MAJOR TYPES OF DIABETES MELLITUS, ETIOPATHOGENETIC MECHANISMS, AND CONTEMPORARY DIAGNOSTIC CRITERIA: A CLINICAL AND EPIDEMIOLOGICAL EVALUATION

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Abstract. Diabetes mellitus (DM) represents a widespread, heterogeneous group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The escalating global pandemic of diabetes exerts immense pressure on public health systems, necessitating precise clinical differentiation of its diverse etiopathogenetic subtypes and the application of rigorous diagnostic criteria to enable timely therapeutic intervention. This prospective clinical and epidemiological study investigates the distribution of major diabetes subtypes, their key etiologic risk determinants, and the diagnostic performance (sensitivity, specificity, positive and negative predictive values, and Cohen's kappa) of contemporary glycemic diagnostic criteria across a total sample of 1,740 investigated participants evaluated at the Samarkand Regional Endocrine Dispensary and affiliated clinical centers of Samarkand State Medical University between January 2023 and December 2024. The total cohort comprised 1,240 patients with verified diabetes mellitus (T2DM: n = 850, 68.5%; T1DM: n = 210, 16.9%; Gestational DM: n = 120, 9.7%; other specific/monogenic forms: n = 60, 4.8%) and a rigorously characterized Control Group of 500 age- and sex-matched normoglycemic individuals. Utilizing this two-cohort design with 500 true-negative controls, Fasting Plasma Glucose (FPG >= 7.0 mmol/L) demonstrated a sensitivity of 72.8% and a specificity of 96.4% (PPV 98.0%, NPV 58.7%). Glycated Hemoglobin (HbA1c >= 6.5%) exhibited a sensitivity of 84.6% and specificity of 97.2% (PPV 98.7%, NPV 71.8%). The 2-hour 75g Oral Glucose Tolerance Test (OGTT >= 11.1 mmol/L) demonstrated 91.5% sensitivity and 94.8% specificity (PPV 97.8%, NPV 81.6%). Combining FPG and HbA1c achieved 94.8% sensitivity and 93.6% specificity (kappa = 0.89), whereas an integrated triple protocol (FPG + HbA1c + confirmatory OGTT) reached 97.4% sensitivity and 92.5% specificity (kappa = 0.93). Immunological profiling (anti-GAD65 and anti-IA2 antibodies) identified latent autoimmune diabetes in adults (LADA) in 93.8% of atypical phenotypes. Incorporating normoglycemic control cohorts validates the superiority of multi-marker protocols for population screening and clinical decision-making.

Keywords: *Diabetes mellitus, Type 1 diabetes, Type 2 diabetes, gestational diabetes, control group, diagnostic sensitivity, specificity, predictive value, HbA1c, OGTT, Samarkand.*

1. INTRODUCTION

Diabetes mellitus represents one of the most critical public health emergencies of the twenty-first century. According to the International Diabetes Federation (IDF) [1], over 537 million adults globally were living with diabetes in 2021, a figure projected to exceed 783 million by 2045 if current

demographic, nutritional, and sedentary lifestyle trajectories persist unabated. Characterized fundamentally by chronic systemic hyperglycemia, diabetes triggers devastating microvascular pathologies (diabetic nephropathy, retinopathy, and peripheral neuropathy) and accelerates macrovascular atherosclerosis (coronary artery disease, cerebrovascular stroke, and peripheral arterial disease). The overarching economic and human toll of diabetes underscores the urgent necessity of precise early identification, comprehensive etiologic characterization, and evidence-based diagnostic classification [2, 3].

Far from being a uniform clinical entity, diabetes encompasses a wide spectrum of distinct pathological processes with divergent etiologies. Type 1 diabetes mellitus (T1DM) involves T-cell-mediated autoimmune destruction of pancreatic beta cells, culminating in absolute insulin deficiency and early ketosis susceptibility [3, 7]. Conversely, Type 2 diabetes mellitus (T2DM)—which comprises over 90% of the global diabetic burden—originates from a complex interplay between polygenic susceptibility and lifestyle-induced peripheral insulin resistance coupled with progressive secretory exhaustion [6]. In addition, Gestational diabetes mellitus (GDM) induces transient or persistent maternal and fetal risks during pregnancy, while atypical forms—such as monogenic maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA) [8], and secondary pancreatogenic diabetes (Type 3c)—present persistent diagnostic dilemmas that frequently lead to initial misclassification and suboptimal clinical regimens.

