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INTEGRATED PHYSIOLOGICAL, BIOCHEMICAL AND PSYCHIATRIC PREDICTORS OF GLYCEMIC CONTROL AND CARDIOMETABOLIC RISK IN ADULTS WITH TYPE 2 DIABETES MELLITUS: AN OBSERVATIONAL STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a complex multisystem disorder driven by metabolic dysfunction, chronic systemic inflammation, and psychiatric co-morbidities. While physiological metrics and metabolic biomarkers are routinely monitored in clinical practice, the combined predictive contribution of biological markers and psychiatric factors (such as depression, anxiety, and diabetes-related distress) toward glycemic control and overall cardiometabolic risk remains insufficiently quantified in integrated observational models.

Objective: To evaluate the integrated predictive value of baseline physiological parameters, systemic biochemical markers, and psychiatric symptom scores for suboptimal glycemic control (HbA1c $\geq$ 8.0%) and elevated 10-year cardiometabolic risk in adults with type 2 diabetes mellitus.

Methods: This prospective observational study evaluated 160 adult patients (aged 30 to 70 years) with established type 2 diabetes mellitus attending outpatient clinics at M.Islam Medical College. Physiological evaluations included resting blood pressure, body mass index (BMI), waist circumference, and pulse wave velocity (PWV). Biochemical assays quantified glycated hemoglobin (HbA1c), lipid profiles (total cholesterol, triglycerides, LDL-C, HDL-C), high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose, and estimated glomerular filtration rate (eGFR). Psychiatric profiles were evaluated using validated psychometric instruments: Patient Health Questionnaire-9 (PHQ-9 for depression), Generalized Anxiety Disorder-7 (GAD-7 for anxiety), and Diabetes Distress Scale-17 (DDS-17 for disease-specific distress). Cardiometabolic risk was estimated using the 10-year UKPDS Risk Engine. Bivariate correlations and multivariable logistic regression analyses were conducted to establish independent predictors.

Results: Among 160 adults (mean age 52.4 +/- 9.8 years; 53.8 percent female), suboptimal glycemic control (HbA1c $\geq$ 8.0%) was present in 46.3 percent (n = 74). Clinically significant depressive symptoms (PHQ-9 score $\geq$ 10) were identified in 33.8 percent (n = 54), generalized anxiety (GAD-7 score $\geq$ 10) in 26.3 percent (n = 42), and high diabetes distress (DDS-17 score $\geq$ 3.0) in 38.8 percent (n = 62). Patients with suboptimal glycemic control exhibited significantly higher hs-CRP ($4.8 +/- 1.8$ vs. $2.2 +/- 0.9$ mg/L, $p < 0.001$), elevated systolic blood pressure ($142.6 +/- 16.2$ vs. $128.4 +/- 12.4$ mmHg, $p < 0.001$), higher DDS-17 scores ($3.4 +/- 0.8$ vs. $2.1 +/- 0.6$, $p < 0.001$), and elevated PHQ-9 scores ($11.8 +/- 4.2$ vs. $6.4 +/- 2.8$, $p < 0.001$). Multivariable logistic regression revealed that high diabetes distress (adjusted OR = 3.84, 95 percent CI: 1.78 to 8.28, p = 0.001), elevated hs-CRP > 3.0 mg/L (adjusted OR = 3.12, 95 percent CI: 1.48 to 6.58, p = 0.003), moderate-to-severe depression (PHQ-9 $\geq$ 10; adjusted OR = 2.76, 95 percent CI: 1.24 to 6.14, p = 0.013), and abdominal obesity (waist circumference; adjusted OR = 2.18, 95 percent CI: 1.04 to 4.56, p = 0.038) independently predicted suboptimal glycemic control. Combined physiological, biochemical, and psychiatric profiling achieved an area under the ROC curve (AUC) of 0.864 for predicting high 10-year cardiovascular risk.

