

# Fas-mediated apoptosis and peripheral polyneuropathy in type 2 diabetes mellitus

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## Objective

To evaluate the role of soluble Fas (sFas) and soluble Fas ligand (sFasL) in the pathogenesis of distal symmetrical polyneuropathy (DSPN) in patients with type 2 diabetes mellitus, and to analyze the relationship between these apoptotic markers with clinical parameters and electrophysiologic profile of DSPN, as well as with different diabetic factors among those patients.

## Patients and methods

The study included 60 Egyptians with type 2 diabetes mellitus. All patients were evaluated clinically for DSPN by using Michigan Neuropathy Screening Instrument. Electrophysiological diagnosis of DSPN was based on the criteria suggested by the European Standardized Telematic tool to Evaluate Electrodiagnostic Methods group. Diabetic patients were divided into two groups according to the electrophysiological findings: group A included patients with DSPN ( $N=42$ ), and group B included patients without DSPN ( $N=18$ ). The severity of DSPN among group A patients was assessed clinically using Toronto Clinical Neuropathy Score and electrophysiologically by the severity score proposed by Hidasi and colleagues. The study also included 30 healthy volunteers as a control group. Serum levels of sFas and sFasL were assessed in all the studied groups.

## Results

Serum level of sFas was significantly elevated in diabetic patients with DSPN compared with diabetics without DSPN and nondiabetic control ( $P=0.029$  and  $0.000$ ). Receiver operating characteristic (ROC) curve analysis detected that sFas was statistically significant in discriminating between diabetic patients with DSPN from those patients without DSPN with an accuracy of 66%. The cutoff point that has the highest sensitivity (61%) and specificity (62%) was 33.3 ng/ml. Serum level of sFas showed a positive significant correlation with the electrophysiological severity of DSPN ( $P=0.020$ ). Serum level of sFasL did not show statistically significant difference between all the studied groups.

## Conclusion

Fas-mediated apoptosis has an important role in the development of diabetic DSPN and is correlated with its electrophysiological severity.

## Keywords:

distal symmetrical polyneuropathy, soluble Fas ligand, soluble Fas

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## Introduction

Diabetes mellitus (DM) is a public disease with rapidly increasing rates worldwide [1]. The prevalence of type 2 DM is ~90% of people with diabetes around the world [2]. It is estimated that by the year 2030, Egypt will have at least 8.6 million adults with diabetes [3]. Diabetic peripheral neuropathy (DPN) is the most prevalent and troublesome complication in patients with DM [4,5]. Distal symmetrical polyneuropathy (DSPN) is the commonest, accounting for 75% of diabetic neuropathy [6]. Despite the advances in methods to control blood glucose level, the development of DPN is probably neither preventable nor controllable [7].

Discussing the pathogenesis of DPN includes various factors [8]. Although hyperglycemia is considered to be the major pathophysiological factor in the development of DPN, indeed the associated mechanisms need to be clarified. Apoptosis is one of these mechanisms that may play a crucial role in the pathogenesis of DPN [9]. Several apoptotic pathways have been described. One of those is the Fas system, which is believed to be the first initiator of apoptosis. It is composed of Fas ligand

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(FasL), a type II transmembrane glycoprotein, and Fas antigen (Fas/Apo-1/CD95), a type I transmembrane glycoprotein receptor. Cross-linking of Fas by FasL triggers apoptosis in various target cells [10]. Fas is widely expressed in the nervous system in both neurons and glial cells [11]. The increased production of soluble Fas (sFas) and soluble Fas ligand (sFasL) proteins indicates a sFas/sFasL interaction in patients with DPN [12]. The rise of sFas could be by overexpression of Fas receptor by peripheral nerve cells. Free oxygen radicals, caspase 8, and growth factors could all regulate Fas expression in nervous system [13].

Although the Fas-mediated apoptosis in DSPN has been discussed previously in the literature, its relation to different factors has to be studied more precisely. The aim of this study was to discover the Fas-mediated apoptosis in DSPN in type 2 diabetic patients and to correlate it with the clinical and electrophysiological severity of DSPN, as well as with different diabetic factors among those patients.

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### Patients and methods

The study included 60 Egyptians with type 2 DM according to the American Diabetes Association Guidelines [14]. Patients were recruited randomly from those attending the Outpatient Clinics of Physical Medicine, Rheumatology and Rehabilitation Department, Alexandria University Hospital. Patients who had peripheral neuropathy (PN) with principal causes other than diabetes such as liver or renal disease, toxic exposure, inflammatory diseases, and endocrine, metabolic, nutritional, or malignant disorders were excluded from the study. Patients with diabetic neuropathy with other forms than distal sensory, motor, or sensorimotor polyneuropathy were also excluded from the study.

