I α ELISA assay (direct sandwich method) Western Blotting	Serum	No significant correlation were observed between serum Reg Iα levels, fasting C-peptide, HbA1c, or age in either newly diagnosed or long-standing patients with type 1 diabetes A significant negative correlation in long-standing patients between disease duration and Reg Iα levels ($P<0.0176$; Spearman $r=-0.36$)
Yang et al., 2015, China [19]	Case control study				Diabetic group Diagnosed according to the ADA criteria 2012 High-risk T2DM: Overweight/obese BMI with ≥ 1 risk factor (inactivity, family history, macrosomia, prediabetes, CVD history, abnormal lipids, hypertension, PCOS) Chronic complications of T2DM: Microangio-, nephro-, retino-, and neuropathy Control group: Healthy individuals with no history of diabetes or pancreatic disease	Human Reg I α ELISA assay (direct sandwich method)	Serum	Correlation of PSP/reg higher and duration of T2DM (Spearman's rank correlation coefficient=0.319, $P<0.001$) Correlation of PSP/reg higher and HbA1c (Spearman's rank correlation coefficient=0.188, $P<0.001$) Correlation of PSP/reg higher and Pulse pressure systolic and diastolic (Spearman's rank correlation coefficient=0.10, $P<0.001$) PSP/reg higher and FBG, 2hPG correlated Positively

Contd...

Table 1: Contd...

Author, publication year, country	Study designs	Groups				Inclusion/exclusion criteria of participants	PSP detection method	Sample taken	Correlation of PSP with other metabolic parameters
		T2DM group		Control group					
		Sex, n (%)	Age (years)	Sex, n (%)	Age (years)				
Li et al., 2017, China [25]	Cross sectional	Long term DM with complication: Male - 45, female - 34	Long term diabetes with complication: 68.0 (57.0-75.0)	Male: 17 (56.67%) Female: 13 (43.3%)	56.50 (53.75-58.50)	Diabetic group	Human Reg I α ELISA assay (direct sandwich method)	Serum	No correlation of PSP/reg higher and age, gender, BMI PSP/reg cut-off was 22 ng/mL in the nondiabetes group Correlation of PSP/reg with HbA1c (Spearman r=0.547)* Correlation of PSP/reg with serum creatinine (Spearman r=0.492)* Correlation of PSP/reg with uric acid (Spearman r=0.620)* Correlation of PSP/reg with eGFR (Spearman r=-0.502)* P<0.001*
		Newly diagnosed T2DM: Male - 14 (46.7%), female - 16 (53.3%) T2DM without DKD: 63.50 (56.50-67.40) DKD: Male - 18 (60.0%), female - 12 (40.0%) T2DM with DKD: 57.50 (54.35-61.20) Male - 16 (53.3%), female: 14 (46.7%)	Newly diagnosed T2DM: 60.00 (56.75-65.00) T2DM without DKD: 63.50 (56.50-67.40) T2DM with DKD: 57.50 (54.35-61.20)	Male: 17 (56.67%) Female: 13 (43.3%)	56.50 (53.75-58.50)	Diagnosed according to the ADA criteria 2012 Exclusion criteria included T1DM, acute diabetic complications, non-DKD renal disease, severe liver dysfunction, active neoplasms or infections/inflammation, pregnancy, and taking medications affecting glucose levels	Human Reg I α ELISA assay (direct sandwich method)	Serum	
Zhi et al., 2016, China [26]	Cross-sectional	Newly diagnosed T2DM: Males - 21, females - 15 Long-term T2DM without complication: 55±8 Males - 15, females - 10 Long-term T2DM with DN: Males - 13, females - 14	Newly diagnosed T2DM: 56±8 Long-term T2DM without complication: 55±8 Long-term T2DM with DN: 55±11	Male: 26 Female: 24	54±9	All participants underwent screening from healthy individuals, as well as inpatients and outpatients at Zhongda Hospital of Southeast University, Nanjing, China, spanning from February 2011 to February 2012	Human Reg I α ELISA assay	Serum	The PSP/reg threshold value for predicting incidence of diabetic nephropathy was 32 ng/mL
Zhu et al., 2020, China [27]	Cross-sectional	T2DM: 50 males, 30 females	T2DM: 61.58±12.11	58.05±14.29		Diabetic group Patient's age >10 years and a diagnosis of T2DM based on the ADA 2012 criteria Having no renal disease other than diabetic nephropathy and no acute DM complication Blood pressure ≤200/100 mmHg	Human Reg I α ELISA assay (direct sandwich method)	Serum	PSP/REG Iα levels negatively correlated with eGFR (r=-0.519, P<0.001) in T2DM, but positively associated with SCr (r=0.440, P<0.001), BUN (r=0.348, P=0.003), age (r=0.259, P=0.031) in T2DM, and UA (r=0.314, P=0.009) in T2DM

Contd...

Table 1: Contd...

