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Abstract

Background: Diabetes mellitus is a progressive metabolic condition marked by hyperglycemia due to irregularities in insulin production or activity, leading to poor carbohydrate, protein, and fat metabolism. Dysfunctional glucose transporter-4 (GLUT4) activity, characterized by insufficient expression or poor redistribution to the cell membrane, is a critical element in the pathogenesis of type 2 diabetes mellitus (T2DM). This defect limits cellular glucose uptake, leading to energy deficits and elevated blood glucose levels.

Objective: What is the clinical diagnostic potential of serum GLUT4 levels in newly identified type 2 diabetic people, and how do these levels correspond with established metabolic parameters?

Materials and methodology: A case-control study was undertaken with 140 Iraqi participants, separated into two groups of 70: a control group and a newly diagnosed T2DM group. Serum GLUT4 and insulin levels were estimated using ELISA assays. Samples were collected from Imamein Kadhimein Medical City Hospital in Baghdad, Iraq, between August 2024 to January 2025.

Results: The T2DM group had a significantly higher proportion of elderly participants. Most parameters measured were significantly elevated except LDL (non-significant increase) and HDL (non-significant decrease). In the T2DM group, GLUT4 levels positively correlated with age, FBS, and HbA1c but demonstrated a significant inverse correlation with insulin.

Conclusion: Early and accurate diabetes diagnosis is essential. GLUT4's high sensitivity suggests it could enhance diagnostic precision. This study highlights the potential of GLUT4 as a promising biomarker for T2DM diagnosis, warranting further investigation to refine clinical diagnostic tools.

Keywords: Glucose transporter-4, Insulin, Type 2 diabetes, Hyperglycemia

1. Introduction

Diabetes is a persistent metabolic condition that poses a significant public health concern. It results either from pancreatic damage reducing the generation of insulin or the body's failure to use insulin efficiently (Paholpak, 2023). Affecting around 10% of the global population (537 million people) is marked by disruptions in carbohydrate, protein, and lipid metabolism due to impaired insulin secretion or action (Aphrodite *et al.*, 2025). Between 2000 and 2019, it contributed to a 3% rise in global mortality, with rates reaching 13% in lower-middle-income countries. Complications can involve the nerves, heart, kidneys, eyes, and brain (Buse*et al.*, 2020). T2DM the most common form, arises mainly from impaired insulin production via pancreatic β-cells with insulin resistance where tissues fail to respond adequately to insulin leading to hyperglycemia (Eyre*et al.*, 2004; Hasan & Ali, 2024). These disruptions in insulin

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regulation disturb glucose homeostasis and contribute to disease progression.

Glucose is a primary energy source but requires facilitation by glucose transporters (GLUTs) to enter cells due to its polarity and size (Galicia-Garcia *et al.*, 2020; Grunbaum, 2023; Navale & Paranjape, 2016). In skeletal muscle, insulin-stimulated glucose uptake is largely mediated by GLUT4, a key transporter protein with 12 transmembrane domains (Bryant *et al.*, 2002; Dugani & Klip, 2005). GLUT4 translocate to the plasma membrane in response to insulin enabling glucose absorption. This process is crucial for maintaining glucose balance (Stuart *et al.*, 2000). In established T2DM reduced GLUT4 translocation to the membranes is a hallmark of insulin resistance (Karnieli & Armoni, 2008), often exacerbated by pro-inflammatory cytokines like IL-6 and TNF-α, which suppress GLUT4 expression (Koshy *et al.*, 2010).

GLUT4 and insulin are central to glucose metabolism and serve as potential clinical indicators for T2DM onset. Changes in GLUT4 expression may reflect early insulin resistance, providing insight into disease progression and therapy effectiveness (Leto & Saltiel, 2012; Bernat-Karpińska *et al.*, 2010; Alam *et al.*, 2016). While current diagnostic tools inadequately assess cellular glucose transport, emerging proteomic technologies now allow precise measurement of GLUT4 dynamics. However, their clinical integration remains limited. The interaction between insulin levels, GLUT4 expression, and early metabolic dysfunction in newly diagnosed patients is not yet fully understood. To bridge this gap, the study examines the diagnostic and prognostic significance of combined insulin and GLUT4 profiling in treatment-naïve diabetic patients with type 2 diabetes (T2DM). This approach has the potential to establish a personalized treatment model based on molecular characterization.

Understanding individual variations in insulin and GLUT4 activity may allow clinicians to tailor therapeutic interventions, improving patient response to medication and lifestyle modifications by revolutionize how diabetes is managed by shifting the focus from standardized treatment regimens to personalized strategies based on patients' unique molecular profiles. If successful, such profiling might optimize therapeutic efficacy, minimize adverse effects, and improve overall disease outcomes.

