THE RELATIONSHIP BETWEEN SERUM CALPROTECTIN AND PERIPHERAL NEUROPATHY IN A SAMPLE OF EGYPTIAN TYPE 2 DIABETIC PATIENTS

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Received: 3/2/2022
Accepted: 10/3/2022

Online ISSN: 2735-3540

ABSTRACT:

Background: *Plasma calprotectin is a persistent biomarker of insulin resistance (IR), gastroenteritis, and cardiovascular disease (CVD). Elevated plasma levels of calprotectin have been reported in a variety of chronic inflammatory conditions. Elevated calprotectin levels have been reported to predict microvascular alterations in type 2 diabetic patients.*

Aim of the Work: *To evaluate if there is a relationship between serum calprotectin and peripheral neuropathy in type 2 Diabetic patients.*

Patients and methods: *This study is a case–control study that was conducted on 60 subjects their age range 45- 60 years old, divided into 3 groups underwent full clinical , neurological assessment and laboratory tests including (s.calprotectin ,hs CRP, HbA1C,cholesterol and TGs)*

Results: *statistically significant higher in diabetic with peripheral neuropathy than diabetic without neuropathy and controls regarding HS CRP,S calprotectin,HbA1c, FbG,2hrpp. ROC curve shows best cut off point for S. calprotectin level between diabetic without neuropathy and diabetic with neuropathy was >3.01 with sensitivity of 55.0%, specificity of 90.0% and AUC of 72.6%. Significant positive correlation between s.calprotectin and (hs.crp , age, SBP,BMI , FbG, TGs)*

Conclusion: *High levels of calprotectin detected in type 2 diabetic patients with peripheral neuropathy suggest that this molecule may have a role in pathogenesis of neuroinflammation among these patients. Serum calprotectin levels in the future may be used as potential markers of its presence, severity and progression of the diabetic peripheral neuropathy. Therapeutic strategies for blocking S100A9 and its activity are recently under development in inflammatory diseases.*

Keywords: *Calprotectin, Diabetes Mellitus, Neuroinflammation, Peripheral Neuropathy*

INTRODUCTION:

Diabetes is a growing global health problem. According to data published by the International Diabetes Federation, there are 425 million diabetic patients (aged 20–79 years) worldwide; by 2045, this number is expected to rise to 693 million **(1).**

The most commonly encountered microvascular complication of type 2 diabetes is Diabetic peripheral neuropathy (DPN) affects over 50% of diabetic patients and has emerged as a severe public health problem**(2).** This chronic complication causes immense financial burden and seriously

decreases the life quality and expectancy of diabetic patients[3].

DPN is induced by multifactorial metabolic disorders, including abnormal metabolism of glucose, lipid, and protein leading to vascular abnormalities, neuro-trophic factor insufficiency, oxidative stress and immune damage[4].

The duration of diabetes and glycemic control is the most significant risk factors for DPN. Other risk factors for cardiovascular disease are also associated with DPN, including: obesity, hypertension, smoking, and dyslipidemia[5] approximately 50% of people with DPN suffer from peripheral neuropathic pain[6]. Many risk factors for painful-DPN have been postulated such as the severity of neuropathy, hyperglycemic burden, and obesity[7]. However, recent studies have demonstrated strong evidence that female sex is a risk factor for painful-DPN[8].

Calprotectin (myeloid related protein 8/14) is a stable heterodimer belonging to S100 protein family composed of two calcium binding cytoplasmic calgranulins which are expressed in activated human granulocyte and macrophages in inflammatory conditions. Among its functions are activations of NADPH oxidase, toll like receptors 4 (TLR4), and advanced glycation end products (AGEs) receptors, which are important signallling pathways in pathogenesis of micro- and macrovascular complications of diabetes[9].

AIM OF THE WORK

This study aims to evaluate the relationship between serum calprotectin and peripheral neuropathy in a sample of Egyptian type 2 Diabetic Patients.

PATIENTS AND METHODS

The aim of this work is to evaluate if there is a relationship between serum calprotectin and perioheral neuropathy in a sample of Egyptian type 2 Diabetic patients.

Patients: This study is a case–control study that was conducted on 60 subjects their age ranging from 45- 60 years old, recruited from Endocrinology & metabolism outpatient clinic at Ain Shams University hospitals during the period from May to October 2020.

The patients were subdivided into three groups:

Group I: Group I included 20 normal subjects as control group.

Group II: Included 20 Diabetic patients newly diagnosed within 5 years of duration have no diabetic neuropathy.

Group III: Included 20 Diabetic patients newly diagnosed within 5 years of duration have diabetic neuropathy.

All persons including the control group and Diabetic without peripheral neuropathy and diabetic with peripheral neuropathy were subjected to:

Medical consent: informed consents were taken from all patients and controls, Full medical history taking: Age, Duration of Diabetes and treatment of diabetes and history of Diabetic complications.

Thorough clinical examination Full Clinical Examination: Vital data (Blood Pressure, Pulse), Weight, Height, BMI (Body mass Index), Waist Hip Ratio

Full neurology Examination: The diagnosis of diabetic peripheral neuropathy according to clinical symptoms using a known questionnaire of neuropathy (total symptom NTSS-6 questionnaire), the total symptom score can then be determined: [10].

What is the sensation felt? Burning, numbness, or tingling in the feet (2 points); fatigue, cramping, or aching (1 point). Maximum is 2 points, What is the location of symptoms? Feet (2 points); calves (1 point); elsewhere (0 points). Maximum is 2

points, Have the symptoms ever awakened you at night? Yes (1 point), What is the timing of symptoms? Worse at night (2 points); present day and night (1 point); present only during the day (0 points). Maximum is 2 points, How are symptoms relieved? Walking around (2 points); standing (1 point); sitting or lying or no relief (0 points). Maximum is 2 points, 0 to 2 points: Normal, 3 to 4 points: Mild neuropathy, 5 to 6 points: Moderate neuropathy and 7 to 9 points: Severe neuropathy

Neurologic examination: deep tendon reflexes, superfacial sensations, tactile sensation, temperature[(10)].