Author, publication year, country	Study designs	Groups				Inclusion/exclusion criteria of participants	PSP detection method	Sample taken	Correlation of PSP with other metabolic parameters
		T2DM group		Control group					
		Sex, n (%)	Age (years)	Sex, n (%)	Age (years)				
Albadr and Haddad, 2023, Iraq [21]	Case control study	T2DM without complications: 23 male/27 female T2DM with complications: 19 male/31 female	T2DM without complications: 23 male/27 female T2DM with complications: 19 male/31 female	22 male/28 female	51.8±8.1 51.1±8.6 52.5±6.1	Diabetic group Diagnosed according to the ADA criteria 2012 Complications of T2DM include: Nephropathy - UAE of at least 2 Specimen >30 mg/24 h or low GFR; retinopathy - evaluated and diagnosed using a standard fundus eye examination; neuropathy - diagnosed on the basis of clinical examination, EMG and NCS	Human Reg I α ELISA assay	Serum	PSP/REG Iα levels negatively correlated with eGFR ($r=-0.474, P<0.001$), but positively associated with SCr ($r=0.366, P<0.001$), BUN ($r=-0.346, P<0.001$), and age ($r=-0.335, P=0.001$) in control PSP/reg levels exhibited positive correlations with markers of glycaemic control, HbA1c (Spearman's $\rho=0.572, P<0.001$) and RBG (Spearman's $\rho=0.577, P<0.001$) A significant positive correlation was observed between PSP/reg and BMI (Spearman's $\rho=0.254, P<0.05$)
					Not diagnosed with cancer and take radiotherapy or chemotherapy within 6 months Control group: Healthy individuals with no history of diabetes or pancreatic disease				

*Significant at $P<0.001$. PSP: Pancreatic stone protein, DM: Diabetes mellitus, DKD: Diabetic kidney disease, T2DM: Type II DM, T1DM: Type I DM, HbA1c: Hemoglobin A1C, ADA: American Diabetes Association, UAE: Urinary albumin excretion, GFR: Glomerular filtration rate, EMG: Electromyography, NCS: Nerve conduction studies, DN: Diabetic nephropathy, NAG: N-acetyl-β-glucosaminidase, CVD: Cardiovascular disease, BMI: Body mass index, ELISA: Enzyme-linked immunosorbent assay, FBG: Fasting blood glucose, 2hPG: 2-h plasma glucose, eGFR: Estimated glomerular filtration rate, SCr: Serum creatinine, UA: Urinary albumin, RBG: Random Blood Glucose, PCOS: Polycystic Ovary Syndrome, BUN: Blood Urea Nitrogen.

also included for each item to show if the results were of significance.

Assessment of risk of bias/quality assessment

Each study categorized as an observational studies was evaluated independently by two separate reviewers using Newcastle–Ottawa Scale (NOS) adopted for cross-sectional and case-control studies. The scale consists of three primary domains: selection process, comparability, and outcome. The overall quality of each study was classified into three groups of total NOS score based on the degree of bias: very high risk of bias (0–3 points), high risk of bias (4–6), and low risk of bias (7–9). A higher score of NOS indicated with a better quality of method. Any discrepancies were discussed among the whole review team until agreement was made.

Synthesis of results and statistical analysis

To extract and pool the data for quantitative synthesis, we used Review Manager (Cochrane Collaboration, Copenhagen, Denmark) version 5.4. All patients were classified into two groups, to obtain the difference between the case (the spectrum of T2DM) and control (healthy participants) groups for the analyses. Statistical analyses were carried out for between-group comparison using totals and subtotals with 95% confidence interval (CI). We converted values from studies that did not report in the form of mean and SD using the formula proposed by Wan *et al.*, 2014 [28] and Luo *et al.*, 2018 [29]. The aforementioned formula requires data of sample size (N), lower quartile (Q1), middle quartile (Median/Q2), and upper quartile (Q3), which can be extracted from each original study.

The meta-analyses utilized a random effects model due to certain studies reported primary outcomes using various evaluation or calculation methods. This approach ensured a more equal weighting for each study and assumed that the impact would be distributed over certain populations. In addition, it facilitated extrapolation to a larger population sample when further studies were subsequently conducted. In terms of numerical (continuous) data, the combined effect measures from an individual intervention were compared by the inverse variance method. Standardized mean differences (SMDs) were employed as the most suitable effect size for continuous data.

Heterogeneity across trials was evaluated using the I^2 statistic. An I^2 value below 25% was considered subtle, 25%–50% indicated low, 50%–75% signified moderate, and above 75% implied high heterogeneity. In cases when heterogeneity was observed, sensitivity analyses were performed to investigate the potential causes. A significance level of $P < 0.05$ was applied.

Confidence in cumulative evidence

The confidence in the cumulative body of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [30]. This system involves a systematic evaluation of the quality of evidence for each outcome of interest. The GRADE system considers factors such as the methodological quality of individual studies (risk of bias), the directness of the

evidence to the research question (indirectness), the level of heterogeneity (inconsistency) in the study findings, the precision of effect estimates (imprecision), and the potential for publication bias. Based on these factors, the overall certainty of the evidence was categorized as high, moderate, low, or very low quality.

Ethical statement

This is a systematic review and meta-analysis study. The Faculty of Medicine, Atma Jaya Catholic University of Indonesia has confirmed that no ethical approval is required.

RESULTS

A visual representation of the study selection process and the yielded results is presented in Figure 1. The initial search strategy identified a total of 289 potentially relevant studies. Following the application of deduplication protocols, this number was refined to 256. Title and abstract screening, aligned with the pre-established selection criteria, further narrowed the selection to 15 studies deemed eligible for full-text evaluation. A rigorous assessment employing predefined criteria resulted in the exclusion of 8 studies. Two studies were excluded due to discrepancies in outcome measurement techniques. An additional five studies were excluded because data extraction for analysis was not feasible owing to missing outcome data and a reliance on graphical representations. Another one study was excluded due to the absence of relevant outcome data within their scope. Ultimately, seven studies were incorporated into the systematic review, and data extraction for meta-analysis was feasible for four of these studies. It is noteworthy that despite an exhaustive search strategy, no unpublished studies meeting the inclusion criteria were identified, unlikely impacting conclusions and mitigating potential publication bias.

