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Evaluation of Sortilin-1 for Discrimination between of Prediabetes and T2DM State

Ali K. Hasan[1*], Mohammed I. Hamzah[2] and Jelal A. Ali[3]
[1,2]Department of Chemistry and Biochemistry, College of Medicine, University of AL-Nahrain, Baghdad, Iraq
[3]Department of Internal Medicine, College of Medicine, University of AL-Nahrain, Baghdad, Iraq

*Corresponding author: Ali K. Hasan (e-mail: ali.k.hasan.med24@ced.nahrainuniv.edu.iq).

Abstract: **Background**: **T2DM** (type two diabetes mellitus) is a metabolic disorder marked by reduced insulin activity and/or secretion. **Objectives:** This study aims to measure serum Sortilin-1 levels in T2DM patients, prediabetes and healthy control groups .and to evaluation their ability discrimination between of Prediabetes and T2DM individuals. M**ethods:** A cross sectional study was consisting of 120 individuals devided into 60 healthy individuals as control group with age range (30-60 years), (31 males,29 females), and 30 prediabetic individuals with age range (30- 60 years) (15 males,15 females), and 30 individuals with T2DM (15 males,15 females), all individuals were diagnosed according to the American Diabetes Association(ADA)2024 criteria. **Results:** The Median (IQR) age in years across groups was 47.15(10.98), and Median (IQR) age within each group (49.5 (23.25),45.5 (21.50),45.0 (21.0)) for the control, prediabetes, and T2DM, respectively. Furthermore, at p>0.05, there was no significant difference in The Median (IQR) age across groups, the data analysis revealed to very high significant difference in the the Median (IQR) study groups (P<0.001) for all parameters in the study. **Conclusion** the findings clearly showed that Sortilin-1 has a significant ability to discrimination between of prediabetes and T2DM individuals.

Key Words: Prediabetes,T2DM, Sortilin-1

INTRODUCTION

T2DM is a metabolic disorder marked by reduced insulin activity and/or secretion. As the disease gets worse, pathological changes like nephropathy, retinopathy, and heart problems show up in the body [1]. Prediabetes is a crucial transitional stage that comes before T2DM, a chronic metabolic disease. Predicting the precise course and progression from prediabetes to overt T2DM is still a major clinical issue, even with the availability of conventional diagnostic indicators like fasting blood glucose (FBG) and HbA1c. Rather than the early molecular changes causing the pathophysiology, these conventional markers frequently reflect dysglycemia that already exists. Furthermore, populations with hemoglobinopathies, like thalassemia, or disorders requiring altered red blood cell turnover, like hemolytic anemias, have significantly reduced clinical utility for HbA1c. HbA1c is unhelpful as a general predictive tool in these patients because it does not accurately reflect long-term glycemic state. Sortilin-1 is a type I membrane glycoprotein that has a large luminal domain with cysteine-rich motifs, a single transmembrane region, and a short cytoplasmic tail that helps it connect with adaptor proteins that help move things around inside cells [2]. Sortilin-1 is involved in the metabolism of glucose and lipids, as shown by recent studies. These results reveal a strong link between this receptor and the pathophysiology of T2DM mellitus, Sortilin-1 may help control how much glucose is taken in by affecting the movement of GLUT4-containing vesicles to the plasma membrane in muscle cells and adipocytes. If the transcript of Sortilin-1 is lowered or changed, it could make it harder for GLUT4 to move, which would mean less glucose uptake and insulin resistance [3]. Higher amounts of Sortilin-1 in the blood have been seen in people with T2DM, which is linked to poor glucose control, higher HbA1c levels, and higher lipid levels, Sortilin-1 levels are also linked to insulin resistance markers and atherogenic lipid profiles, which suggests that it could be used as a biomarker for metabolic disorders [4].