Conclusion: Suboptimal glycemic control and elevated cardiometabolic risk in T2DM are strongly governed by an interplay between systemic bio-inflammatory pathways and psychological burden. High diabetes distress, elevated systemic inflammation (hs-CRP), and depressive symptoms are independent predictors of adverse metabolic trajectories. Incorporating routine psychiatric screening alongside standard physiological and biochemical testing is essential for comprehensive diabetes care and cardiovascular risk reduction.

KEYWORDS: Type 2 diabetes mellitus; Glycemic control; HbA1c; Cardiometabolic risk; Diabetes distress; Depression; Systemic inflammation; hs-CRP; Psychometric evaluation.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most pressing global public health challenges, accounting for extensive cardiovascular morbidity, renal impairment, premature mortality, and reduced quality of life. The clinical management of T2DM traditionally focuses on physiological metrics (such as blood pressure, body mass index, and arterial stiffness) and biochemical markers (including glycated hemoglobin [HbA1c], lipid subfractions, and inflammatory biomarkers). However, despite pharmacotherapy and lifestyle guidelines, a substantial proportion of patients fail to achieve target glycemic control (HbA1c $< 7.0\%$) or experience persistent microvascular and macrovascular complications.[1-3]

This persistent treatment gap highlights the complex, multi-system nature of diabetes. Beyond classic metabolic pathways, systemic inflammation plays a central role in driving both insulin resistance and vascular endothelial decay. Elevated levels of acute-phase reactants—specifically high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha)—induce vascular smooth muscle proliferation, accelerate atheromatous plaque formation, and disrupt vascular reactivity.[4-5]

Simultaneously, the psychiatric and psychological burden associated with managing a chronic disease is increasingly recognized as a key determinant of clinical outcomes. Adults with T2DM experience a two- to three-fold higher prevalence of major depressive disorder, generalized anxiety disorder, and specialized "diabetes distress"—defined as the severe emotional burden, stress, and burnout directly stemming from daily self-management demands.

The biological mechanisms linking psychiatric symptoms to poor cardiometabolic outcomes are bidirectional and multifaceted:

1. **Neuroendocrine Hyperactivation:** Chronic psychological stress and depression activate the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), leading to sustained cortisol release, elevated circulating catecholamines, hepatic gluconeogenesis, and reduced peripheral insulin sensitivity.

2. **Behavioral Mediators:** Psychological distress frequently impairs self-care behaviors, leading to poor dietary adherence, sedentary lifestyle, medication non-compliance, and infrequent self-monitoring of blood glucose.

3. **Pro-Inflammatory Signaling:** Stress-induced neuro-immune signaling directly upregulates systemic inflammatory cascades, elevating circulating cytokines that exacerbate both vascular damage and central neuro-inflammation.[6-8]

Although physiological, biochemical, and psychiatric domains have been studied individually, clinical models integrating these three distinct spheres into a unified observational framework remain limited.[8-10]

Therefore, this prospective observational study was conducted to evaluate the combined predictive value of baseline physiological parameters, systemic biochemical markers, and psychiatric symptom profiles for glycemic control and estimated 10-year cardiometabolic risk in adult patients with type 2 diabetes mellitus.

2. Rationale of the Study

Clinical diabetes care frequently operates within narrow physiological and biochemical silos, focusing primarily on adjusting hypoglycemic agents, antihypertensives, and statins. Psychological distress and depression are often underdiagnosed and unmanaged in routine outpatient metabolic clinics. Evaluating physiological metrics (blood pressure, BMI, arterial stiffness), biochemical markers (HbA1c, lipids, hs-CRP), and psychometric symptom scores (PHQ-9, GAD-7, DDS-17) within a unified prospective cohort provides crucial empirical evidence for adopting holistic, multi-disciplinary care models that integrate psychiatric screening into standard cardiometabolic risk management.

3. Objectives

Primary Objective

- To assess the integrated predictive value of physiological variables, biochemical markers, and psychiatric symptom scores (PHQ-9, GAD-7, DDS-17) for suboptimal glycemic control (HbA1c $\geq 8.0\%$) in adult patients with type 2 diabetes mellitus.

Secondary Objectives

1. To quantify the prevalence of clinical depression, generalized anxiety, and severe diabetes distress within the study cohort.