Characteristics of the included studies

The inclusion criteria were met by a total of seven studies with the primary classification of newly diagnosed T2DM, T2DM without complications, and DM with complications, as shown in Table 1. The most reported microvascular complication is DN [25,26], with one study [23] assessing the albuminuria incidence as a marker of diabetic-associated kidney damage. Two studies also examined other microvascular complications such as diabetic retinopathy and neuropathy [19,21]. The Human Reg1 α enzyme-linked immunosorbent assay using the direct sandwich method was the primary technique for measuring PSP levels across all studies. Western blotting was employed additionally for confirmatory purposes of Reg1 α antibodies [24]. Serum was the primary sample source, with the exception of Sobajima *et al.* who utilized urine samples [23].

The primary diagnosis of T2DM was utilizing the American Diabetes Association 2012 criteria, with age-matched healthy individuals with no history of diabetes or pancreatic diseases. A total of 1239 T2DM subjects comprising 602 males and 637 females were collected, with the oldest age found in long-term DM with complications (68.0 [57.0–75.0]) [19] and the youngest was found in T2DM without complications (51.1 \pm 8.6) [21].

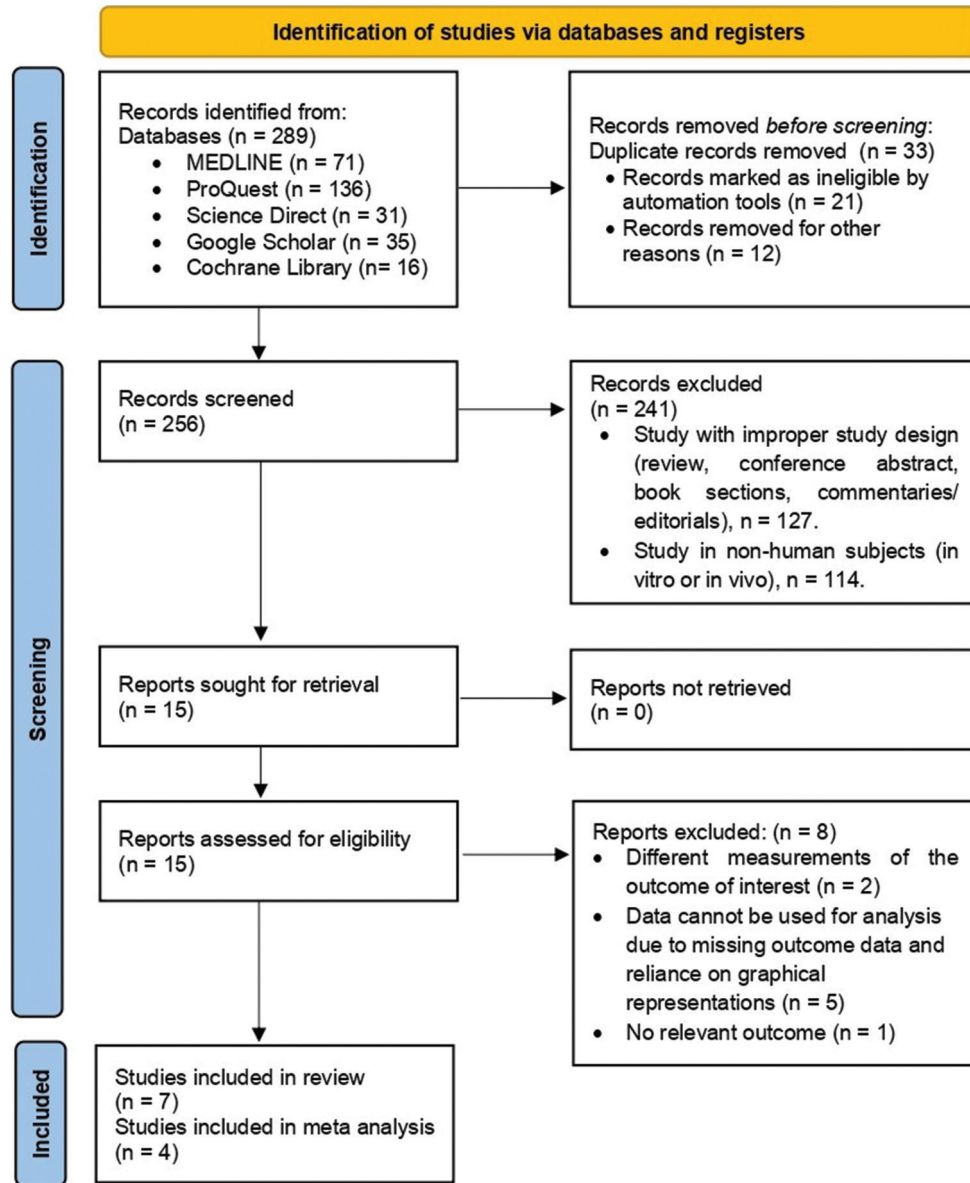


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 flow diagram of the literature search

Some studies reported a significant positive correlation between PSP levels and several glycemic parameters, namely HbA1c [21,25], fasting blood glucose (FBG) [19], and 2-h plasma glucose [19]. Similarly, evidence for a positive association was observed between PSP levels and kidney function parameters, such as urinary albumin-to-creatinine ratio [23] and estimated glomerular filtration rate (eGFR) [25,27], as well as serum uric acid [25,27]. In addition, the same correlations were found between PSP and body mass index (BMI) and systolic–diastolic blood pressure [19,21].