What is the Achilles tendon reflex? Absent (2 points for each foot); present with reinforcement (1 point for each foot).

What is vibration sense? Absent or reduced (1 point for each foot), what is pin prick sensation? Absent or reduced (1 point for each foot) and what is temperature sensation? Reduced (1 point for each foot).

The neurologic signs score can then be determined:

0 to 2 points: Normal, 3 to 5 points: Mild neuropathy, 6 to 8 points: Moderate neuropathy, 9 to 10 points: Severe neuropathy and nerve conduction Studies performed with standard electromyography equipment.

The following laboratory investigations: Fasting plasma glucose FPS: by electrochemiluminescence method using cobas integra 800 model auto –analyser, 2 hPP post prandial blood glucose, HbA1c: HPLC (high performance liquid chromatography) method using trinity biotech- premier Hb210 auto-analyser, high sensitive c-reactive protein (hsCRP) levels standard biochemistry tubes with gel by immunonephelometey assay on Dade Behring Nephelometer II device, microalbuminuria (urinary albumin by a sensitive RIA), GFR: can be measured by specific techniques, such as insulin clearance,51Cr-EDTA, 125 I-iothalamate, and iohexol calculated by the MORD (Modified Diet In Renal Disease) (ml'min-1' 1.73 m-2) =186* (s.creat inine (mg/dl)-1.154*Age (yeares)-0.203* (0.742 if female)* (1.210 if African American), serum calprotectin: using an enzyme linked immunosorbent assay detection kit (ELISA) and total Cholesterol level, Low density lipoprotein (LDL), High density lipoprotein (HDL), Triglycerides

Fundus examination: by indirect-4 ophthalmoscope to assess diabetic retinopathy[(11)].

Inclusion criteria: 60 patients at endocrinology outpatient clinic at Ain shams hospitals, age: 45 – 60 years, gender: males and females and type 2 Diabetic patients with 5 years of early prediction

Exclusion criteria: Smokers, patients who are unwilling for screening, subjects with infectious disease or inflammatory diseases, liver failure or malignancies, neurodegenerative disease or history of serious limbs trauma and use of neurotoxic medication or vitamin B 12 deficiency

Methodology: 20 ml of venous blood was collected by venipuncture. 5 ml of the sample was used for measurement of s. calprotectin and the 5 ml was used for measurement of hs CRP, and 10 ml for (Total Cholesterol level, low density lipoprotein (LDL), High density lipoprotein (HDL), Triglycerides, GFR, HbA1C, 2 hPP post prandial blood glucose and Fasting plasma glucose) then serum was separated by centrifugation. It was frozen at -20°C until assayed and urine sample for Microalbuminuria test.

Caloprotectin Assay: Serum calprotectin was measured by a commercial ELISA ***Immundiagnostik and Germany (2011).***

A blood sample (5mL) for serum calprotectin measurements was collected in blood collection tubes containing ethylene-diamino tetra acetic acid (EDTA), collect serum samples, using centrifuge at the speed of 2000-3000 r.p.m. for 20 min of collection.

If precipitation appeared, centrifuge again and frozen at -20◦Cfor subsequent measurement, all reagents and samples were brought to room temperature (18-26°C) and the serum was diluted 1: 50, and 100µL of each sample was added to the wells of a plate and incubated at room temperature for 45min. The plate was then washed 3 times with diluted washing solution, and 100µL of purified rabbit anti-calprotectin antibodies conjugated with alkaline.

Phosphatase were added and incubated for 45min at room temperature. A second washing procedure was performed, 100µL of enzyme substrate solution was added to each well, and optical density was read at 405 nm. Serum calprotectin concentration was calculated from the standards and expressed as µg/mL, run around the time is about 4 hours.

hs CRP quantitative assay: samples collected at standard biochemistry tubes with gel and assayed on Dade Behring Nephelometer II device

Interpretation of hs CRP: Lower than 1.0 mg / L low risk of cardiovascular disease (CVD), 1.0 mg/ L -3.0 mg/L moderate risk of CVD and more than 3.0 mg/L high risk of CVD.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** when the expected count in any cell found less than 5. The comparison between two groups regarding quantitative data and parametric distribution was done by using ***Independent t-test*** while with non parametric distribution was done by using ***Mann-Whitney test.*** The comparison between more than two groups regarding quantitative data and parametric distribution was done by using ***One Way ANOVA test*** while with non parametric distribution was done by using ***Kruskall-Wallis test.*** ***Spearman correlation coefficients*** were used to assess the correlation between two quantitative parameters in the same group. ***Receiver Operating Characteristic Curve (ROC)*** was used to assess the best cut off point between two groups with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC). **The significance of the test was determined according to the P value to be:** Non-significant (NS) if P > 0.05, Significant (Sig) if P < 0.05. Highly significant (HS) if P < 0.001.

RESULTS:

Table (1): Comparison between Control group and patients group regarding Gender, Age, HTN, and BMI

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
Gender	Females	8 (40.0%)	16 (40.0%)	0.000*	1.000	NS
	Males	12 (60.0%)	24 (60.0%)			
Age	Mean ± SD	51.15 ± 6.53	53.55 ± 4.91	-1.594•	0.116	NS
	Range	45 – 60	45 – 60			
HTN	No	20 (100.0%)	20 (50.0%)	15. 000*	0.000	HS
	Yes	0 (0.0%)	20 (50.0%)			
BMI	Mean ± SD	25.40 ±2.27	26.98 ± 3.12	-2.009	0.049	S
	Range	21.7 – 29.6	22.7 – 34.20			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: Independent t-test

Table (2): Comparison between Control group and patients group regarding (hs CRP, s. calprotectin, SBP, DBP, HbA1c, FbG,…etc):