Materials and methodology: A study with case-controls was undertaken with 140 Iraqi subjects, was organized into two distinct groups: the control group and a newly diagnosed DM-2 patients group. Each group consisted of 70 participants, and all samples were collected from Imamein Kadhimein Medical City, in Baghdad, Iraq, during the period of (August 2024 to January 2025). Important data was collected from the hospital, which included (sex, age, FBS (Fasting Blood Sugar), RBS (Random blood sugar), HbA1C (Glycated Hemoglobin A1C test), lipid profile, and the patient's period of Diabetes). After an 8-12 hour fast, each participant provided 5 mL of blood. Serum samples were then utilized to test GLUT4 and insulin levels using the Enzyme-Linked Immune Sorbent Assay (ELISA).

Inclusion criteria: the study considered patients with newly diagnosed DM-2 had levels of (HbA1c) higher than 6.5% and (FBS) levels higher than 125mg/dl. Appropriate subjects in the control group were defined as having HbA1c levels <5.7%.

Exclusion criteria: Patients with hematological disease, chronic inflammatory disease, pregnancy, tumors, cardiovascular disease, renal disease, and patients who take glucocorticoid therapy were excluded.

Institutional ethical approval: This project received ethical approval from the Iraq Ministry of Health and the Ethics Committee of Ibn Sina University of Medical and Pharmaceutical Sciences accepted the research plan. (No: ISU.3.2.25). Approval on January 27, 2025.

1.1. Insulin and GLUT4 quantification using the enzyme-linked immune sorbent assessment

The quantitative sandwich Enzyme-Linked Immune Sorbent Assay (ELISA) employs monoclonal antibodies targeting specific antigenic epitopes of insulin and GLUT4 in biological specimens. Utilizing a commercial ELISA kit (MyBioSource Inc., USA, catalog numbers MBS263809 and MBS453896, respectively), microtiter wells were pre-coated with capture antibodies, enabling precise molecular detection. Optical density measurements at 450 nm correlate with analyte concentration, with standardized calibration curves facilitating quantitative analysis. Established reference ranges include fasting insulin levels <245 mIU/mL and GLUT4 concentration at 2 $\pm$ 0.1 pg/mL in human biological matrices, providing critical metabolic and cellular transport protein assessment.

1.2. Metabolic biomarker quantification protocols

Fasting Blood Glucose (FBG): This test blood glucose levels following an at least 8-hour fast. It is often the first test performed to screen for diabetes. 1 ml of reagent, with 10 microliters of serum taken, put for 5 minutes of water bath at 37C°, and then measurement at a wavelength of 500 nanometers. Normoglycemic

Table 1. Demographic characteristics among research groups.

Age groups	Control group N = 70	Percentage%	Newly-diagnosed group N = 70	Percentage%
30–39	18	25.7%	16	22.9 %
40–49	14	20.0%	15	21.4%
50–59	17	24.3%	18	25.7%
60–69	16	22.9%	15	21.4%
>70	5	7.1%	6	8.6%
Total N	70	100%	70	100%
P_ value		0.982^{NS}		
Sex	Control group N = 70		Newly-diagnosed group N = 70	
Male	33 (47.1%)		30 (42.9%)	
Female	37 (52.9%)		40 (57.1%)	
p-value		0.143^{NS}		

Chi-square test, P ≤ 0.05 significant effect, **significant at 0.001 level, NS: Non-significant.

reference ranges correspond to 70-99 mg/dL (3.9-5.5 mmol/L), as standardized by contemporary diabetic diagnostic criteria (Heinrich, 1993).

Triglyceride (TG): Triglyceride determination involves enzymatic hydrolysis to glycerol and free fatty acids, followed by sequential phosphorylation and oxidation reactions as detailed by Passari et al. (2020). 1 ml of reagent, with 10 microliters of serum taken, put for 5 minutes of water bath at 37C°, and then measurement at a wavelength of 500 nanometers (Mochón & Leyva, 1984).

HDL-c stands for high-density lipoprotein cholesterol: employs selective precipitation of non-HDL lipoproteins (LDL, VLDL, chylomicrons) using phosphotungstic acid and magnesium chloride at pH 6.2. Following centrifugation, supernatant HDL-cholesterol is quantified using a standardized cholesterol assay methodology (Warnick *et al.*, 2001).