Quality assessment

Among the ten studies evaluated using NOS, one [25] had very good quality, four [19,21,29,30] were classified as good quality studies, and two [23,26] belonged to a satisfactory quality. The results of the study quality assessment from each case–control and cross-sectional studies are depicted

in Supplementary File 4. Publication bias was analyzed as a funnel plot, shown in Supplementary File 5.

Meta-analysis results

Quantitative analysis encompassing four studies on the T2DM spectrum [Table 2] revealed a consistently elevated mean PSP across the disease progression continuum. This observation suggests a positive correlation between disease severity and PSP, manifested by higher PSP values in chronic T2DM patients compared to those newly diagnosed or with early-onset diabetes. Furthermore, this trend aligns with the findings from comparisons between individuals with T2DM with complications and those without complications, where the complication group exhibited higher PSP values.

Statistical analyses revealed significant effect sizes for PSP values across all groups of observation ($P < 0.0001$).

This includes comparisons between newly diagnosed T2DM, T2DM with and without complications [Figure 2], as well as T2DM and healthy controls [Supplementary File 6]. Similar significant differences in PSP were observed between newly diagnosed (SMD = -1.85, 95% CI: -2.96, -0.74) and T2DM without complications (SMD = -1.39, 95% CI: -2.17, -0.61) compared to those with complications (SMD = -1.57, 95%CI: -2.12, -1.02, $P < 0.00001$). However, it is important to acknowledge the presence of substantial heterogeneity, reflected by I^2 values of 59% ($P = 0.09$), 82% ($P = 0.004$), and 91% ($P < 0.00001$) for these comparisons, respectively.

Confidence in cumulative evidence

According to the NOS assessment, there was majoritarily good quality studies in the investigated papers, meaning that conceivable bias was unlikely to have a major impact on the outcomes. All studies reported elevated PSP levels across the entire spectrum of observed case groups, therefore depicting consistent findings. In light of the restricted number of studies identified, a qualitative analysis was chosen to explore publication bias. Notably, the literature search yielded no evidence of unpublished studies, potentially reducing publication bias in the overall effect estimate. However, all outcomes demonstrated imprecision due to small sample sizes. Importantly, the analysis revealed no substantial indirectness

that could significantly influence the final results. Following this assessment, the GRADE approach was utilized to develop an evidence profile, ultimately determining a moderate quality of evidence, as presented in Table 3.

DISCUSSION

This systematic review investigated the functional significance of PSP/Reg1 α as a potential biomarker of pancreatic-derived systemic stress, triggered by apoptotic beta cells in T2DM population. In addition, the review evaluated the predictive ability of PSP/Reg1 α in assessing disease progression. We reviewed and analyzed a total of seven studies encompassing 1239 participants with T2DM (602 males and 637 females). Our meta-analysis revealed a significantly elevated mean PSP level in T2DM patients compared to healthy controls. This elevation persisted consistently across the disease spectrum, suggesting a potential positive correlation between PSP severity and T2DM progression. This is further supported by the observation of higher PSP values in chronic T2DM patients compared to newly diagnosed or early-onset patients, as well as in those with microvascular complications compared to those without.

It has been postulated that PSP/reg is a product of acinar cells in normal conditions, however, under pathological

Table 2: Pancreatic stone protein values in various spectrums of type II diabetes mellitus (newly diagnosed type II diabetes mellitus, type II diabetes mellitus without complications, and type II diabetes mellitus with complications) compared to healthy control groups

Author, year	T2DM				Healthy control			
	Newly diagnosed		Without complications		With complications			
	Mean \pm SD	<i>n</i>	Mean \pm SD	<i>n</i>	Mean \pm SD	<i>n</i>	Mean \pm SD	<i>n</i>
Yang <i>et al.</i> , 2015 [19]	21.77 \pm 10.90	213	27.38 \pm 15.61	116	36.82 \pm 25.22	79	17.07 \pm 5.18	117
Zhi <i>et al.</i> , 2016 [26]	18.13 \pm 6.80	36	23.58 \pm 7.19	25	56.92 \pm 21.39*	27	14.21 \pm 3.33	50
Li <i>et al.</i> , 2017 [25]	18.74 \pm 3.84**	30	25.84 \pm 10.49**	30	50.32 \pm 20.21**	30	14.16 \pm 4.04	30
Albadr and Haddad, 2023 [21]	N/A	N/A	30.4 \pm 15.38	50	202.2 \pm 143.47	50	17 \pm 7.07	50

N/A: Not available, SD: Standard deviation, T2DM: Type II diabetes mellitus. *Significant at $P < 0.01$. **Significant at $P < 0.001$

Table 3: Grading of recommendations, assessment, development, and evaluation evidence profile