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
SBP mmHg	Mean ± SD	119.50 ± 11.91	128.75 ± 13.43	-2.607•	0.012	S
	Range	100 – 140	110 – 160			
DBP mmHg	Mean ± SD	75.50 ± 6.05	74.00 ± 8.41	0.710•	0.481	NS
	Range	70 – 90	60 – 90			
HbA1c (%)	Mean ± SD	5.24 ± 0.42	7.70 ± 1.23	-8.668•	0.000	HS
	Range	4.5 – 5.8	6.1 – 11.1			
FPG mg/dL	Mean ± SD	88.55 ± 6.60	134.40 ± 42.69	-4.755•	0.000	HS
	Range	75 – 100	79 – 274			
2hrpp mg/dL	Mean ± SD	100.65 ± 7.10	191.18 ± 68.67	-5.855•	0.000	HS
	Range	90 – 115	108 – 441			
HS CRP mg/L	Median (IQR)	0.19 (0.09 – 0.33)	2.59 (1.08 – 3.65)	-6.189≠	0.000	HS
	Range	0.01 – 0.5	0.4 – 5.9			
S.calprotectin µg/mL,	Median (IQR)	0.96 (0.5 – 1.25)	2.75 (1.25 – 3.2)	-4.307≠	0.000	HS
	Range	0.01 – 1.8	0.3 – 5.2			
Microabuminuria	Median (IQR)	–	70 (42.5 – 112.5)	–	–	–
	Range	–	20 – 290			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test; ≠: Mann-Whitney test

Table (3): Comparison between Control group and patients group regarding LDL, HDL, TGs and cholesterol

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
LDL mg/dl	Mean ± SD	83.25 ± 19.94	138.13 ± 36.44	-6.264•	0.000	HS
	Range	49 – 123	45 – 218			
HDL mg/dl	Mean ± SD	45.80 ± 13.51	53.33 ± 10.78	-2.339•	0.023	S
	Range	24 – 76	19 – 77			
TGs mg/dl	Mean ± SD	96.95 ± 33.30	152.73 ± 69.53	-3.388•	0.001	HS
	Range	38 – 161	54 – 384			
Cholesterol mg/dl	Mean ± SD	147.85 ± 18.11	226.10 ± 38.21	-8.657•	0.000	HS
	Range	112 – 175	146 – 322			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

Table (4): Descriptive data regarding GFR and Fundus in patients group

		Patients group
		No. = 40
GFR	Mean ± SD	89.45 ± 7.49
	Range	70 – 99
Fundus	No	29 (72.5%)
	Yes	11 (27.5%)

Table (5): Comparison between Control group, Diabetic without peripheral neuropathy, and Diabetic with peripheral neuropathy regarding Gender, Age, HTN, BMI,…etc

		Control group	Diabetic without peripheral neuropathy	Diabetic with peripheral neuropathy	Test value	P-value	Sig.
		No. = 20	No. = 20	No. = 20			
Gender	Females	8 (40.0%)	9 (45.0%)	7 (35.0%)	0.417*	0.812	NS
	Males	12 (60.0%)	11 (55.0%)	13 (65.0%)			
Age (years)	Mean ± SD	51.15 ± 6.53	53.05 ± 4.89	54.05 ± 5.01	1.420•	0.250	NS
	Range	40 – 60	45 – 60	45 – 60			
HTN	No	20 (100.0%)	12 (60.0%)	8 (40.0%)	16.800*	0.000	HS
	Yes	0 (0.0%)	8 (40.0%)	12 (60.0%)			
BMI kg/m2	Mean±SD	25.40 ±2.27	26.81 ± 2.95	27.14 ± 3.36	2.053•	0.138	NS
	Range	21.7 – 29.6	23.2 – 32.4	22.7 – 34.20			
SBP mmHg	Mean ± SD	119.50 ± 11.91	127.00 ± 12.61	130.50 ± 14.32	3.747•	0.030	S
	Range	100 – 140	110 – 150	110 – 160			
DBP mmHg	Mean ± SD	75.50 ± 6.05	71.00 ± 7.88	77.00 ± 8.01	3.591•	0.034	S
	Range	70 – 90	60 – 80	70 – 90			
HbA1c %	Mean ± SD	5.24 ± 0.42	7.23 ± 0.77	8.17 ± 1.43	47.841•	0.000	HS
	Range	4.5 – 5.8	6.2 – 8.9	6.1 – 11.1			
FbG mg/dL	Mean ± SD	88.55 ± 6.60	115.60 ± 18.87	153.20 ± 51.39	20.806•	0.000	HS
	Range	75 – 100	79 – 146	82 – 274			
2hrpp mg/dL	Mean ± SD	100.65 ± 7.10	175.90 ± 46.71	206.45 ± 83.71	19.255•	0.000	HS
	Range	90 – 115	108 – 260	120 – 441			
HS CRP mg/L	Median (IQR)	0.19 (0.09 – 0.33)	1.35 (0.9 – 2.35)	3.65 (2.59 – 4.85)	44.437≠	0.000	HS
	Range	0.01 – 0.5	0.4 – 3.5	0.6 – 5.9			
S.calprotectin µg/mL	Median (IQR)	0.96 (0.5 – 1.25)	2.6 (1 – 2.9)	3.15 (1.8 – 4.15)	22.793≠	0.000	HS
	Range	0.01 – 1.8	0.3 – 3.2	0.5 – 5.2			
Microabuminuria	Median (IQR)	–	45 (31.5 – 62.5)	112.5 (77.5 – 160)	-4.291≠≠	0.000	HS
	Range	–	20 – 100	40 – 290			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: One Way ANOVA test

Table (6): Comparison between Control group and patient groups regarding LDL, HDL,TGs and cholesterol

		Control group	Diabetic without peripheral neuropathy	Diabetic with peripheral neuropathy	Test value	P-value	Sig.
		No. = 20	No. = 20	No. = 20			
LDL mg/dl	Mean ± SD	83.25 ± 19.94	132.10 ± 46.62	144.15 ± 21.80	20.481•	0.000	HS
	Range	49 – 123	45 – 218	91 – 178			
HDL mg/dl	Mean ± SD	45.80 ± 13.51	52.20 ± 12.63	54.45 ± 8.75	2.887•	0.064	NS
	Range	24 – 76	19 – 77	42 – 68			
TGs mg/dl	Mean ± SD	96.95 ± 33.30	139.45 ± 72.68	166.00 ± 65.34	6.827•	0.002	HS
	Range	38 – 161	54 – 384	96 – 343			
Cholesterol mg/dl	Mean ± SD	147.85 ± 18.11	220.00 ± 49.03	232.20 ± 22.68	38.405•	0.000	HS
	Range	112 – 175	146 – 322	189 – 277			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: One Way ANOVA test