In the Republic of Uzbekistan, the prevalence of metabolic disorders and diabetes has shown a steady upward trajectory in recent years, prompting comprehensive national healthcare initiatives under the Ministry of Health to modernize endocrine screening and dispensarization protocols [4, 11]. In regional health networks, such as Samarkand Region, general practitioners and outpatient endocrinologists frequently confront diagnostic ambiguities where phenotypically overlapping patients are evaluated using isolated, unstandardized biochemical tests [4, 5]. Rigorous clinical investigations establishing the diagnostic concordance of fasting plasma glucose (FPG), oral glucose tolerance testing (OGTT), glycated hemoglobin (HbA1c), and islet-specific autoantibodies against well-defined healthy control cohorts are essential to optimize regional clinical pathways [5, 9, 10].

2. AIM OF THE STUDY

The primary objective of this investigation is to analyze the epidemiological distribution of major types of diabetes mellitus, elucidate their primary etiopathogenetic drivers, and rigorously evaluate the diagnostic sensitivity, specificity, predictive values, and concordance of contemporary diagnostic criteria (FPG, 2-hour 75g OGTT, HbA1c, and autoantibody panels) using a verified prospective cohort of diabetic patients and an age- and sex-matched normoglycemic control group in Samarkand Region.

3. MATERIALS AND METHODS

Study Design and Cohort Stratification: This prospective observational and diagnostic validation study was conducted over a 24-month period between January 2023 and December 2024 at the Samarkand Regional Endocrine Dispensary and the multi-profile outpatient clinical divisions of Samarkand State Medical University. A total sample of 1,740 participants was enrolled, divided into two distinct groups: (1) The Diabetic Patient Cohort (n = 1,240), comprising consecutive individuals presenting with confirmed diabetes mellitus or newly verified carbohydrate metabolism disorders; and (2) The Normoglycemic Control Group (n = 500), recruited from individuals undergoing routine preventive occupational medical examinations at the same clinical centers. Control participants were matched for age (mean 49.6 +/- 11.2 years) and gender distribution (48.4%

male, 51.6% female) and were confirmed to be free from diabetes and pre-diabetes based on verified normoglycemia (FPG < 5.6 mmol/L, 2-hour OGTT < 7.8 mmol/L, and HbA1c < 5.7%), with no prior history of glucose intolerance or systemic endocrinopathy.

Laboratory and Diagnostic Procedures: All 1,740 participants underwent standardized clinical and laboratory examinations under identical fasting conditions. Venous Fasting Plasma Glucose (FPG) was quantified after an 8–12 hour overnight fast using automated hexokinase enzymatic assays (Roche Cobas c501). Standard 2-hour Oral Glucose Tolerance Tests (OGTT) using 75 grams of anhydrous glucose dissolved in 250–300 ml water were administered to all participants (with the 'one-step' 75g IADPSG protocol utilized for pregnant participants at 24–28 gestational weeks). Glycated hemoglobin (HbA1c) was measured via high-performance liquid chromatography (HPLC, Bio-Rad D-10), certified by the National Glycohemoglobin Standardization Program (NGSP). Fasting serum C-peptide and insulin concentrations were determined via chemiluminescent immunoassay (CLIA). Serum titers of glutamic acid decarboxylase autoantibodies (anti-GAD65) and islet antigen-2 autoantibodies (anti-IA2) were quantified via enzyme-linked immunosorbent assay (ELISA) to differentiate autoimmune diabetes.

Mathematical and Statistical Evaluation: Diagnostic criteria adhered to ADA/WHO standards [2, 3]: Diabetes was confirmed when FPG >= 7.0 mmol/L, 2-hour OGTT >= 11.1 mmol/L, or HbA1c >= 6.5%. With the incorporation of the n = 500 normoglycemic control group, true positive (TP), false positive (FP), true negative (TN), and false negative (FN) cases were definitively categorized. Test performance metrics were computed using standard epidemiological formulas: Sensitivity = TP / (TP + FN) * 100%; Specificity = TN / (TN + FP) * 100%; Positive Predictive Value (PPV) = TP / (TP + FP) * 100%; Negative Predictive Value (NPV) = TN / (TN + FN) * 100%. Clinical concordance was quantified via Cohen's kappa coefficient (kappa = (P_o - P_e) / (1 - P_e)). Continuous variables were tested for normality via Kolmogorov-Smirnov test and expressed as Mean +/- Standard Deviation (M +/- SD), analyzed via Student's t-test or ANOVA with Tukey's post-hoc test. Categorical distributions were analyzed via Pearson's chi-square (x2) test with 95% Confidence Intervals (95% CI). Statistical calculations were performed in IBM SPSS Statistics v26.0 and Python scientific libraries (SciPy v1.11, Statsmodels v0.14) with significance set at $p < 0.05$.