METHOD

Subjects and Materials

This A cross sectional study was conducted between November 2025 and March 2026. Participants were recruited from at Al-Imamain Alkadhimain Medical City, where a comprehensive clinical history was obtained from each participant using a designated questionnaire following ethical approval. The practical and analytical procedures were carried out at the biochemical laboratories of Al-Imamain Alkadhimain Medical City and the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University. The study included a total of 120 subjects, aged 30 to 60 years, who were categorized into three age- and sex-matched groups P-value ≥0.05. Group A (Control) consisted of 60 healthy individuals Controls (31 males, 29 females) were randomly selected from among the patient's companions and attendees without strict matching, but we adjusted for sex, age, P-value ≥0.05. with normal fasting serum glucose (FSG: 65-99 mg/dL), 2-hour post-OGTT (<140 mg/dL), and HbA1c (4.0-5.6%). Group B (Prediabetes) included 30 individuals (15 males, 15 females) characterized by FSG levels between 100-125 mg/dL, 2-hour post-OGTT of 140-199 mg/dL, or HbA1c of 5.7-6.4%. Group C comprised 30 patients (15 males, 15 females), presenting with FSG > 125 mg/dL or HbA1c ≥ 6.5%. Individuals were strictly excluded if they had a history of type 1, gestational, severe hepatic, renal, or cardiac diseases; acute infections; malignancies; or if they were pregnant or lactating and individuals with current use of antidiabetic medications. For biochemical analysis, 5 mL of venous blood was drawn from each participant following an 8-hour fast. The sample was divided into two portions: 2 mL was collected in an EDTA tube specifically for glycated hemoglobin (HbA1c) measurement. The remaining 3 mL was placed in a plain tube, left to coagulate for 20 minutes at room temperature, and centrifuged at 1000 xg for 10 minutes to extract the serum. The serum was then divided into two aliquots in Eppendorf tubes. The first aliquot was used immediately to measure fasting serum glucose (FSG), fasting insulin, and the lipid profile. The second aliquot was preserved at -80°C for the subsequent quantification of serum Sortilin-1, using Enzyme-Linked Immunosorbent Assay (ELISA) techniques according to the manufacturer of (ELK BIOTECHNOLOGY USA, Human SORT-1 (Sortilin-1, Cat NO: ELK3281),detection rang:0.16-10 ng/mL,sensitivity= 0.056 ng/mL. HOMA-IR was calculated by using this equation (FSG (mg/dl) *F.Insulin(μU/mL)/405.

Statistical Analysis

Statistical analyses were performed using Jamovi software (v2.7.17). Data normality was evaluated via the Shapiro-Wilk test. Non-normally distributed continuous variables are presented as median (interquartile range) and compared using the Kruskal-Wallis test with Dunn's post-hoc analysis. Categorical data are presented as frequencies (%) and compared using the Chi-square test. Correlations were evaluated using Spearman's rank test. Receiver Operating Characteristic (ROC) curves were generated to assess the diagnostic performance of the biomarkers (AUC, sensitivity, specificity, and optimal cut-offs) was selected by using Youdens index. Statistical significance was defined as p-<0.05.

RESULT AND DISCUSSION

Demographic Characteristics of the Study Population

Table 1 summarizes the baseline demographic data of the enrolled subjects. The study participants were well-matched, with no statistically significant differences in age or gender among the control, prediabetes, and T2DM groups. The median age was comparable across all categories, ranging from 45.00 to 49.50 years (p-value 0.316, Kruskal-Wallis test). Also, the gender distribution was highly homogenous; both the prediabetic and diabetic groups consisted of an exact 1:1 male-to-female ratio (50% for each sex). The control group maintained a closely parallel distribution with 31 males (51.67%) and 29 females (48.33%). A Chi-square test confirmed the independence of sex distribution across the study groups (p-value 0.95), ensuring that these demographic variables would not act as confusing factors in subsequent analyses.