2. To compare inflammatory markers (hs-CRP), lipid profiles, and hemodynamic metrics between patients with optimal (HbA1c $< 7.0\%$), moderate ($7.0 - 7.9\%$), and suboptimal ($\geq 8.0\%$) glycemic control.

3. To evaluate bivariate correlations between psychometric scores, systemic inflammatory markers, and estimated 10-year UKPDS cardiovascular risk percentages.

4. To establish a multivariable predictive regression model identifying independent cross-domain risk factors for poor metabolic and cardiovascular outcomes.

4. MATERIALS AND METHODS

4.1 Study Design and Setting

A prospective observational study was conducted at M.Islam Medical College Gujranwala.

4.2 Study Duration

The study was conducted over an eight-month period, encompassing prospective patient recruitment, baseline physiological mapping, laboratory biochemical processing, standardized psychometric scoring, follow-up monitoring, and statistical risk modeling.

4.3 Study Population

Adult male and female patients aged 30 to 70 years with a confirmed clinical diagnosis of type 2 diabetes mellitus for at least 1 year attending the diabetes outpatient clinic.

4.4 Sample Size

A sample size of 160 adult T2DM cases was prospectively enrolled. The sample size was calculated using G-Power software based on estimating an expected prevalence of suboptimal glycemic control of 45 percent, an alpha error level (α) of 0.05, a statistical power ($1 - \beta$) of 85 percent, and accommodating up to 12 multivariable regression predictor variables.

4.5 Inclusion Criteria

1. Adults aged 30 to 70 years with established T2DM (duration ≥ 1 year).
2. Patients maintained on stable glucose-lowering therapy (oral hypoglycemic agents and/or insulin) for at least 3 months prior to enrollment.
3. Ability to complete structured psychometric questionnaires independently or via standardized clinical interview.
4. Provision of written informed consent.

4.6 Exclusion Criteria

1. Diagnosis of Type 1 Diabetes Mellitus, secondary diabetes, or gestational diabetes.
2. Presence of severe organic brain syndrome, acute psychosis, advanced dementia, or active substance dependence preventing reliable psychometric evaluation.
3. Pre-existing severe end-stage renal disease (eGFR < 15 mL/min/1.73m^2 or chronic dialysis), active malignancy, or advanced heart failure (NYHA Class III/IV).
4. Current acute infection, systemic autoimmune disorder, or corticosteroid therapy capable of altering systemic inflammatory markers (hs-CRP).
5. Pregnancy or active lactation.

4.7 Baseline Physiological Assessment

Physiological parameters were measured using standardized clinical protocols:

- **Anthropometry:** Height (cm) and weight (kg) were recorded to compute Body Mass Index (BMI $=$ kg/m^2). Waist circumference (cm) was measured at the midpoint between the lower rib margin and the iliac crest.

- **Hemodynamics:** Resting Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were recorded in a seated position after 10 minutes of quiet rest using a validated digital sphygmomanometer; the mean of two readings was calculated. Resting heart rate (bpm) was logged.
- **Arterial Stiffness:** Carotid-femoral Pulse Wave Velocity (PWV in m/s) was non-invasively assessed using applanation tonometry to evaluate vascular compliance.

4.8 Biochemical and Inflammatory Investigations

Venous blood samples were collected after a 12-hour overnight fast:

- **Glycemic Control:** Glycated hemoglobin (HbA1c, %) measured via High-Performance Liquid Chromatography (HPLC). Fasting Plasma Glucose (FPG, mg/dL) was quantified using enzymatic hexokinase assays.
- **Lipid Profile:** Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C) were measured on an automated clinical chemistry analyzer.
- **Systemic Inflammatory Biomarker:** High-sensitivity C-reactive protein (hs-CRP, mg/L) quantified via high-sensitivity immunoturbidimetric assay. Values > 3.0 mg/L were categorized as high systemic inflammatory risk.
- **Renal Function:** Serum creatinine was measured to calculate estimated Glomerular Filtration Rate (eGFR) via the CKD-EPI formula.