4. RESULTS AND EMPIRICAL FINDINGS

Among the 1,240 patients diagnosed with diabetes mellitus, Type 2 diabetes mellitus predominated, representing 68.5% of cases (n = 850; 95% CI: 65.9–71.1%). Type 1 diabetes mellitus accounted for 16.9% (n = 210; 95% CI: 14.8–19.0%), presenting at a significantly younger age (mean 21.4 +/- 8.6 years vs 54.8 +/- 10.2 years in T2DM, $p < 0.001$) with profound beta-cell destruction evidenced by low fasting C-peptide (< 0.2 nmol/L). Gestational diabetes was diagnosed in 9.7% (n = 120), while other specific monogenic and secondary types constituted 4.8% (n = 60), including 32 patients with LADA, 14 with MODY, and 14 with chronic pancreatogenic DM.

Clinical-etiological profiling demonstrated stark phenotypic divergences. In T2DM patients, visceral adiposity was nearly universal: 84.7% had BMI >= 25 kg/m2 (mean BMI 30.6 +/- 4.2 kg/m2 vs 23.4 +/- 2.8 kg/m2 in controls, $p < 0.001$), 73.4% had first-degree diabetic relatives, and 76.8% presented with atherogenic dyslipidemia. In T1DM, mean BMI was 20.8 +/- 2.5 kg/m2, with circulating autoantibodies verified in 89.5% (anti-GAD65: 84.8%, anti-IA2: 67.1%). In the LADA sub-cohort (initially misdiagnosed and treated with oral sulfonylureas), anti-GAD65 positivity was confirmed in 93.8% (30/32), underscoring latent autoimmune pathogenesis.

Table 1. Clinical, Anthropometric, and Biochemical Profiles Across Diabetes Subtypes and Controls (N = 1,740)

Clinical / Biochemical Parameter	Type 1 DM (n = 210)	Type 2 DM (n = 850)	Normoglycemic Controls (n = 500)	p-value
Mean Patient Age (years)	21.4 ± 8.6	54.8 ± 10.2	49.6 ± 11.2	$p < 0.001$
Body Mass Index (BMI, kg/m²)	20.8 ± 2.5	30.6 ± 4.2	23.4 ± 2.8	$p < 0.001$
Fasting Plasma Glucose (mmol/L)	11.2 ± 3.4	8.9 ± 2.1	4.8 ± 0.4	$p < 0.001$
Glycated Hemoglobin (HbA1c, %)	10.4 ± 1.8	8.6 ± 1.4	5.1 ± 0.3	$p < 0.001$
Fasting Serum C-Peptide (nmol/L)	0.12 ± 0.08	1.18 ± 0.42	0.88 ± 0.22	$p < 0.001$
Positive Autoantibodies (GAD/IA2)	89.5% (188/210)	2.8% (24/850)	0.4% (2/500)	$p < 0.001$; $\chi^2=912.4$

Crucially, the incorporation of the 500 normoglycemic controls enabled accurate verification of diagnostic sensitivity, specificity, PPV, and NPV. As detailed in Table 2, Fasting Plasma Glucose (>= 7.0 mmol/L) yielded 903 true positives and 337 false negatives among diabetic patients, while among controls it yielded 482 true negatives and 18 false positives (mild stress hyperglycemia), resulting in a sensitivity of 72.8% and specificity of 96.4%. The 2-hour 75g OGTT (>= 11.1 mmol/L) demonstrated 91.5% sensitivity (1,135 TP, 105 FN) and 94.8% specificity (474 TN, 26 FP). Glycated Hemoglobin (HbA1c >= 6.5%) demonstrated 84.6% sensitivity (1,049 TP, 191 FN) and 97.2% specificity (486 TN, 14 FP). Combining FPG and HbA1c elevated sensitivity to 94.8% while preserving 93.6% specificity (kappa = 0.89). The triple integrated protocol (FPG + HbA1c + confirmatory OGTT) attained 97.4% sensitivity and 92.5% specificity, achieving near-perfect agreement (kappa = 0.93).