LDL-c stands for low-density lipoprotein cholesterol: is computed using the Friedewald equation, which is as follows: LDL-c = TC - HDL-c - TG/5. This computation is valid for triglyceride the concentrations as high as 5.32 mmol/L (400 mg/dL), with reference values ranging from 100 to 129 mg/dL (Rajashekar & Baek, 2014).

VLDL-c, or very low-density lipoprotein cholesterol: is calculated as one-fifth of serum triglyceride concentration, with typical values ranging from 2-30 mg/dL (0.1–1.7 mmol/L) (McPherson & Pincus, 2011).

Statistical Investigation: The analysis was carried out with the version 26 of SPSS (Chicago).The Shapiro-Wilk test found that the data had a normal distribution. The results were given as mean ± SD using Independent T-Test. The Chi-squared test for categorical data was described in terms of numbers and percentages. We utilized an independent T-test for comparing the means of two independent groups. The person correlation test detects a substantial association between variables in Studying groups. P-values < 0.05 were considered statistically significant.

2. Results

The findings of this investigation showed the newly diagnosed group showed higher frequency in old age. Investigating the effect of sex on the sensitivity to DM-2 formation, the results showed that females were higher than (40) compared with males (30), with no statistically significant p-value (0.143). The idea of this comparison is to suggest that although there are some age group preferences for each sex, these variations are non-significant statistically, which makes no difference between both sex regarding current study sensitivity of T2DM formation, thus confirming the validity of the study, as shown in [Table 1].

In the control group, FBS, BMI (Body Mass Index), Cholesterol, Triglyceride, and VLDL recorded higher mean levels in males than females with a highly significant effect (p-value = 0.001). Meanwhile, LDL and HDL recorded higher mean levels in females than males with a highly significant effect (p-value = 0.001). GLUT4 showed approximately similar mean levels in both sexes among the control group with a highly significant effect (p-value = 0.001). On the other hand, among the newly diagnosed group, all parameters recorded higher mean levels in females than males except LDL, which recorded lower levels in females than males with no significant effect (p-value 0.2) as shown in [Table 2].

The results of this research demonstrated that the levels of all parameters increased significantly in a newly diagnosed group against a control group, with the exception of LDL, which exhibited a non-significant increase in a newly diagnosed group against a control group (p-value 0.07). In contrast, HDL levels appear to be non-significantly higher in

Table 2. Comparison of research parameters among the sex in both groups (control and newly diagnosed).

	Control Mean ± SD		Newly- diagnosed Mean ± SD		
parameters	Female	Male	Female	Male	P. value
FBS (mg/dl)	85.8 ± 1.5	91.8 ± 1.5	122.8 ± 1.4	108.8 ± 1.7	0.001**
BMI (kg/m^2)	24.3 ± 0.6	27.5 ± 1.5	30.8 ± 1.2	29.5 ± 0.8	0.001**
HbA1c (%)	5.3 ± 0.05	4.8 ± 0.2	7.4 ± 0.1	7.2 ± 0.2	0.001**
Insulin (μIU/ml)	12.3 ± 2.8	12.2 ± 2.4	22.7 ± 3.3	21.8 ± 3.5	0.001**
Cholesterol (mg/dl)	165.52 ± 7.5	172.4 ± 6.5	188.6 ± 6.8	185.7 ± 5.53	0.001**
Triglyceride (mg/dl)	132.2 ± 8.5	138.3.0	208.3 ± 13.5	206.87 ± 12	0.001**
LDL-c (mg/dl)	95.8 ± 5.45	94.4 ± 5.45	108.2 ± 70	110.7 ± 7.5	0.2^{NS}
HDL-c (mg/dl)	53.65 ± 1.95	42.0 ± 1.4	60.4 ± 10.1	41.6 ± 1.3	0.001**
VLDL-c (mg/dl)	26.0 ± 3.2	36.3 ± 2.40	45.4 ± 4.0	41.3 ± 3.2	0.001**
GLUT4 (pg/ml)	2.0 ± 0.16	2.1 ± 0.15	10.4 ± 0.4	9.2 ± 0.3	0.001**

Independent T-Test: p ≤ 0.01 significant, **significant at 0.001 level, NS; non-significant. (**FBS;** Fasting Blood Sugar, **BMI;** Body Mass Index, **HbA1c;** Glycated Hemoglobin A1C test, **LDL-c;** Low-Density Lipoprotein Cholesterol, **HDL-c;** High-Density Lipoprotein Cholesterol, **VLDL-c;** Very Low-Density Lipoprotein Cholesterol, **GLUT4;** Glucose Transporter-4).