The clinical and biochemical characteristics of the study groups are summarized in Table 2. Data are presented as the median and interquartile range (IQR), along with the minimum and maximum values. The analysis revealed highly significant differences (p<0.001) across the three study groups (Control, prediabetes, and T2DM) for all evaluated parameters. Specifically, there was a statistically significant variation in HOMA-IR, Insulin, HbA1c, (FBG), and body mass index (BMI), as well as in the levels of the biomarker Sortilin-1. showed a steady rising trend in tandem with this declining glycemic control. The baseline median values Sortilin-1 were lowest in the healthy controls, significantly increased in the prediabetic stage, and finally peaked in the diabetic group This implies increased of sortilin-1 associated with study of [5]. These results are in line with research that has repeatedly shown a link between obesity and a higher risk of diabetes [6] Obesity and higher body mass index (BMI) are intimately linked to physiological changes in adipose tissue, which lead to insulin resistance, chronic inflammation, altered release of

Table 1: Demographic Characteristics of the Study Population

Study groups	Age (year) Median (IQR)	p-VALUE	SEX		p-VALUE
			Male n (%)	Female n (%)	
Control	49.50 (23.25)	=0.316*	31 (51.67%)	29 (48.33%)	=0.95**
Prediabetes	45.50 (21.50)		15(50%)	15 (50%)	
T2DM	45.00 (21.00)		15(50%)	15 (50%)	

*p-VALUE calculated by Kruskal-Wallis test, **P-VALUE calculated by Chi-Square Test, IQR: Inter quartile range

Table 2: Comparison of Parameters between Study Groups

	Study groups	Median	IQR	P1	P2	P3	p-value
HOMA-IR	Control	0.95	0.16	<.001	<.001	<.001	<.001*
	Prediabetes	1.90	0.28				
	T2DM	3.95	1.25				
Insulin µUl/ml	Control	4.23	0.88	<.001	<.001	<.001	<.001*
	Prediabetes	6.86	1.46				
	T2DM	7.00	0.27				
HbA1c%	Control	5.28	0.16	<.001	<.001	<.001	<.001*
	Prediabetes	5.99	0.31				
	T2DM	8.27	0.27				
FBS (mg/dl)	Control	89.0	9.00	<.001	<.001	<.001	<.001*
	Prediabetes	112.5	11.75				
	T2DM	222.0	73.00				
BMI kg/m2	Control	26.0	8.00	<.001	<.001	<.001	<.001*
	Prediabetes	27.75	4.43				
	T2DM	31.10	4.27				
Sortilin-1 ng/ml	Control	1.93	0.63	<.001	<.001	<.001	<.001*
	Prediabetes	2.47	1.00				
	T2DM	3.16	0.52				

The overall p * was calculated using the Kruskal-Wallis test. Pairwise comparisons (P1, P2, and P3) were evaluated using the Dunn's post-hoc test. P1: Control vs. Prediabetes, P2: Control vs. Diabetes, and P3: Prediabetes vs. Diabetes. Statistical significance was set at p<0.05. IQR: Inter quartile range

Table 3: Spearman's Correlation for Sortilin-1 with other Parameters in Prediabetes and T2DM Groups

	Prediabetes state	T2DM State
Parameters	Sortilin-1 ng/ml	Sortilin-1 ng/ml
FBS (mg/dl)	0.75***	0.85***
Insulin µUl/ml	0.48**	0.65***
HOMA-IR	0.61***	0.88***
HbA1c%	0.82***	0.87***
BMI kg/m2	0.62***	0.70***
Triglyceride (mg/dl)	0.82***	0.65***
VLDL (mg/dl)	0.82***	0.65***
Total-cholesterol (mg/dl)	-0.19	-0.02
LDL (mg/dl)	-0.32	-0.22
HDL (mg/dl)	-0.74***	0.16

*p<0.05, **p<0.01, ***p<0.001

Table 4: Diagnostic performance of Serum Sortilin-1, Discriminating between Prediabetes Patients and Healthy Controls

Variable	AUC	Cut-off	Accuracy	Sens.	Spec.	SE	95% CI	*p*
Sortilin-1	0.89	≥2.04	75.6	100.0	63.3	0.03	0.82 to 0.95	<0.001

AUC: Area under the Curve, SE: Standard Error, Sens: Sensitivity, Spec: Specificity, CI: Confidence Interval

Table 5: Diagnostic Performance of Serum Sortilin-1, Discriminating between Prediabetes Patients and T2DM