4.9 Psychiatric and Psychological Evaluation

Psychometric evaluations were administered at baseline using validated instruments:

- **Patient Health Questionnaire-9 (PHQ-9):** Assesses depressive symptom severity over the preceding 2 weeks (scored 0 to 27). Scores ≥ 10 defined clinically significant depression.
- **Generalized Anxiety Disorder-7 (GAD-7):** Measures anxiety symptom severity (scored 0 to 21). Scores ≥ 10 indicated clinically significant generalized anxiety.
- **Diabetes Distress Scale-17 (DDS-17):** Measures disease-specific emotional distress across four domains: emotional burden, physician-related distress, regimen-related distress, and interpersonal distress (17 items, 1 to 6 scale). Mean overall score ≥ 3.0 defined high diabetes distress.

4.10 Estimated 10-Year Cardiometabolic Risk

The 10-year risk of hard cardiovascular events (fatal or non-fatal myocardial infarction and stroke) was calculated for each patient using the UKPDS Risk Engine (incorporating age, sex, ethnicity, smoking status, SBP, HbA1c, TC, and HDL-C). High 10-year cardiometabolic risk was defined as a calculated UKPDS score $\geq 20\%$.

4.11 Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality using the Kolmogorov-Smirnov test and expressed as mean +/- standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as absolute numbers and percentages (n, %).

Inter-group comparisons between patients with optimal/moderate glycemic control (HbA1c $< 8.0\%$) and suboptimal control (HbA1c $\geq 8.0\%$) were performed using Student's independent t-test, Mann-Whitney U test, or Pearson's Chi-square (χ^2) test. Spearman rank correlation coefficients evaluated linear relationships across psychometric scores, inflammatory markers, and cardiovascular risk. Multivariable binary logistic regression was performed to determine independent predictors of suboptimal glycemic control (HbA1c $\geq 8.0\%$) and high UKPDS cardiovascular risk ($\geq 20\%$). Receiver Operating Characteristic (ROC) curve analysis evaluated the predictive performance of combined models. Statistical significance was defined as a two-sided $p < 0.05$.

5. RESULTS

5.1 Baseline Demographic and Clinical Characteristics

The total study sample comprised 160 adult patients with type 2 diabetes (mean age 52.4 ± 9.8 years; 86 females [53.8 percent], 74 males [46.2 percent]; mean diabetes duration 7.6 ± 4.2 years). Overall, 46.3 percent (n = 74) presented with suboptimal glycemic control (HbA1c $\geq 8.0\%$). Insulin therapy was utilized by 36.3 percent (n = 58) of the cohort. Baseline characteristics stratified by glycemic control are detailed in Table 1.

Demographic / Clinical Variable	Optimal Control (HbA1c < 7.0%) (n = 48)	Moderate Control (HbA1c 7.0–7.9%) (n = 38)	Suboptimal Control (HbA1c >= 8.0%) (n = 74)	Total Cohort (n = 160)	p-value
Age (years)	51.2 +/- 9.2	52.1 +/- 10.1	53.4 +/- 9.9	52.4 +/- 9.8	0.442
Female Sex, n (%)	25 (52.1)	20 (52.6)	41 (55.4)	86 (53.8)	0.914
Male Sex, n (%)	23 (47.9)	18 (47.4)	33 (44.6)	74 (46.2)	0.914
Diabetes Duration (years)	5.8 +/- 3.1	7.2 +/- 3.8	9.1 +/- 4.6	7.6 +/- 4.2	<0.001
Body Mass Index (kg/m squared)	26.4 +/- 3.8	27.8 +/- 4.1	29.6 +/- 4.6	28.2 +/- 4.4	<0.001
Waist Circumference (cm)	88.4 +/- 8.2	92.6 +/- 9.1	98.2 +/- 10.4	93.9 +/- 10.2	<0.001
Current Insulin Therapy, n (%)	10 (20.8)	12 (31.6)	36 (48.6)	58 (36.3)	0.006
Antihypertensive Use, n (%)	22 (45.8)	20 (52.6)	48 (64.9)	90 (56.3)	0.082

Table 1: Baseline demographic and physiological characteristics stratified by glycemic control category.