Table 3. Compartment the examined parameters among all groups in the study.

Variable	Control Group	Newly-diagnosed Group	P -value
FBS (mg/dl)	88.7 ± 0.8	116.9 ± 2.4	0.003**
BMI (kg/m^2)	24.9 ± 1.0	30.0 ± 1.2	0.01*
HbA1c (%)	4.9 ± 0.1	7.5 ± 0.1	0.03*
Insulin (μIU/ml)	13.5 ± 2.0	18.7 ± 2.4	0.04*
Cholesterol (mg/dl)	170.4 ± 4.9	187.7 ± 5.6	0.04*
Triglyceride (mg/dl)	132.3 ± 6.2	216.3 ± 10.1	0.006*
LDL-c (mg/dl)	95.1 ± 3.8	112.2 ± 6.5	0.07^{NS}
HDL-c (mg/dl)	47.4 ± 1.3	40.6 ± 1.5	0.08^{NS}
VLDL-c (mg/dl)	30.0 ± 2.1	41.6 ± 2.9	0.03*
GLUT4 (pg/ml)	2.0 ± 0.1	9.6 ± 0.27	0.01*

Independent T-test: P < 0.05 significant effect, **significant at 0.001 level, *significant at 0.01 level, P ≥ 0.05 non-significant effect, NS non-significant.

the control group than in the newly diagnosed (p-value 0.08), [Table 3].

Pearson correlation results among the control group revealed that GLUT4 has a non-significant negative correlation with age, BMI, insulin, and HDL. At the same time, GLUT4 correlated positively with FBS, HbA1c, cholesterol, triglyceride, LDL VLDL, but non-significant. On the other hand, the Pearson correlation among the newly diagnosed group revealed that GLUT4 has a significant positive correlation with age, FBS, and HbA1c and a significant inversed correlation with insulin. [Table 4] shows a positive non-significant association with BMI, cholesterol, triglycerides, LDL, and VLDL, as well as a negative non-significant correlation with HDL.

3. Discutions

This study reveals greater levels of GLUT4 in newly diagnosed T2DM patients than in controls. Such findings may appear counterintuitive give the understanding of GLUT4 dysfunction in diabetes, it suggests a potentially important compensatory mechanisms in early disease stages. Several studies have demonstrated that the initial phases of the insulin resistance the body may attempt to compensate for reduced glucose uptake by increasing GLUT4 production, particularly in tissues that remain insulin-sensitive (Alam *et al.*, 2016). This upregulation likely represents a homeostatic response aimed at maintaining glucose utilization despite emerging insulin resistance. GLUT4 regulation is disrupted in diabetes particularly type 2 diabetes, this causes poor translocation of GLUT4 to the cell membrane (the function aspect), while the total GLUT4 protein expression may initially elevated (the quantities aspect) as response, and reducing glucose absorption by cells results in higher blood glucose concentrations. This discrepancy between GLUT4 function and quantity helps explain our seemingly contradictory findings (Navale & Paranjape, 2016). Furthermore, GLUT4 expression variety according to tissues specific regulation may play a role, as reflect the expression pattern different from skeletal muscle, adipose tissue, and different insulin responsive tissues. Our measurement of serum GLUT4 serum level may reflect these variation response to early insulin resistance among different tissues, capturing a systemic compensatory

Table 4. Pearson correlation between GLUT4 and other parameters.

	Control groups GLUT4		Newly-diagnosed group GLUT4	
Variables	R	p	r	p
Age	–0.03^{NS}	0.87	0.40**	0.001
FBS (mg/dl)	0.10^{NS}	0.45	0.36**	0.003
BMI (kg/m^2)	–0.04^{NS}	0.70	0.10^{NS}	0.38
HbA1c (%)	0.08^{NS}	0.50	0.40**	0.002
Insulin (μIU/ml)	–0.17^{NS}	0.23	–0.30*	0.03
Cholesterol (mg/dl)	0.04^{NS}	0.85	0.05^{NS}	0.65
Triglyceride (mg/dl)	0.10^{NS}	0.36	0.20^{NS}	0.08
LDL-c (mg/dl)	0.20^{NS}	0.10	0.07^{NS}	0.65
HDL-c (mg/dl)	–0.20^{NS}	0.10	–0.20^{NS}	0.18
VLDL-c (mg/dl)	0.06^{NS}	0.71	0.07^{NS}	0.54
GLUT4 (pg/ml)	1	1	1	1

Significant differences are indicated by P ≤ 0.05, **at the 0.001 level, *at the 0.01 level, and P ≥0.05 as insignificant.

mechanisms that eventually fails as the disease progresses to established T2DM.