Table (7): Comparison between Diabetic without peripheral neuropathy and diabetic with peripheral neuropathy regarding GFR and Fundus

		Diabetic without peripheral neuropathy	Diabetic with peripheral neuropathy	Test value	P-value	Sig.
		No. = 20	No. = 20			
GFR	Mean ± SD	90.25 ± 7.76	88.65 ± 7.31	0.671•	0.506	NS
	Range	75 – 99	70 – 98			
Fundus	No	17 (85.0%)	12 (60.0%)	3.135*	0.077	NS
	Yes	3 (15.0%)	8 (40.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test

Table (8): Correlation between HS CRP and (S.calprotectin,Age, BMI,SBP,DBP, HBA1C, FbG,2hrPP,AST, ALT, creat, urea and …etc)In all patients, Diabetic without peripheral neuropathy, and Diabetic with peripheral neuropathy

	HS CRP					
	All patients group		Diabetic without peripheral neuropathy		Diabetic with peripheral neuropathy	
	R	P-value	R	P-value	r	P-value
S.calprotectin µg/mL	0.872**	0.000	0.839**	0.000	0.886**	0.000
Age (years)	0.406**	0.009	0.192	0.417	0.496*	0.026
BMI kg/m2	0.338*	0.033	0.444	0.050	0.349	0.131
SBP mmHg	0.505**	0.001	0.729**	0.000	0.270	0.249
DBP mmHg	0.298	0.062	-0.134	0.572	0.211	0.373
HbA1c %	0.282	0.078	0.309	0.185	-0.114	0.633
FbG mg/dL	0.463**	0.003	0.315	0.176	0.154	0.518
2hrpp mg/dL	0.148	0.362	0.261	0.266	-0.208	0.379
Microabuminuria	0.577**	0.000	0.301	0.198	0.163	0.491
LDL mg/dl	0.115	0.479	0.369	0.109	-0.376	0.103
HDL mg/dl	-0.327*	0.039	-0.475*	0.034	-0.494*	0.027
TGs mg/dl	0.546**	0.000	0.464*	0.039	0.642**	0.002
Cholesterol mg/dl	0.215	0.183	0.512*	0.021	-0.208	0.378
GFR	-0.240	0.136	-0.141	0.552	-0.182	0.443

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
Spearman correlation coefficient

Table (9): Relation between HS CRP and gender, HTN and fundus in Diabetic without peripheral neuropathy

		Diabetic without peripheral neuropathy		**Test value**	**P-value**	**Sig.**
		HS CRP				
		Median (IQR)	**Range**			
Gender	Females	1.2 (1 – 2.7)	0.4 – 3.5	-0.038	0.970	NS
	Males	1.5 (0.8 – 2)	0.5 – 3			
HTN	No	1.35 (0.9 – 2.35)	0.4 – 2.9	-0.386	0.699	NS
	Yes	1.35 (0.95 – 2.4)	0.5 – 3.5			
Fundus	No	1.19 (0.8 – 1.8)	0.4 – 2.8	-2.703	0.007	HS
	Yes	3 (2.9 – 3.5)	2.9 – 3.5			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
≠: Mann-Whitney test

Table (10): Relation between HS CRP and gender, HTN and fundus in Diabetic peripheral neuropathy

		Diabetic with peripheral neuropathy		Test value	P-value	Sig.
		HS CRP				
		Median (IQR)	Range			
Gender	Females	3.69 (2.57 – 5.2)	0.8 – 5.9	-0.317≠	0.751	NS
	Males	3.6 (2.6 – 4.8)	0.6 – 5.6			
HTN	No	2.5 (0.85 – 4.35)	0.6 – 5.9	-1.582≠	0.114	NS
	Yes	4.55 (3.55 – 4.85)	2.57 – 5.6			
Fundus	No	3.25 (1.73 – 4.75)	0.6 – 5.9	-1.196≠	0.232	NS
	Yes	4.55 (3.55 – 4.95)	2 – 5.6			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
≠: Mann-Whitney test

Table (11): Correlation between S.calprotectin and (HS CRP,Age, BMI,SBP, …etc)In all patients(Diabetic without peripheral neuropathy, and Diabetic with peripheral neuropathy)

	S.calprotectin					
	All patients group		Diabetic without peripheral neuropathy		Diabetic with peripheral neuropathy	
	R	P-value	r	P-value	r	P-value
HS CRP mg/L	0.872**	0.000	0.839**	0.000	0.886**	0.000
Age yerars	0.409**	0.009	0.180	0.448	0.455*	0.044
BMI kg/m2	0.341*	0.032	0.345	0.136	0.269	0.252
SBP mmHg	0.605**	0.000	0.657**	0.002	0.434	0.056
DBP mmHg	0.164	0.313	-0.372	0.107	0.221	0.349
HbA1c %	0.272	0.090	0.411	0.072	0.095	0.691
FbG mg/dL	0.455**	0.003	0.329	0.157	0.340	0.142
2hrpp mg/dL	0.139	0.394	0.190	0.422	-0.018	0.940
Microabuminuria	0.372*	0.018	0.168	0.479	0.157	0.510
LDL mg/dl	0.006	0.970	0.184	0.438	-0.316	0.175
HDL mg/dl	-0.212	0.190	-0.364	0.115	-0.216	0.360
TGs mg/dl	0.588**	0.000	0.426	0.061	0.678**	0.001
Cholesterol mg/dl	0.191	0.237	0.409	0.074	-0.101	0.672
GFR	-0.298	0.062	-0.186	0.433	-0.322	0.167

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
Spearman correlation coefficient

Table (12): Relation between S.calprotectin and gender, HTN and fundus in Diabetic without peripheral neuropathy