Variable	AUC	Cut-off	Accuracy	Sens.	Spec.	S.E	95% CI	p
Sortilin-1	0.77	≥2.56	76.7	100.0	53.3	0.06	0.64 to 0.89	<0.001

AUC: Area under the Curve, SE: Standard Error, Sens: Sensitivity, Spec: Specificity, CI: Confidence Interval

inflammatory mediators [7]. T2DM group had considerably higher Median (IQR) HOMA-IR values than controls and pre-diabetics (p<0.001). These results align with earlier research conducted by [8]. In comparison to controls and pre-diabetics, diabetics had considerably higher insulin levels (p<0.001). This result is consistent with research by [9] that found that people with diabetes had higher insulin levels. In reaction to insulin resistance, compensatory hyperinsulinemia is indicated by elevated insulin levels. Diabetics' markedly elevated insulin levels highlight their poor glucose regulation and the necessity of careful diabetic care. These results demonstrate the significant beta-cell malfunction and insulin resistance linked to T2DM. A major contributing factor to the onset and advancement of T2DM is insulin resistance, which impairs glucose metabolism and raises the risk of complications. The study's findings are in line with previous research on insulin levels and insulin resistance in diabetic populations. Although not as noticeable as those seen in diabetics, the variations in HOMA-IR and insulin levels between pre-diabetics and controls were statistically significant. This implies that early indicators of insulin resistance and beta-cell malfunction are already present in those with pre-diabetes. The results highlight the significance of lifestyle changes and early intervention for people who are at risk of developing T2DM.

Table 3 presents the Spearman's correlation coefficients assessing the association of Sortilin-1 with standard metabolic parameters across the prediabetes and T2DM study groups. Sortilin-1 shows there are correlation with poor fasting serum glucose control (FSG and HbA1c) as well as insulin resistance (Insulin and HOMA-IR). Notably, these connections become more clearly to discrimination between

of Prediabetes and T2DM individuals. Sortilin-1 is also consistently linked to a higher BMI and elevated levels of certain blood fats, specifically triglycerides and VLDL, across both stages. The most interesting shift occurs with "good" cholesterol (HDL); during prediabetes, higher Sortilin-1 is strongly associated with a harmful drop in HDL, but this significant negative relationship disappears once T2DM fully develops that may be due to the small sample size. Meanwhile, total cholesterol and LDL showed no meaningful connection to Sortilin-1 in either group.

To evaluation the diagnostic utility of the Sortilin-1 in discrimination the onset of prediabetes, (ROC) curve analysis was performed. As illustrated in Table.4 and Figure. 1, serum Sortilin-1 demonstrated outstanding discriminatory performance in discriminating prediabetic patients from healthy controls. Sortilin-1 exhibited robust diagnostic potential with an AUC of 0.89 (95% CI: 0.82–0.95, p<0.001) at a cut-off of ≥ 2.04 ng/ml. Especially, Sortilin-1 displayed a remarkable sensitivity of 100.0%, making it potential marker for early screening to rule out of glucose dysregulation. Furthermore, the high AUC values observed in our study strongly support the hypothesis that early pathological shifts in these proteins occur prior to the onset of full T2DM, which is consistent with the mechanisms proposed by [10] which also indicated correlation between the elevation of this parameter and disease discrimiation. Furthermore, [11] confirmed in their research that sortilin-1 levels tend to rise as a physiological response to the disease state. Moving beyond the initial onset of glucose dysregulation, we further evaluated the capacity of Sortilin-1 to discriminate between the prediabetic state and overt T2DM Table.5 Sortilin-1 showed a slightly lower overall AUC of 0.77 (95% CI: 0.64–0.89, p<0.001) at a cut-off of ≥