Outcome	Number of participants (studies)	Quality assessment						Summary findings	
		NOS	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	SMD total	95% CI (lower-upper)
Newly diagnosed T2DM versus control	Case: 279 Control: 197 (3 studies)	Not serious	Not serious ^a	Not serious	Serious ^b	Not serious ^c	Moderate	0.74	0.38–1.10
T2DM without complications versus control	Case: 171 Control: 197 (4 studies)	Not serious	Not serious ^a	Not serious	Serious ^b	Not serious ^c	Moderate	1.36	0.74–1.99
T2DM with complications versus control	Case: 186 Control: 247 (4 studies)	Not serious	Not serious ^a	Not serious	Serious ^b	Not serious ^c	Moderate	2.14	1.28–3.00
Newly diagnosed T2DM versus T2DM with complications	Case: 279 Control: 136 (3 studies)	Not serious	Not serious ^a	Not serious	Serious ^b	Not serious ^c	Moderate	-1.85	-2.96–-0.74
T2DM without versus with complications	Case: 221 Control: 186 (4 studies)	Not serious	Not serious ^a	Not serious	Serious ^b	Not serious ^c	Moderate	-1.57	-2.12–-1.02

^aAll studies reported elevated PSP levels across the entire spectrum of observed case groups, therefore depict consistent findings, ^bEffect estimates come from a small number of studies (no more than four studies in each outcome), ^cPublication bias was assessed qualitatively, and no unpublished studies were found in the literature search, thus not affecting the publication bias. T2DM: Type 2 diabetes mellitus, SMD: Standardized mean difference, CI: Confidence interval, NOS: Newcastle–Ottawa Scale

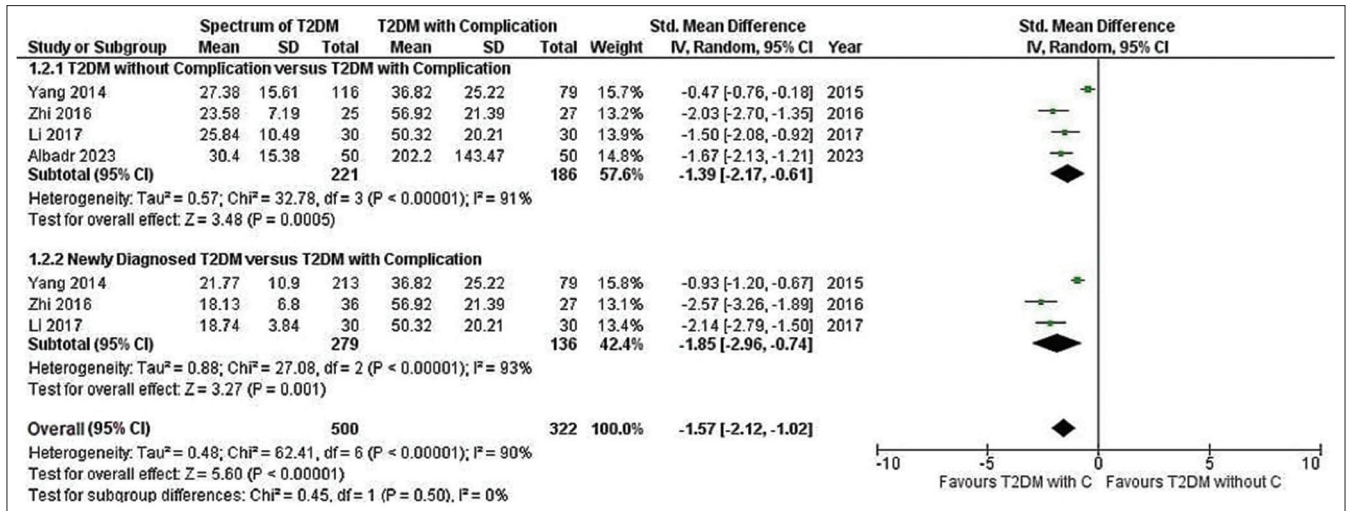


Figure 2: Meta-analysis results [forest plot] for pancreatic stone protein values in various spectrum of type 2 diabetes mellitus (T2DM) (1.2.1. Newly Diagnosed T2DM, 1.2.2. T2DM without complication) compared to T2DM with complication groups

conditions, other tissues such as regenerating islets, stomach, and intestine appear to also produce PSP/reg [31]. Although T2DM does not directly induce islet β -cell destruction at the initial stage, the β -cell mass decreases as β -cell failure is progressive along with the duration of diabetes [32,33]. PSP/reg expression is stimulated along with β -cell apoptosis, and this 16 kDa polypeptide could facilitate the recovery of β -cell mass [19,20]. This process was in line with our quantitative synthesis findings, where values of PSP/reg in the spectrum of T2DM (newly diagnosed, with and without complication) were significantly higher compared to healthy control. Stone *et al.* also reported that PSP/reg had potential to be a biomarker for endoplasmic reticulum stress in beta cells, which is crucial in the pathogenic process of T2DM, as well as Type 1 DM (T1DM) and genetic forms of diabetes such as Wolfram syndrome [34].

The cutoff values of PSP to predict the occurrence of T2DM and their complications were varied between studies. Yang *et al.* indicated PSP/reg threshold of 22 ng/ml in the nondiabetic group, suggesting that patients with PSP/reg values of >22 ng/mL were more likely to develop diabetes in future compared to those below, with 54% sensitivity and 65% specificity [19]. The number was higher when applied to differentiate T2DM patients with complications and those without complications, as stated in Li *et al.* [25], Zhi *et al.* [26], and Albadr and Haddad [21] studies, with a cutoff of 30.4 ng/mL (AUC = 0.854), 32 ng/mL (AUC = 0.902), and 65 ng/mL (AUC = 0.973), respectively. Given the higher accuracy represented by its AUC values, PSP/reg holds promise as a potential biomarker for differentiating patients with T2DM from healthy controls, as well as those without and with complications.