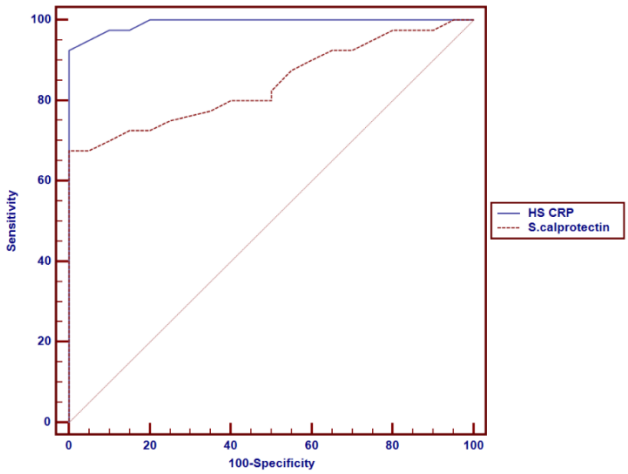
		Diabetic without peripheral neuropathy		Test value	P-value	Sig.
		S.calprotectin				
		Median (IQR)	Range			
Gender	Females	2.6 (1.1 – 2.9)	0.8 – 3.01	-0.228≠	0.820	NS
	Males	2.6 (0.7 – 2.9)	0.3 – 3.2			
HTN	No	1.95 (0.85 – 2.85)	0.5 – 3.01	-0.927≠	0.354	NS
	Yes	2.65 (1.6 – 3.05)	0.3 – 3.2			
Fundus	No	2 (0.9 – 2.8)	0.3 – 3.1	-1.907≠	0.056	NS
	Yes	3 (2.7 – 3.2)	2.7 – 3.2			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
≠: Mann-Whitney test

Table (13): Relation between S.calprotectin and gender, HTN and fundus in Diabetic with peripheral neuropathy

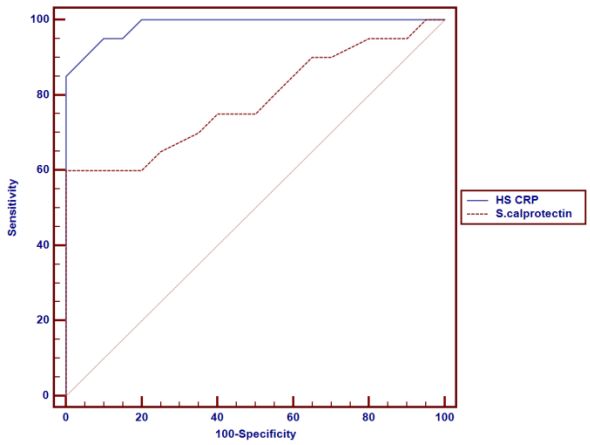
		Diabetic with peripheral neuropathy		Test value	P-value	Sig.
		S.calprotectin				
		Median (IQR)	Range			
Gender	Females	3.1 (1 – 4.5)	0.9 – 4.9	-0.040≠	0.968	NS
	Males	3.2 (1.9 – 4.09)	0.5 – 5.2			
HTN	No	2 (1.3 – 3.95)	0.5 – 4.9	-1.312≠	0.190	NS
	Yes	3.35 (2.85 – 4.15)	0.9 – 5.2			
Fundus	No	2.6 (1.35 – 4.35)	0.5 – 5.01	-1.003≠	0.316	NS
	Yes	3.45 (3 – 4)	1.6 – 5.2			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
≠: Mann-Whitney test



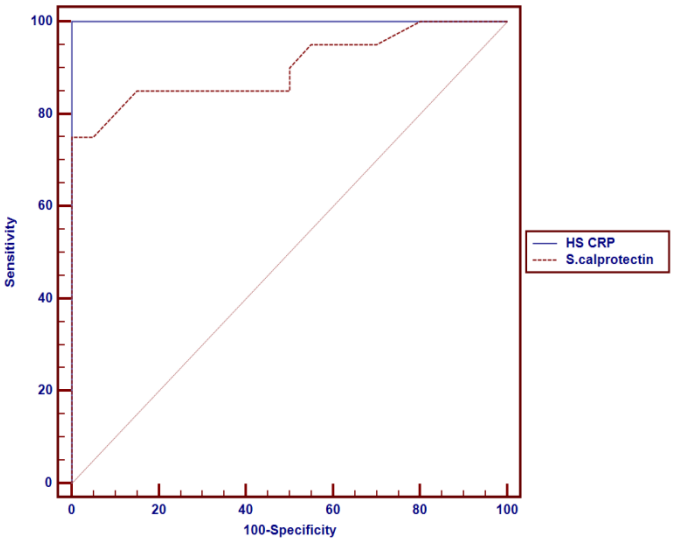
Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HS CRP	>0.5	0.993	92.50	100.00	100.0	87.0
S.calprotectin	>1.8	0.843	67.50	100.00	100.0	60.6

Diagram (1): ROC curve between control and patients group



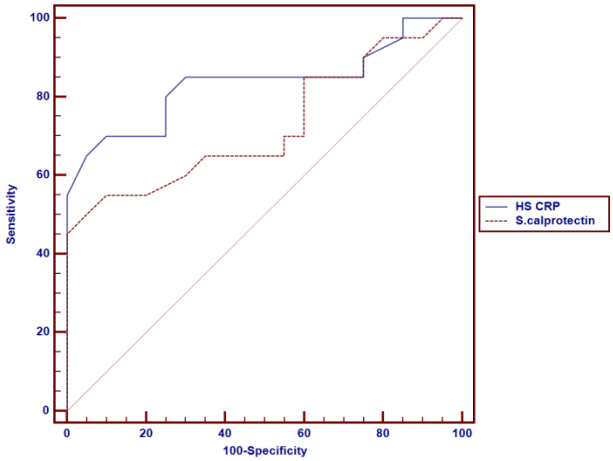
Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HS CRP	>0.45	0.986	95.00	90.00	90.5	94.7
S.calprotectin	>1.8	0.785	60.00	100.00	100.0	71.4

Diagram (2): ROC curve between control and Diabetic without peripheral neuropathy



Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HS CRP	>0.5	1.000	100.00	100.00	100.0	100.0
S.calprotectin	>1.8	0.901	75.00	100.00	100.0	80.0

Diagram (3): ROC curve between control and Diabetic with peripheral neuropathy



Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
HS CRP	>2.9	0.835	70.00	90.00	87.5	75.0
S.calprotectin	>3.01	0.726	55.00	90.00	84.6	66.7

Diagram (4): ROC curve between diabetic without peripheral neuropathy and diabetic with peripheral neuropathy

DISCUSSION:

The most commonly encountered microvascular complication of type 2 diabetes is diabetic neuropathy with the prevalence of 50-60%. Neuropathy may cause decrease nerve function, nerve blood perfusion with persistent nerve damage. Diabetic peripheral neuropathy increases development of foot ulceration and developmental risk of necrosis, which may cause lower extremity amputations. Diabetic peripheral neuropathy has significant contributions in morbidity and mortality in diabetic patients **(Mohammed et al., 2020)** **(12)**.

Although it is predicted that hyperglycemia is an important pathophysiological factor in development of diabetic neuropathy. Opinions suggesting that inflammatory processes may play a role in pathogenesis of diabetic neuropathy are increasing. In previous studies, it has been shown that peripheral neuropathy was associated with increased levels of proinflammatory immune mediators in patients with type 2diabetes **(Tabur et al., 2015)[13].**

The inflammatory Myeloid-related protein complex Calprotectin, also known as MRP8/14, is a heterodimer comprised of two intracellular calcium binding proteins, S100A8 (MRP8) and S100A9 (MRP14). Predominantly expressed in activated human neutrophils, monocytes and macrophages **(Velayutham et al., 2021)[14].**

Calprotectin is actively secreted during the stress response of phagocytes and was found to be associated with inflammation more than 20 years ago. It was identified as an endogenous activator of Toll-like receptor 4 (TLR4) and as receptor for advanced glycation end products (RAGE). Calprotectin is believed to function both as an intracellular differentiation marker for phagocytes and as an extracellular protein complex (a damage-associated molecular pattern (DAMP) molecule).

An elevation of plasma levels of Calprotectin have been reported in a variety of chronic inflammatory conditions, including rheumatoid arthritis, allograft rejection, inflammatory bowel disease, and cancer lung diseases. Elevated levels of this inflammatory marker have been reported to predict microvascular alterations in type 2 diabetic (T2DM) patients **(Pedersen et al., 2014)[15].**

The aim of this study is to evaluate the relationship between serum calprotectin and peripheral neuropathy in a sample of Egyptian type 2 diabetic patients.

In our this current case- control study it has been found that blood pressure was statistically significant higher in diabetic with peripheral neuropathy (group III) than diabetic without peripheral neuropathy (group II) & controls (group I), with mean SBP was 130.50 mmHG ±14.32 SD with (p-value=0.030) in Group III, 127.00 mmHG ± 12.61 SD mmHg in group II and 119.50 mmHG ± 11.91 SD in group I, and regarding DBP mean was 77.00 mmHG ± 8.01 SD with P value 0.034 in group III, 71.00 mmHG ± 7.88 SD in group II and 75.50 mmHG ± 6.05 SD in group I. There was No statistically significant difference found between the three studied groups regarding Gender and Age. Regarding BMI there was a statistically significant difference between group II&III compared to group I with mean 26.98 kg/m2 ± 3.12 SD for (group II&III)and 0.049 p-value, and 25.40 kg/m2±2.27 SD for group I.

In agreement to our study, (**El-hafez et al., 2021**)[16] a conducted case-control study on total number of 90 subjects aged between 20-75 years, the patients were classified into 3 groups. Group I: 15 healthy control subject, group II: 15 diabetic patients without peripheral neuropathy and group III: 60 diabetic patients with early peripheral neuropathy reported that there was no statistically difference between the three studied groups in age and gender that assures there was no age related variation can affect the results. While, regarding BMI **(El-hafez et al., 2021)[16] reported a highly statistically significant** Difference between the 3 studied groups focused on BMI. It was more in patients with DPN **with mean 28.11 ± 1.62 SD and a** p-value <0.001 than diabetic patients and controls. furthermore, it was higher in diabetic patients than controls with a mean of **26.88 ± 1.49** SD and p-value <0.001.

Similarly in **(Tabur et al., 2015)** [13] a conducted study on 29 type 2 diabetic with peripheral neuropathy and 30 diabetic without peripheral neuropathy and 40 controls. It has been reported that no

significant deference regarding the age with p-value = 0.077, nor gender with p-value = 0.609 between the three studied groups

In contrast to this study, (Spasić et al., 2014)[17] a cross -sectional study included 86 patients with type 2 DM over 6- month period considered age as a **significant risk** of lower quality of life particularly in elderly patients (over 65 years old) as they take several medications at the same time for comorbidities as well as cognitive dysfunction that impair their quality of life.

In agreement to this study, **(Velayutham et al., 2021) [14] a** cross-sectional study was conducted in 126 diabetic patients, the subjects were divided into two groups (with and without peripheral neuropathy). Certainly**,** there was no difference between the two patients groups regarding BMI (P=0.58).

In agreement to this study, (Tabur et al., 2015) [13] There was high significant difference found between the studied groups regarding BMI with (p-value<0.001).

In agreement to this study, **(El-hafez et al., 2021) [16] regarding SBP** illustrated that the patients of group I had lower systolic blood pressure than other groups II&III.

In addition,(Sowers et al., 2011) [18] reported that more than half of diabetic patients presented with coexisting hypertension and that hypertension is a potent risk factor for both micro and macro vascular diseases in diabetic patients.

In the our present study we found that there was highly statistically significant difference between 3 groups regarding HbA1c, Fasting blood glucose & 2hours post 75 g oral glucose tolerance test. it was **higher** in group III (DPN) with mean 8.17 %± 1.43 SD regarding the HbA1c and 153.20 mg/dL ± 51.39 SD regarding Fasting blood glucose and 206.45 mg/dL ± 83.71 SD for the 2hours post 75 g oral glucose tolerance test with p-value 0.000 compared to group II &group I. Furthermore, it was higher in group II (DM) with mean 7.23% ± 0.77 SD for HbA1c, and with mean 115.60 mmol/L ± 18.87 SD and 175.90 mmol/L± 46.71 SD with p-value 0.000 for FBG&2hrpp respectively compared to group I.