5.2 Physiological and Biochemical Profiles

Patients with suboptimal glycemic control exhibited significantly impaired physiological and biochemical profiles ($p < 0.001$). Systolic blood pressure, pulse wave velocity, total cholesterol, triglycerides, and serum hs-CRP were significantly elevated in the suboptimal group. Mean hs-CRP in the suboptimal group was 4.8 ± 1.8 mg/L compared to 2.2 ± 0.9 mg/L in the optimal control group ($p < 0.001$).

Physiological / Biochemical Metric	Optimal Control (HbA1c < 7.0%) (n = 48)	Moderate Control (HbA1c 7.0–7.9%) (n = 38)	Suboptimal Control (HbA1c >= 8.0%) (n = 74)	p-value
Systolic Blood Pressure (mmHg)	126.2 +/- 11.4	131.4 +/- 13.2	142.6 +/- 16.2	<0.001
Diastolic Blood Pressure (mmHg)	78.4 +/- 7.2	81.2 +/- 8.1	86.8 +/- 9.6	<0.001
Pulse Wave Velocity (m/s)	8.2 +/- 1.1	9.1 +/- 1.4	10.8 +/- 1.8	<0.001
Fasting Plasma Glucose (mg/dL)	118.4 +/- 16.2	146.2 +/- 21.4	204.8 +/- 42.6	<0.001

Physiological / Biochemical Metric	Optimal Control (HbA1c < 7.0%) (n = 48)	Moderate Control (HbA1c 7.0–7.9%) (n = 38)	Suboptimal Control (HbA1c >= 8.0%) (n = 74)	p-value
Glycated Hemoglobin (HbA1c, %)	6.4 +/- 0.4	7.4 +/- 0.3	9.4 +/- 1.2	<0.001
Total Cholesterol (mg/dL)	176.4 +/- 28.2	192.6 +/- 32.4	218.4 +/- 41.2	<0.001
Triglycerides (mg/dL)	134.2 +/- 36.8	168.4 +/- 44.2	212.6 +/- 58.4	<0.001
HDL Cholesterol (mg/dL)	46.8 +/- 8.2	42.4 +/- 7.6	38.2 +/- 6.8	<0.001
LDL Cholesterol (mg/dL)	102.8 +/- 22.4	116.4 +/- 26.8	137.4 +/- 34.2	<0.001
High-Sensitivity CRP (hs-CRP, mg/L)	**2.2 +/- 0.9**	**3.1 +/- 1.2**	**4.8 +/- 1.8**	**<0.001**
eGFR (mL/min/1.73m squared)	88.4 +/- 14.2	82.6 +/- 16.1	74.2 +/- 18.6	<0.001

Table 2: Comparison of physiological, biochemical, and inflammatory parameters.

5.3 Psychiatric and Psychometric Symptom Profiles

Prevalence of psychiatric symptoms was high across the cohort: clinically significant depression (PHQ-9 ≥ 10) was identified in 33.8 percent (n = 54), generalized anxiety (GAD-7 ≥ 10) in 26.3 percent (n = 42), and high diabetes distress (DDS-17 ≥ 3.0) in 38.8 percent (n = 62). Psychometric scores were markedly worse among patients in the suboptimal glycemic group ($p < 0.001$).

Psychiatric Instrument / Category	Optimal Control (HbA1c < 7.0%) (n = 48)	Moderate Control (HbA1c 7.0–7.9%) (n = 38)	Suboptimal Control (HbA1c >= 8.0%) (n = 74)	Total Cohort (n = 160)	p-value
PHQ-9 Depressive Score	5.8 +/- 2.4	7.2 +/- 3.1	11.8 +/- 4.2	8.9 +/- 4.4	<0.001
- PHQ-9 >= 10 (Moderate to Severe), n (%)	7 (14.6)	9 (23.7)	38 (51.4)	54 (33.8)	<0.001
GAD-7 Anxiety Score	4.6 +/- 2.1	6.1 +/- 2.8	9.6 +/- 3.8	7.3 +/- 3.7	<0.001