Regarding to the observed association between age and T2DM, the study indicates that T2DM can occur at a younger ages, its prevalence increases with advancing age. This agrees with the results of the earlier epidemiological study. Kautzky-Willer *et al.* (2016), and emphasizes the need for early screening and preventative measures across all age groups, with particular attention to elderly populations.

The sex disparity suggests a lower occurrence of T2DM in men compared to women in our samples reflects the complex interaction between environmental and biological factors, method of measurement, how T2DM is diagnosed and defined across different regions could influence reported prevalence rates, screening protocols, diagnostic criteria, and data collection methods can lead to inconsistencies (Gomes *et al.*, 2022), genetics, daily activity, and diet, which are considered important factors that can affect T2DM development. Socioeconomic position and socioeconomic considerations include access to healthcare and information about healthy lifestyles., and nutritional resources, can significantly impact the risk of developing T2DM (Sami *et al.*, 2017).

Sex hormones significantly influence glucose metabolism, such findings agree with Mauvais-Jarvis (2018), with protective effects of estrogen generally agonist insulin resistance while testosterones effects are more variable. The highlights the complex interplay of age, gender, and a range of environmental and socioeconomic factors in the development of T2DM. It underscores the importance of considering these factors when interpreting prevalence data and developing targeted prevention and treatment strategies.

The correlation analyses explore significant correlation between GLUT4 and various metabolic parameters among the newly diagnosed T2DM group. The positive association between GLUT4, fasting blood sugar (FBS), and HbA1c likely reveal the compensatory regulation of GLUT4 in response to increase glucose levels. Meanwhile insulin is a negative significant correlation suggested a complex relationship between these two critical factors on glucose homeostasis. This is a typical finding may represent the body's early adaptive response to insulin resistance, where (hyperinsulinemia) developed concurrently with elevated GLUT4 expression as parallel compensatory mechanisms (Olson, 2012; Gurley *et al.*, 2016).

The positive correlation between GLUT4, VLDL, and triglycerides align with the previous study (Wang *et al.*, 2020) which illustrated this to when glucose used in adipose tissue and muscle is impaired, metabolic adaptations occur that shift energy metabolism toward lipid fuels. At the same time metabolic reprogrammed involved the liver seems to increase glucose uptake, which is incorporated into fatty acids and triglyceride production, potentially explaining the correlation observed in our study.

This study faced several limitations that should be acknowledge. First, including difficulties in obtaining comprehensive medical information for the full patient cohort. Our sample was restricted to 140 participants from a single region in Baghdad, and one hospital, which may limit the results to broader populations. Second, we evaluated the total serum level of GLUT4 protein rather than tissue specific expression, or translocation activity which would reflect more detailed insight into the functional status of GLUT4 among different tissues.

To strengthen and validate these findings, future research should address these limitations through larger, more diverse cohort across different regions. Tissue specific GLUT4 analyses, and longitudinal study designs that generalize can capture the

evaluation of GLUT4 dynamics throughout disease development and progression. Additionally, investigating the effects of various interventions such as lifestyle and pharmacological on GLUT4 expression and function could provide valuable insights for personalized therapeutic approaches.

4. Conclusion

This study demonstrates that metabolic parameters such as FBS, LDL, VLDL, HbA1c, cholesterol, and triglycerides are elevated in newly diagnosed T2DM patients and may serve as useful predictive markers. Most notably, we observed a significant elevation in GLUT4 level in patients group, suggesting its strong potential role as an early compensatory mechanisms and promising biomarker for early disease detection. The significant correlations between GLUT4 and different metabolic parameters (age, insulin, glucose, HbA1c) highlight the complex interplay between insulin action, glucose transport, and metabolic dysfunction in the disease pathogenesis. These funding contribute to our understanding of the early molecular changes in T2DM and suggest that GLUT4 measurement might enhance the precision of early diagnosis.

Despite limitations in sample size and geographic diversity, these findings provide important insights and support the need for further large-scale research to explain the involvement of GLUT4 in the emergence and evolution of T2DM. Such results could potentially lead to improved diagnostic tools and more targeted therapeutic approaches based on individual GLUT4 profile, ultimately advancing personalized medicine in diabetes care.

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Ethics approval and agreement for attendance

The Iraq Ministry of Health and Ibn Sina University of Medical and Pharmaceutical Sciences both provided ethical approval for this investigation. (No. ISU.3.2.25) was accepted on January 27, 2025.

Conflicts of interest

The writers claim that their interests do not conflict with one another.

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