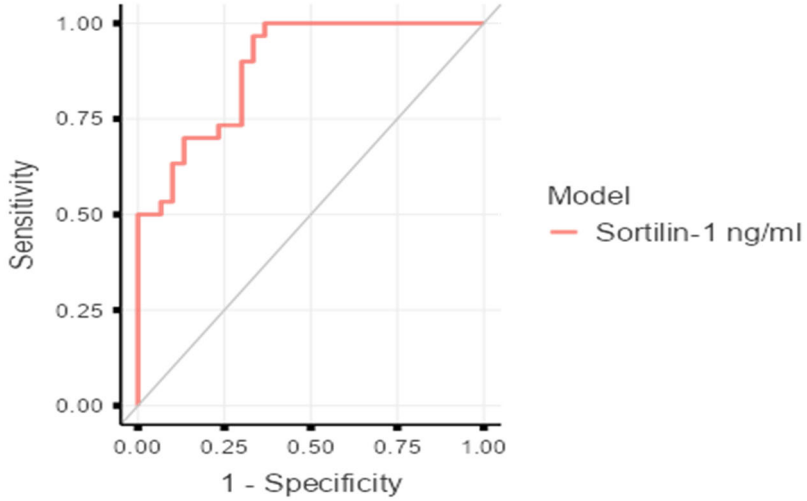

Figure 1: ROC Curves Demonstrating the Discriminatory Value of Sortilin-1 For The Progression from a Healthy State to Prediabetes

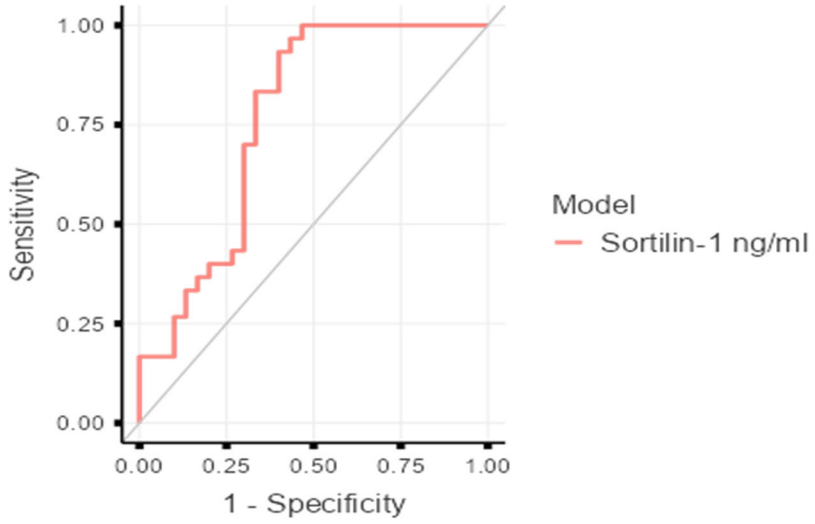

Figure 2: ROC Curve to Demonstrating the Discriminatory Value of Sortilin-1 for the Progression from Prediabetes State to T2DM

2.56 ng/ml, yet it consistently demonstrated an extraordinary sensitivity of 100.0%. However, this absolute sensitivity was accompanied by a reduced specificity of 53.3%, indicating a higher rate of false positives when distinguishing T2DM from prediabetes. Despite these variations in their specific metrics, Sortilin-1 as biomarker achieved an identical overall diagnostic accuracy of 76.7%. These findings suggest that while Sortilin-1 remains a progression marker for capturing all progressing cases.Our observations align with the research of [12], who reported confirming that Sortilin-1 contributing factor to the metabolic condition linked to diabetes. The sustained elevation and predictive value of these specific cut-offs underscore their active involvement in the continuous pathogenesis of T2DM (Figure 2).

CONCLUSIONS AND SUGGESTIONS

our study found significant correlation between Sortilin-1 and the other clinical variables. Also, the levels of Sortilin-1 higher in prediabetes and T2DM comparing with healthy control, Also the findings clearly demonstrate that Sortilin-1 have an ability to discrimination of prediabetes and (T2DM). Therefore, these proteins can serve as valuable for early tracking of the disease. The relatively small sample size and the single-center design may limit the generalizability of our findings. Therefore, it is highly recommended that future research focuses on validating these results through large-scale, multicenter studies with a broader demographic representation. Increasing the number of participants across various clinical settings will help confirm the reliability of these biomarkers and further establish their routine clinical utility in the early detection of type 2 diabetes.

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