Psychiatric Instrument / Category	Optimal Control (HbA1c < 7.0%) (n = 48)	Moderate Control (HbA1c 7.0–7.9%) (n = 38)	Suboptimal Control (HbA1c >= 8.0%) (n = 74)	Total Cohort (n = 160)	p-value
- GAD-7 >= 10 (Moderate to Severe), n (%)	5 (10.4)	7 (18.4)	30 (40.5)	42 (26.3)	<0.001
DDS-17 Diabetes Distress Score	1.9 +/- 0.5	2.4 +/- 0.6	3.4 +/- 0.8	2.7 +/- 0.9	<0.001
- High Diabetes Distress (DDS >= 3.0), n (%)	6 (12.5)	10 (26.3)	46 (62.2)	62 (38.8)	<0.001
- Regimen-Related Distress Subscore	2.1 +/- 0.6	2.6 +/- 0.7	3.8 +/- 0.9	3.0 +/- 1.0	<0.001
- Emotional Burden Subscore	2.0 +/- 0.5	2.5 +/- 0.6	3.6 +/- 0.8	2.9 +/- 0.9	<0.001

Table 3: Distribution of psychiatric symptom scores across glycemic control categories.

5.4 Correlation Analysis

Spearman rank correlation analysis established significant positive correlations between psychometric scores, systemic inflammation, and 10-year UKPDS cardiovascular risk percentages. DDS-17 score correlated strongly with HbA1c ($r = 0.54$, $p < 0.001$) and hs-CRP ($r = 0.46$, $p < 0.001$). PHQ-9 depression score correlated positively with 10-year UKPDS cardiovascular risk ($r = 0.42$, $p < 0.001$).

Variable Pair	Spearman Correlation (r)	p-value
Diabetes Distress (DDS-17) vs. HbA1c	0.54	<0.001
High-Sensitivity CRP vs. HbA1c	0.51	<0.001
PHQ-9 Depressive Score vs. HbA1c	0.48	<0.001
Diabetes Distress (DDS-17) vs. High-Sensitivity CRP	0.46	<0.001
PHQ-9 Depressive Score vs. 10-Year UKPDS Risk Score	0.42	<0.001
Pulse Wave Velocity vs. 10-Year UKPDS Risk Score	0.58	<0.001
GAD-7 Anxiety Score vs. Regimen Distress Subscore	0.62	<0.001

Table 4: Bivariate correlation matrix linking psychiatric, inflammatory, and cardiometabolic variables.

5.5 Multivariable Logistic Regression Analysis
Multivariable logistic regression models were developed for two primary clinical outcomes:

- **Model 1: Suboptimal Glycemic Control (**HbA1c ≥ 8.0%**):** Independent predictors included High Diabetes Distress (DDS-17 ≥ 3.0; adjusted OR = 3.84, 95 percent CI: 1.78 to 8.28, p = 0.001), elevated systemic inflammation (hs-CRP > 3.0 mg/L; adjusted OR = 3.12, 95 percent CI: 1.48 to 6.58, p = 0.003), moderate-to-severe depression (PHQ-9 ≥ 10; adjusted OR = 2.76, 95 percent CI: 1.24 to 6.14, p = 0.013), and abdominal obesity (waist circumference ≥ 90 cm females / ≥ 100 cm males; adjusted OR = 2.18, 95 percent CI: 1.04 to 4.56, p = 0.038).

- **Model 2: High 10-Year UKPDS Cardiovascular Risk (≥** 20%**):** Independent predictors included Elevated Pulse Wave Velocity (> 10.0 m/s; adjusted OR = 4.14, 95 percent CI: 1.88 to 9.12, p < 0.001), hs-CRP > 3.0 mg/L (adjusted OR = 3.48, 95 percent CI: 1.62 to 7.46, p = 0.001), Suboptimal Glycemic Control (adjusted OR = 3.26, 95 percent CI: 1.52 to 6.98, p = 0.002), and PHQ-9 Depressive Score ≥ 10 (adjusted OR = 2.45, 95 percent CI: 1.12 to 5.36, p = 0.024).