Sufficient evidence has already demonstrated the utilization of PSP/Reg1 α levels as a predictive factor for complications such as sepsis [35]; however, this is lacking in the spectrum of T2DM. One study by Bacon *et al.*, including patients with T1DM and maturity-onset diabetes of the young, only concluded that PSP/Reg1 α levels are associated

with the disease progression and did not specifically state DM complications [36]. Nevertheless, it is found in our quantitative analysis that both newly diagnosed T2DM and T2DM without complications have a significantly negative SMD when it is compared to T2DM with complications. The mechanism of complications associated with DM is mainly elucidated by the formation of advanced glycation end-products (AGEs), which further leads to prolonged and severe inflammation [37,38]. This state or condition of severe inflammation could lead to elevated serum levels of PSP/Reg1 α [9].

As one of the most common microvascular complications in T2DM [39], DN or diabetic kidney disease (DKD) was reported in five of our included studies. Li *et al.* reported a threshold of 30.4 ng/mL and an AUC value of 0.854 for DKD [25], whereas Zhi *et al.* found a cutoff of 32 ng/mL and AUC of 0.902 [26]. These findings suggest that PSP/reg may serve as a marker for renal injury and the progression of kidney-associated complications in diabetes. Sobajima *et al.* particularly studied the progression of nephropathy with urinary PSP/reg [23]. Despite the significance of urinary PSP excretion levels as indicative markers, additional factors must be considered to accurately define the initial stages of DKD, particularly given instances where PSP levels fail to increase despite the severity of nephropathic manifestations [23]. Renal impairment represents a predominant chronic complication observed in individuals with T2DM. Renal tubular epithelial cells are subject to tubular injury and interstitial fibrosis due to pro-inflammatory and profibrotic factors. This deleterious process results in a progressive impairment of cellular integrity, exacerbated by ROS and AGEs mediated in a hyperglycemic state [40].

The heterogeneity test using the I^2 statistic showed moderate-to-high heterogeneity across the categories of T2DM compared to the control group. The I^2 values are 91% for T2DM, 59% for newly diagnosed T2DM, 82% for T2DM without complications, and 91% for T2DM with complications. Furthermore, newly diagnosed T2DM and

T2DM without complications compared to T2DM with complication also exhibit high heterogeneity with I^2 values of 93% and 91%, respectively. This variability may arise from clinical, methodological, and statistical perspectives.

From a clinical perspective, several factors may contribute to high heterogeneity. The study's participant range, spanning from 30 to 213 individuals, which represented differences in sample size could increase disparity [41]. Furthermore, highlighting advanced age as a major risk factor of T2DM development, Yang *et al.* [19] employed a control group with a markedly younger age range (25–33 years) compared to the T2DM groups (56–75 years). This significant age discrepancy may raise a concern, as a recent survey in 2023 revealed that individuals aged 40–49 displayed a prevalence of 11.1% for diabetes, compared to 23.9% in those aged 60–69 [42]. The history of smoking has also been observed in some participants across studies. Yang *et al.* [19] identified a correlation between PSP and smoking, whereas Albadr and Haddad [21] did not detect a statistically significant association. Interestingly, both studies reported elevated PSP levels in smokers, potentially linked to the documented pro-inflammatory effects of smoking that may elevate several markers in the bloodstream [43,44].

From a methodological perspective, the ethnicities of participants involved in the studies are not described, and the generalizability between ethnicities remains unknown, thus raising potential risks of bias. From a statistical perspective, variation in reported effects and results contributed to higher heterogeneity. Studies exhibited variability in data normality, with some reporting results as median and IQR, whereas others utilized mean and SD. To address this issue and minimize potential bias, this meta-analysis employed the SMD as the effect size metric. Most studies addressed other variables that may influence PSP levels, thus enhancing the reliability of PSP measurements and their interpretations. Demographic and anthropometric factors, such as age, gender, blood pressure, BMI, and smoking status were not found to be statistically significant in the analysis, as reported by Ling Li *et al.* [25], Zhi *et al.* [26], Yang *et al.* [19], and Albadr *et al.* [21]. In contrast, a study by Zhu *et al.* [27] identified significant associations with PSP for eGFR ($P < 0.001$), uric acid ($P = 0.009$), and serum creatinine (SCr) ($P < 0.001$). Only studies by Sobajima *et al.* [23] and Astorri *et al.* [24] did not control for potential confounding variables related to PSP.

Strengths and limitations of the study

To the best of our knowledge, this is the first meta-analysis representing the inaugural attempt to systematically evaluate PSP as a candidate biomarker for microvascular complications in patients with T2DM. Our comprehensive review also incorporates data on PSP levels from both urine and serum samples, as well as explores the relationship between PSP levels and other glycemic-metabolic parameters. However, our investigation is subject to certain constraints. While our study encompassed a broad spectrum of T2DM presentations, DN was the primary focus of microvascular complications analyzed. Limited data availability from a small number of studies restricted our ability to comprehensively assess

neuropathy and retinopathy. In addition, we were unable to identify cohort studies which directly compare the incidence of microvascular complications using PSP against established glycemic markers, namely HbA1c or FPG.

Future directions

Given the compelling evidence for PSP as a key factor in T2DM course, we propose future research to delineate the applicability of PSP as a prognostic tool in predicting disease progression across other diabetes types. Consequently, PSP has the potential to serve as a valuable noninvasive biomarker for clinicians to implement targeted preventive measures. Moreover, future studies should evaluate the diagnostic accuracy meta-analysis of PSP in predicting diabetes-related complications, incorporating their sensitivity, specificity, and area under the ROC curve (AUC-ROC) values for a thorough assessment.