In agreement to this study, **(El-hafez et al., 2021)[16]** reported that glycemic parameters Random blood glucose & HbA1c of the 3 studied groups was significantly higher in Diabetic with peripheral neuropathy with mean 237.04± 58.2 SD for RBS,7.49 ± 0.78 SD for HbA1c with p-value<0.001 than Diabetic without peripheral neuropathy and controls.

Similarly to this study, (**Tabur et al., 2015) [13]** reported that **FBG**, and HbA1c levels of diabetic patients with and without neuropathy were significantly higher than the controls (p = 0.001, for each). While **FBG** and HbA1c levels in patients with neuropathy were significantly higher than patients without neuropathy.

In our study all the patient groups (diabetic with neuropathy and Diabetic without neuropathy) was diagnosed recently within five years. Consequently, patients without DPN were diagnosed within less than three years with regular follow up of controlling glycemic parameters. In addition, diabetics with peripheral neuropathy were simultaneously together discovered in more than 60% of patients within 5 years. On the other hand, 40% of patients gradually developed Neuropathy over 5 years with poor glycemic control

In agreement to this study, (Velayutham et al., 2021) [14] indicated that patients with DPN had diabetes for a longer duration as compared to those without neuropathy. A study done by (**Oguejiofor et al., 2010) [19]** from the United Kingdom showed that the prevalence of DPN was highest among patients with longer duration of diabetes (>15 years).

In another study, **(Pawde et al., 2013) [20]** from south India, it was found that

patients with peripheral neuropathy had long-standing diabetes.

In our study found a high statistically significant difference between the three groups regarding **LDL, cholesterol & TGs**. These parameters were higher in Diabetic with peripheral neuropathy with **mean value of 144.15 ± 21.80 SD, 232.20 ± 22.68SD & 166.00 ± 65.34 SD (mg/dL) respectively with (p-value0.000)** than diabetic without neuropathy and controls. However, No difference has been found between the three groups regarding **HDL** with (p-value 0.064).

in agreement to this study, (El-hafez et al., 2021) [16] concluded that **cholesterol, TG, LDL** levels were significantly higher **in diabetic with PN** with mean **201.2± 32.1 SD,192.33± 3.4 SD & 103.3± 21 SD respectively (p-value <0.001)** compared to **diabetic without neuropathy and controls**. However, they were higher in diabetic without neuropathy patients compared to controls. **Regarding HDL** levels, they were higher in **Diabetic with peripheral** neuropathy with **mean 63.54± 14 SD (p-value 0.007)** compared to **diabetic without neuropathy and controls**. This may explain atherosclerotic changes as a risk factor of diabetes alone or if also associated with neuropathy.

In our study there was statistically significantly higher **in group III in compared** to **group II and group I** regarding Serum calprotectin with median 3.15 µg/mL (1.8 – 4.15) & (p-value 0.000), regarding HS CRP with median 3.65 (2.59 – 4.85)mg/L & (p-value 0.000), and microalbuminurea with median 112.5 (p-value 0.000).

In agreement to our study,**(El-hafez et al., 2021) [16]** reported that diabetic groups with peripheral neuropathy **had calprotectin levels higher** than diabetic group without neuropathy and healthy controls

Similarly to this study, (Velayutham et al., 2021) [14] reported that the mean serum calprotectin levels **were significantly elevated** in diabetic subjects with peripheral neuropathy compared to those without neuropathy.

Similar results were reported by (Tabur et al., 2015) [13], serum calprotectin and HS CRP levels were significantly higher in patients with and without neuropathy than healthy controls (regarding serum calprotectin in patients with DPN compared to Controls $p < 0.001$, and with $p = 0.017$ in patients without DPN compared to controls, and regarding hs.crp in patient with DPN compared to controls $p < 0.001$ and $p = 0.001$ in patients without compared to controls) respectively. Serum calprotectin and HS CRP levels were higher in diabetics with neuropathy than the ones without ($p = 0.021$ for s. calprotectin and $p < 0.001$ for hs.crp).

Similarly, a study by **(El-adawy et al.,2017) [21]** (a study conducted on 3 groups. (group I 20 diabetic patients, group II 20 pre-diabetic patients and group III were 0n 20 healthy subjects) revealed that level of serum calprotectin was **significantly elevated** in Diabetic patients with peripheral neuropathy with (p-value<0.001) compared to other groups. Suggesting that this molecule may have a **role in pathogenesis of neuro-inflammation** among these patients. The proinflammatory stage seems to begin from the very early preclinical stages.in addition, pre diabetic patients are at risk of developing diabetic neuropathy even before progression to type 2 Diabetes.

In our study we found that All diabetic (without and with neuropathy). There was a direct statistically significant positive correlation between s.calprotectin and (hs.crp, FPG, age, SBP, BMI, TGs and microalbuminurea) with p value of (**0.000, 0.003, 0.009, 0.000, 0.032, 0.000, 0.018) respectively**. In Diabetic **without peripheral neuropathy** there was a direct significant positive correlation between s.calprotectin and (hs CRP and SBP) with p value of

(**0.000, 0.002) respectively.** In **Diabetic with peripheral neuropathy** there was a direct statistically significant positive correlation between s.calprotectin and (Hs.CRP, age and TGs) with p value of (**0.000,** 0.044, 0.001) respectively.

In agreement to this study, (**Tabur et al., 2015)** [(13)] reported that serum calprotectin is direct significantly correlated with hs-CRP levels supporting the role of calprotectin as an inflammation marker. On the other hand, there was also a direct significant positive correlation between calprotectin and HbA1c, the marker of long-term elevation of blood sugar.