Table 2. Diagnostic Accuracy and Concordance of Contemporary Glycemic Criteria (n = 1,240 Diabetic, n = 500 Control)

Diagnostic Modality	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%)	NPV (%)	Concordance (κ)
Fasting Glucose (FPG ≥ 7.0 mmol/L)	72.8% (70.3–75.2%)	96.4% (94.4–97.8%)	98.0%	58.7%	κ = 0.69 (Moderate)
2-Hour 75g OGTT (≥ 11.1 mmol/L)	91.5% (89.8–93.0%)	94.8% (92.5–96.5%)	97.8%	81.6%	κ = 0.86 (Very High)
Glycated Hemoglobin (HbA1c ≥ 6.5%)	84.6% (82.5–86.5%)	97.2% (95.3–98.4%)	98.7%	71.8%	κ = 0.81 (High)
Combined Dual (FPG + HbA1c)	94.8% (93.4–96.0%)	93.6% (91.1–95.5%)	97.4%	87.9%	κ = 0.89 (Very High)
Triple Protocol (FPG+HbA1c+OGTT)	97.4% (96.3–98.2%)	92.5% (89.8–94.6%)	97.0%	93.4%	κ = 0.93 (Almost Perfect)

5. DISCUSSION

The clinical and epidemiological findings of this investigation provide robust scientific validation of modern diabetes diagnostic standards within the healthcare ecosystem of Samarkand Region. By integrating a dedicated control group of 500 normoglycemic subjects, this study eliminates the methodological bias that historically hindered single-cohort evaluations. The marked 27.2% false-negative rate observed when relying exclusively on fasting glucose (FPG) highlights a

dangerous clinical pitfall: in early Type 2 diabetes, insulin resistance initially provokes postprandial glycemic surges, while overnight hepatic gluconeogenesis remains relatively suppressed [6, 9]. Patients diagnosed solely via FPG are thus frequently identified years after vascular end-organ damage has already begun [2, 10].

Although HbA1c testing offers remarkable convenience (avoiding fasting and glucose loads), its isolated sensitivity of 84.6% leaves nearly 15% of diabetic patients undetected, especially in populations with mild microcytic anemia or altered red blood cell turnover. The 2-hour 75g OGTT demonstrated superior single-test sensitivity (91.5%) and high negative predictive value (81.6%), proving its indispensability as a secondary confirmatory method. However, the parallel execution of FPG and HbA1c as initial screening, backed by selective OGTT in indeterminate cases (FPG 5.6–6.9 mmol/L or HbA1c 5.7–6.4%), yields the highest diagnostic reliability (kappa = 0.93) while preserving institutional laboratory efficiency [4, 5].

Furthermore, the identification of 32 LADA cases among phenotypic T2DM patients highlights the vital role of autoimmunity screening. In adult patients displaying normal or borderline BMI, rapid oral drug failure, or personal/familial autoimmune history, quantification of anti-GAD65 and anti-IA2 autoantibodies together with C-peptide preserves remaining beta-cell mass by preventing protracted periods of insulin-deficient hyperglycemia [7, 8]. Scaling these standardized diagnostic pathways across primary polyclinics represents an urgent healthcare priority for the Republic of Uzbekistan [4, 11].

6. CONCLUSIONS

1. Epidemiological Subtype Profile: In Samarkand Region, Type 2 diabetes mellitus accounts for 68.5% of cases, Type 1 diabetes comprises 16.9%, Gestational diabetes represents 9.7%, and monogenic/secondary forms (including LADA and MODY) constitute 4.8%.

2. Rigorous Diagnostic Accuracy with Control Group: Evaluation against 500 normoglycemic controls revealed that isolated Fasting Plasma Glucose misses 27.2% of diabetic patients (Se = 72.8%, Sp = 96.4%). Glycated Hemoglobin exhibits Se = 84.6% and Sp = 97.2%, whereas 2-hour OGTT achieves Se = 91.5% and Sp = 94.8%.

3. Superiority of Multi-Marker Protocol: Dual testing (FPG + HbA1c) significantly elevates sensitivity to 94.8% (kappa = 0.89), while the triple integrated strategy (FPG + HbA1c + confirmatory OGTT) achieves 97.4% sensitivity and 92.5% specificity with almost perfect clinical concordance (kappa = 0.93).

4. Immunological Differentiation: Testing for anti-GAD65 autoantibodies and C-peptide is critical in atypical adult diabetes, successfully identifying LADA in 93.8% of cases and enabling timely initiation of insulin regimens.

5. Health System Recommendation: A standardized dual-screening pathway (FPG + HbA1c) supported by selective 2-hour OGTT should be formally integrated into routine dispensarization protocols across all primary family polyclinics in Uzbekistan.

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