CONCLUSION

Significantly higher levels of PSP/Reg were detected across the entire spectrum of T2DM, with levels continuing to increase as the disease progresses. Patients suffering from diabetic complications exhibited the highest levels of PSP/Reg, with DKD/nephropathy (DKD/DN) being the most studied complication. Notably, PSP/Reg appears to have the ability to not only differentiate between individuals with and without T2DM but also to predict the occurrence of complications in those already diagnosed.

Acknowledgments

The authors are grateful to all colleagues from Atma Jaya Catholic University of Indonesia and staff from the Internal Medicine Department, Faculty of Medicine, Padjadjaran University for all the support and contributions provided.

Data availability statement

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File 1: Participant, intervention or exposure, comparator, outcomes, time, setting, study design

PICOTS-SD	Criteria
Patients	Subjects with T2DM with or without complications
Intervention or exposure	PSP/REG-1 α
Comparator	Healthy (normoglycemic) individuals
Outcomes	Differences in PSP/REG-1 α value between <ol style="list-style-type: none"> Healthy subjects and newly diagnosed T2DM patients Healthy subjects and T2DM patients without complications Healthy subjects and T2DM patients with complications Newly diagnosed T2DM patients and T2DM patients with complications T2DM patients without complications and T2DM patients with complications
Time	No publication year restrictions
Setting	Subjects visiting medical facilities
Study design	Observational study

T2DM: Type 2 diabetes mellitus, PSP: Pancreatic stone protein, REG-1 α : Regenerating 1-alpha protein

Supplementary File 2: Search strategy

Database	Query	Results
Medline	((((("Diabetes Mellitus, Type 2"[MeSH Terms]) OR ("Type 2 Diabetes Mellitus"[Title/Abstract]) OR ("Non-Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR (MODY[Title/Abstract]) OR ("Maturity-Onset Diabetes Mellitus"[Title/Abstract]))) OR (NIDDM[Title/Abstract]))	181,407
Filter: Full text	(((Lithostathine[MeSH Terms]) OR ("Pancreatic Stone Protein"[Title/Abstract]) OR (PSP[Title/Abstract]) OR ("Pancreatic Stone Protein/regenerating Protein"[Title/Abstract]) OR (PSP/reg[Title/Abstract]))	7637
	#1 AND #2	71
ProQuest	("Diabetes Mellitus, Type 2") OR ("Type 2 Diabetes Mellitus") OR ("Non-Insulin-Dependent Diabetes Mellitus") OR (MODY) OR ("Maturity-Onset Diabetes Mellitus") OR (NIDDM)	176,103
Filter: Full text, document type: Article	(Lithostathine) OR ("Pancreatic Stone Protein") OR (PSP) OR ("Pancreatic Stone Protein/regenerating Protein") OR (PSP/reg)	22,062
	#1 AND #2	136
Science Direct	"Diabetes Mellitus, Type 2" OR "Non-Insulin-Dependent Diabetes Mellitus" OR "MODY" OR "Maturity-Onset Diabetes Mellitus" OR "NIDDM"	14,085
Filter: Research articles, medicine and dentistry	"Lithostathine" OR "Pancreatic Stone Protein" OR "PSP" OR "Pancreatic Stone Protein/regenerating Protein" OR "PSP/reg"	4559
	#1 AND #2	31
Google Scholar	"Diabetes Mellitus", "Pancreatic stone protein OR PSP/REG"	35
Filter: Advance search: With all the words		
Cochrane Library	"Diabetes Mellitus, Type 2" OR "Non-Insulin-Dependent Diabetes Mellitus" OR "MODY" OR "Maturity-Onset Diabetes Mellitus" OR "NIDDM"	41,122
Filter: Title, abstract, keyword, trials	"Lithostathine" OR "Pancreatic Stone Protein" OR "PSP" OR "Pancreatic Stone Protein/regenerating Protein" OR "PSP/reg"	772
	#1 AND #2	16
Total		289

Supplementary File 3: Excluded of potential relevant studies

1. Bonner C. PSP/reg: A potent and enigmatic trophic factor, which is upregulated during the pathogenesis of diabetes. *Endocrine* 2015;48:725-7.
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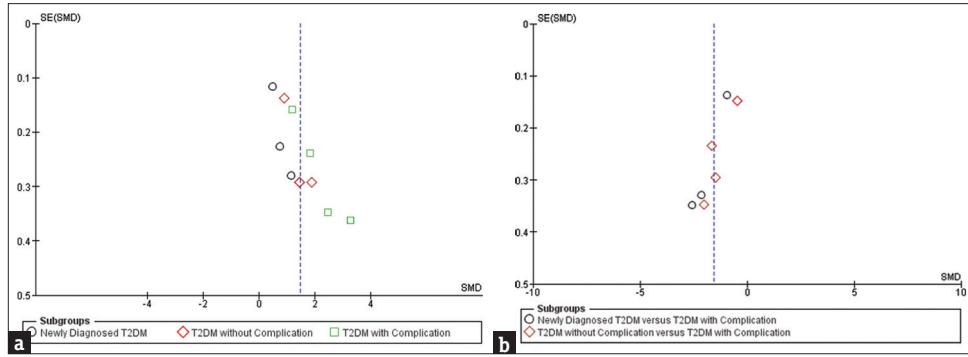
Supplementary File 4: Results of study quality assessment using Newcastle-Ottawa Scale tools