Dependent Model / Predictor Variable	**Unadjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Model 1: Suboptimal Glycemic Control (HbA1c >= 8.0%)				
High Diabetes Distress (DDS-17 >= 3.0)	6.42 (3.12–13.24)	<0.001	**3.84 (1.78–8.28)**	**0.001**
High-Sensitivity CRP > 3.0 mg/L	5.28 (2.58–10.82)	<0.001	**3.12 (1.48–6.58)**	**0.003**
Moderate-to-Severe Depression (PHQ-9 >= 10)	4.86 (2.32–10.18)	<0.001	**2.76 (1.24–6.14)**	**0.013**
Abdominal Obesity (Elevated Waist Circumference)	3.45 (1.72–6.92)	0.001	**2.18 (1.04–4.56)**	**0.038**
Generalized Anxiety (GAD-7 >= 10)	3.12 (1.48–6.58)	0.003	1.62 (0.74–3.54)	0.224
Model 2: High 10-Year UKPDS Risk (>= 20%)				
Elevated Pulse Wave Velocity (> 10.0 m/s)	6.18 (2.94–12.98)	<0.001	**4.14 (1.88–9.12)**	**<0.001**
High-Sensitivity CRP > 3.0 mg/L	5.12 (2.46–10.64)	<0.001	**3.48 (1.62–7.46)**	**0.001**
Suboptimal Glycemic Control (HbA1c >= 8.0%)	4.92 (2.36–10.24)	<0.001	**3.26 (1.52–6.98)**	**0.002**
Moderate-to-Severe Depression (PHQ-9 >= 10)	3.84 (1.82–8.12)	<0.001	**2.45 (1.12–5.36)**	**0.024**

Table 5: Multivariable logistic regression modeling predictors of suboptimal glycemic control and high cardiovascular risk.

5.6 Receiver Operating Characteristic (ROC) Curve Performance

ROC curve analysis demonstrated that incorporating psychiatric variables (DDS-17, PHQ-9) alongside conventional physiological and biochemical markers significantly improved discrimination for high 10-year UKPDS cardiovascular risk (≥ 20%). The Area Under the Curve (AUC) increased from 0.768 (biochemical + physiological model alone) to 0.864 (integrated bio-psycho-physiological model, p = 0.004).

6. DISCUSSION

This prospective observational study evaluated the integrated predictive value of physiological metrics, biochemical parameters, and psychiatric symptom scores for glycemic control and 10-year cardiometabolic risk in adults with type 2 diabetes mellitus. The primary finding indicates that combining systemic inflammation (hs-CRP), vascular stiffness (PWV), and psychiatric symptom profiles (diabetes distress and depression) provides high diagnostic accuracy for identifying patients at risk for suboptimal glycemic control (HbA1c ≥ 8.0%) and high 10-year cardiovascular risk (≥ 20%).[11-1]

6.1 The Role of Diabetes Distress and Depressive Symptoms

Psychiatric co-morbidities are frequently overlooked in routine diabetes care, yet our findings demonstrate that diabetes distress (DDS-17 ≥ 3.0; adjusted OR = 3.84) and depression (PHQ-9 ≥ 10; adjusted OR = 2.76) are strong independent predictors of suboptimal glycemic control. Diabetes distress represents a distinct emotional burden associated with the relentless daily demands of glycemic monitoring, dietary restrictions, and medication adherence. High distress leads directly to self-care burnout, erratic glucose checking, and missed insulin or oral medication doses. [13-14]

Furthermore, major depression exerts direct neuroendocrine effects. Chronic depressive states drive dysregulation of the HPA axis, increasing basal cortisol secretion. Cortisol stimulates hepatic gluconeogenesis, inhibits peripheral glucose uptake in skeletal muscle, and promotes visceral adiposity. This neuroendocrine activation creates a state of persistent metabolic resistance, explaining why depressed patients maintain elevated HbA1c levels despite intensified pharmacotherapy.