Similar to our results, **(Peng et al., 2011)** [(22)] showed **a statistically direct significant** positive correlation between calprotectin and hs-CRP. This result suggests that levels of glucose or glycation products **may affect regulation of high calprotectin levels** in diabetic complications.

Furthermore, our study revealed that calprotectin is an inflammatory mediator that increased in inflamed tissues and probably has a role in the neuroinflammatory conditions as it directly proportionate with CRP in patients with DPN. **(Pedersen et al., 2014)** [(15)] **study also reported** positive correlation between calprotectin and CRP.

In agreement to this study, **(El-hafez et al., 2021)**[(16)] reported a significant positive correlation between calprotectin and HbA1c in patients with DPN. This point suggests that levels of glucose or glycation end products **may affect metabolism of high calprotectin levels in diabetics**.

Similar results were reported by (**Schmaderer et al., 2014)**[(23)] addressed also a positive correlation **between calprotectin and microalbuminuria**; a predictive marker of **cardiovascular disease in type 2 diabetic patients**.

In our current study **a ROC curve** (receiver operating characteristic curve) between (Diabetic without peripheral neuropathy and Diabetic with peripheral neuropathy) regarding s. Calprotectin shows that the best cut off point for S. calprotectin level was **found >3.01 with sensitivity of 55.0%, specificity of 90.0% and AUC of 72.6%,** and between controls and all patients specificity results was **100.0% and sensitivity was 67.0%**.

Another study by (Velayutham et al., 2021)[(14)] reveals that the levels of serum calprotectin between(diabetic without and diabetic with peripheral neuropathy) by ROC curve, it was found that the area under the curve **was 0.92. Sensitivity of serum calprotectin was 88.9% and specificity was 85.7%** at a cut-off level of 1722.83 ng/ml

Silmilar to our study, **(El-hafez et al., 2021)**[(16)] Roc Curve between (controls to Diabetic with and without peripheral neuropathy) regarding s.calprotectin showed sensitivity **was 63.0% and specificity was 90.0%.**

In our current study, a ROC curve between(Diabetic without peripheral neuropathy and Diabetic with peripheral neuropathy) regarding Hs.CRP shows that the best cut off point was **found > 2.9 with sensitivity of 70.0%, specificity of 90.0% and area under curve (AUC) of 83.5%**.

In **(Chuengsamarn et al., 2017)** [(24)] a cohort study randomly enrolled 608 patients with DM between 2007–2008 on Diabetic patients with chronic vascular compli-cations**.** Regarding **Hs CRP between the diabetic peripheral neuropathy and diabetic without neuropathy, best Cut-off point level was 2.82, with sensitivity 79.4%, specificity was 77.9% and AUC was 84.4%**

Conclusion:

High levels of calprotectin detected in type 2 diabetic patients with peripheral

neuropathy suggest that this molecule may have a role in pathogenesis of neuroinflammation among these patients. Serum calprotectin levels in the future may be used as potential markers of its presence, severity and progression of the diabetic peripheral neuropathy. Therapeutic strategies for blocking S100A9 and its activity are recently under development in inflammatory diseases. Therefore, Diabetic neuropathy is associated with increased serum level of calprotectin.

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العلاقة بين نسبة الكالبروتكتين والاعتلال العصبي الطرفى لمرضى السكري من النوع الثانى في عينة من المصريين

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الخلفية: اعتلال الأعصاب السكري هو حالة سريرية شائعة يلاحظها أطباء الرعاية الأولية في قسم العيادات الخارجية. يمكن أن يساعد التشخيص المبكر في تقليل معدلات الإصابة بالأمراض بين المرضى. يتم تشخيص الاعتلال العصبي السكري في المقام الأول على أساس الأعراض والعلامات العصبية جنبًا إلى جنب مع دراسة التوصيل العصبي.

الهدف من العمل: تقييم ما إذا كانت هناك علاقة بين مصل الكالبروتكتين والاعتلال العصبي المحيطي في عينة من مرضى السكري المصريين من النوع ٢.

الموضوعات والطرق: هذه الدراسة عبارة عن دراسة حالة وشواهد أجريت على ٦٠ شخصًا تتراوح أعمارهم بين ٤٥-٦٠ عامًا ، تم تجنيدهم من العيادات الخارجية لأمراض الغدد الصماء والتمثيل الغذائي في مستشفيات جامعة عين شمس ، مقسمة إلى ٣ مجموعات: (المجموعة الأولى): شملت ٢٠ طبيعيًا الأشخاص كمجموعة تحكم، (المجموعة الثانية): يشمل ٢٠ مريضًا مصابًا بمرض السكر تم تشخيصهم حديثًا خلال ٥ سنوات من عدم وجود اعتلال الأعصاب السكري ، (المجموعة الثالثة): من بينهم ٢٠ مريضًا مصابًا بمرض السكري تم تشخيصهم حديثًا خلال ٥ سنوات من الإصابة باعتلال الأعصاب السكري ، خلال الفترة من مايو إلى أكتوبر ٢٠٢٠.

النتائج: وجدت فروق ذات دلالة إحصائية عالية بين مجموعة التحكم ومجموعة المرضى بخصوص ارتفاع ضغط الدم مع (القيمة الاحتمالية = ٠.٠٠٠) ووجد فرق معتد به إحصائياً بين المجموعتين فيما يتعلق بمؤشر كتلة الجسم (القيمة الاحتمالية = ٠.٠٤٩) ، بينما لم يكن هناك فرق معتد به إحصائياً بين المجموعتين. مجموعتين بخصوص الجنس والعمر. وجد فرق ذو دلالة إحصائية عالية بين مجموعتين فيما يتعلق باختبار البروتين المتفاعل عالي الحساسية والكالبوتيكتين و الهيموجلوبين A1c و تحليل السكر اثناء الصيام و hrpp٢ مع (قيمة p ٠.٠٠٠).

الاستنتاج: نوصي بإجراء مزيد من الدراسات على المرضى الأكبر حجمًا وفترة المتابعة الأطول للتأكيد على استنتاجنا.

الكلمات المفتاحية: كالبروتكتين، داء السكري، التهاب الأعصاب، الاعتلال العصبي الطرفي