Case control									
First author, year of publication, country	Selection 1: Is the case definition adequate?	Selection 2: Representativeness of the cases	Selection 3: Selection of controls	Selection 4: Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Exposure 1: Ascertainment of exposure	Exposure 2: Same method of ascertainment for cases and controls	Exposure 3: Nonresponse rate	Overall risk of bias
Yang <i>et al.</i> , 2015 [19]	*	*	*	*	**	*	0	*	Good quality
Astorri <i>et al.</i> , 2010 [24]	*	*	*	*	**	*	*	0	Good quality
Albadr and Haddad, 2023 [21]	*	*	0	*	**	*	0	*	Good quality

Cross sectional

First author, year of publication, country	Selection 1: Representativeness of the sample	Selection 2: Sample size	Selection 3: Nonrespondents	Selection 4: Ascertainment of the exposure	Comparability 1: Potential confounding factor	Outcome 1: Assessment of outcome	Outcome 2: Statistical test	Overall risk of bias
Li <i>et al.</i> , 2017 [25]	0	*	*	**	**	**	*	Very good quality
Zhu <i>et al.</i> , 2020 [27]	*	0	0	**	**	**	*	Good quality
Sobajima <i>et al.</i> , 1998 [23]	*	0	0	**	0	**	*	Satisfactory quality
Zhi <i>et al.</i> , 2016 [26]	*	0	0	**	0	**	*	Satisfactory quality

All risk-of-bias evaluations were conducted according to the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional or case-control study guidelines. Applied for both NOS types, 2 stars (***) are awarded if all or most of the requirements are fulfilled in each section, and 1 star (*) is given if only half of the requirements are fulfilled, or if the question is answered but not sufficiently. No star (0) is assigned if no information is provided or if there is no description at all.



Supplementary File 5: (a) Publication bias as a funnel plot diagram for pancreatic stone protein values in various spectrums of type 2 diabetes mellitus (T2DM) (newly diagnosed T2DM, T2DM without complication, and T2DM with complication) compared to healthy control groups. (b) Publication bias as a funnel plot diagram for pancreatic stone protein values in various spectrums of type 2 diabetes mellitus (T2DM) (newly diagnosed T2DM and T2DM without complication) compared to T2DM with complication groups

Study or Subgroup	Spectrum of T2DM			Healthy Control			Weight	Std. Mean Difference IV, Random, 95% CI	Year	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total				
1.1.1 T2DM with Complication										
Yang 2014	36.82	25.22	79	17.07	5.18	117	10.9%	1.19 [0.88, 1.50]	2015	
Zhi 2016	56.92	21.39	27	14.21	3.33	50	8.8%	3.28 [2.57, 3.99]	2016	
Li 2017	50.32	20.21	30	14.16	4.04	30	9.0%	2.45 [1.77, 3.13]	2017	
Albadr 2023	202.2	143.47	50	17	7.07	50	10.1%	1.81 [1.34, 2.28]	2023	
Subtotal (95% CI)			186			247	38.7%	2.14 [1.28, 3.00]		
Heterogeneity: Tau ² = 0.68; Chi ² = 34.34, df = 3 (P < 0.00001); I ² = 91%										
Test for overall effect: Z = 4.90 (P < 0.00001)										
1.1.2 T2DM without Complication										
Yang 2014	27.38	15.61	116	17.07	5.18	117	11.0%	0.89 [0.62, 1.15]	2015	
Zhi 2016	23.58	7.19	25	14.21	3.33	50	9.6%	1.88 [1.31, 2.45]	2016	
Li 2017	25.84	10.49	30	14.16	4.04	30	9.6%	1.45 [0.88, 2.02]	2017	
Albadr 2023	30.4	15.38	50	17	7.07	50		Not estimable	2023	
Subtotal (95% CI)			171			197	30.2%	1.36 [0.74, 1.99]		
Heterogeneity: Tau ² = 0.25; Chi ² = 10.94, df = 2 (P = 0.004); I ² = 82%										
Test for overall effect: Z = 4.27 (P < 0.0001)										
1.1.3 Newly Diagnosed T2DM										
Yang 2014	21.77	10.8	213	17.07	5.18	117	11.1%	0.50 [0.28, 0.73]	2015	
Zhi 2016	18.13	6.8	36	14.21	3.33	50	10.3%	0.77 [0.32, 1.21]	2016	
Li 2017	18.74	3.84	30	14.16	4.04	30	9.7%	1.15 [0.60, 1.70]	2017	
Subtotal (95% CI)			279			197	31.1%	0.74 [0.38, 1.10]		
Heterogeneity: Tau ² = 0.06; Chi ² = 4.92, df = 2 (P = 0.09); I ² = 59%										
Test for overall effect: Z = 4.05 (P < 0.0001)										
Overall (95% CI)			636			641	100.0%	1.48 [1.05, 1.92]		
Heterogeneity: Tau ² = 0.43; Chi ² = 99.87, df = 9 (P < 0.00001); I ² = 91%										
Test for overall effect: Z = 6.69 (P < 0.00001)										
Test for subgroup differences: Chi ² = 10.11, df = 2 (P = 0.006), I ² = 80.2%										

Supplementary File 6: Meta-analysis results [forest plot] for pancreatic stone protein values in various spectra of type 2 diabetes mellitus (T2DM) (1.1.1. newly diagnosed T2DM, 1.1.2. T2DM without complication, and 1.1.3. T2DM with complication) compared to healthy control groups