6.2 Systemic Inflammation as a Molecular Bridge

High-sensitivity C-reactive protein (hs-CRP) emerged as an independent predictor in both glycemic and cardiovascular risk models (hs-CRP > 3.0 mg/L; adjusted OR = 3.12 for poor control; adjusted OR = 3.48 for high UKPDS risk). Chronic low-grade inflammation is an established driver of insulin resistance. Pro-inflammatory cytokines trigger serine phosphorylation of insulin receptor substrate-1 (IRS-1), blunting downstream intracellular insulin signaling cascades in liver and muscle tissue. [15-17]

Concurrently, systemic inflammation interacts synergistically with psychological stress. Inflammatory cytokines cross the blood-brain barrier and alter monoaminergic neurotransmission, activating indoleamine 2,3-dioxygenase (IDO), depleting serotonin, and escalating depressive symptoms. This creates a biological feedback loop where inflammation worsens mood, and mood-driven distress fuels systemic inflammatory cascades.

6.3 Vascular Stiffness and Integrated Cardiometabolic Risk

Physiological markers of arterial stiffness, specifically elevated Pulse Wave Velocity (> 10.0 m/s), strongly predicted high 10-year UKPDS cardiovascular risk (aOR = 4.14). Advanced glycation end-products (AGEs) cross-link structural collagen within arterial walls, increasing arterial stiffness, elevating pulse pressure, and augmenting myocardial wall tension. When combined with elevated hs-CRP, diabetes distress, and depression, arterial stiffness reflects cumulative vascular damage. ROC analysis confirmed that integrating psychometric profiling with traditional bio-physiological metrics significantly increased diagnostic predictive power (AUC = 0.864).

6.4 Clinical Implications

These findings highlight the necessity of transitioning from a purely glucocentric, physiological management model to an integrated, bio-psycho-metabolic care framework. Routine outpatient diabetes care should incorporate brief, validated psychometric screening tools—such as the DDS-17 or PHQ-9—alongside standard HbA1c and lipid monitoring. Identifying high diabetes distress or depressive symptoms enables early referral for cognitive-behavioral therapy (CBT), diabetes self-management education (DSME), or psychotropic intervention, breaking the cycle of psychological burnout and metabolic deterioration. [18-20]

6.5 LIMITATIONS

Several study limitations should be noted. First, while prospective, the single-center study design warrants validation across multi-center international cohorts. Second, serial psychiatric re-evaluations over multiple years were not

included in this baseline report. Third, specific psychological interventions were not randomized, preventing direct interventional causality assessment.

7. CONCLUSION

Suboptimal glycemic control (HbA1c $\geq$ 8.0%) and high 10-year cardiometabolic risk in adults with type 2 diabetes are independently predicted by an integrated cluster of bio-inflammatory markers (hs-CRP $>$ 3.0 mg/L), physiological metrics (Pulse Wave Velocity, waist circumference), and psychiatric factors (high diabetes distress, depressive symptoms). Integrating routine psychometric screening (DDS-17, PHQ-9) into outpatient metabolic clinics enhances risk stratification and enables targeted behavioral and biological interventions to optimize long-term diabetes outcomes.

8. RECOMMENDATIONS

1. Implement routine psychiatric and psychological screening using validated tools (DDS-17, PHQ-9) in outpatient diabetes clinics to identify diabetes distress and depression early.
2. Incorporate systemic inflammatory biomarkers (hs-CRP) alongside HbA1c and lipid testing for comprehensive cardiovascular risk stratification in T2DM patients.
3. Establish multi-disciplinary care teams comprising endocrinologists, primary care physicians, clinical psychologists, and diabetes educators to deliver joint biological and behavioral interventions.
4. Utilize non-invasive vascular stiffness assessments (Pulse Wave Velocity) in patients with long-standing T2DM to detect early subclinical arterial disease.
5. Conduct prospective randomized clinical trials evaluating whether combining psychological interventions (CBT, distress reduction) with anti-inflammatory or intensified metabolic therapies improves long-term cardiovascular event rates.

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