All patients were evaluated clinically for DSPN by using Michigan Neuropathy Screening Instrument questionnaire and physical examination [15]. The standard electrophysiological study was done for all patients [16]. All procedures were carried out on Neuropack 2 electromyograph apparatus from Nihon Kohden (Tokyo, Japan). Electrophysiological diagnosis of DSPN was based on criteria for diagnosis of polyneuropathy suggested by the European Standardized Telematic tool to Evaluate Electrodiagnostic Methods group [17]. The same set of criteria was used to define the prevalent pathology among all patients with DSPN [17]. Diabetic patients were divided according to the electrophysiological

findings into two groups: group A included diabetic patients with DSPN ( $N=42$ ), and group B included diabetic patients without DSPN ( $N=18$ ). The study also included 30 healthy volunteers as a control group with matching age, sex, and general constitution. The severity of DSPN among group A patients was assessed clinically using Toronto Clinical Neuropathy Score (TCNS) [18]. In the TCNS, clinical severity of DPN was scored by a numerical value ranging from 0 to 19 points, which was calculated by summing symptom score points (the presence or absence of foot pain, numbness, tingling, weakness, ataxia, and upper limb symptoms), reflex score points (bilateral knee and ankle reflexes, each graded as absent, reduced, or normal), and physical examination score points (the presence or absence of pinprick, temperature, light touch, vibration, and position sense) [18]. Electrophysiological severity of DSPN was assessed according to the score proposed by Hidasi *et al.* [19], according to which the electrophysiologic parameters of eleven segments were measured (two segment of the motor fibers of ulnar and peroneal nerves, and one segment of the motor fibers of the median nerve and of the sensory fibers of the median, ulnar, and sural nerves). The distal latency of peroneal nerves and the conduction velocities and amplitudes of the motor and the sensory potentials were assessed. The quantitative electrophysiological abnormalities in each nerve were assessed using electrophysiologic nerve score for evaluation of the degree of the peripheral neuropathy in each nerve. Assessment of DM control was done using glycated hemoglobin (HbA1c) by immunoinhibition method [20]. Serum levels of sFas and sFasL were measured by enzyme-linked immunosorbent assay method [21].

Written consent, which was approved by the Alexandria Ethical Committee, was obtained from all patients after a full explanation of the study.

### Statistical methods

Data were analyzed using the statistical package for the social sciences (SPSS version 20; SPSS Inc., Chicago, Illinois, USA). The distributions of quantitative variables were tested for normality using Kolmogorov–Smirnov test. Normally distributed data were described using mean and SD, whereas non-normally distributed data were described using median and range. Qualitative data were described using number and percent. One-way analysis of variance test was used to compare parametric variables between more than two groups, followed by Games–Howell post-hoc test if significant, whereas Kruskal–Wallis test was used to compare nonparametric data, followed by pairwise

comparisons if significant. Comparison of quantitative normally distributed variables between two groups was done using independent samples *t*-test, and Mann–Whitney *U*-test was used for nonparametric data. Pearson  $\chi^2$  was used to compare 2x2 categorical variables, and Fisher's exact test when if more than 20% of cells had expected cell count less than 5. Spearman rank correlation test was used to correlate between two quantitative groups. In all statistical tests, level of significance of 0.05 was used, below which the results were considered to be statistically significant.

## Results

The mean age was 50.9±7.2 years in group A, 51.16±6.89 years in group B, and 51.06±7.74 years in group C. Most diabetic patients with and without DSPN were female (66.7 and 72.2%, respectively). The mean BMI was 31.3±5.7 kg/m<sup>2</sup> in group A, 30.4±6.14 kg/m<sup>2</sup> in group B, and 28.5±2.1 kg/m<sup>2</sup> in group C. Group A patients had a statistically significant longer duration of diabetes as compared with patients of group B (12.8±5.77 vs. 4.1±2.26 years, *t*=3.6 at *P*=0.001). The HbA1c level was significantly higher in group A patients than in group B patients (9.73±2.32 vs. 7.7±1.5% and *P*=0.001). Based on the results of TCNS, most of our patients had moderate and severe DSPN (76.3%), whereas 23.7% had mild DSPN. Results of the electrophysiologically assessed severity score constructed by Hidasi *et al.* [19] revealed that 67% of group A patients had moderate and severe DSPN, whereas 33% had mild DSPN. Axonal degeneration was the most prevalent pathology among patients with DSPN included in the study (60%), whereas only 9% of the patients had demyelinating pathology, 19% had mixed pathology, and the remaining 12% of the patients were considered neuropathic and could not be classified into any of the previous categories. There were significant positive correlations between both diabetes duration and HbA1c level with clinical

severity, assessed by TCNS, and electrophysiologic severity of DSPN (*P*<0.000; Table 1).

Serum level of sFas was significantly elevated in group A patients as compared with groups B and C (*P*=0.029 and 0.000, respectively). sFas serum level was significantly high in group B when compared with group C (*P*=0.000; Table 2). On the contrary, the mean value of sFasL serum levels did not show any statistically significant difference between all the studied groups (Table 2). The receiver operating characteristic (ROC) curve analysis of sFas was statistically significant in discriminating between diabetic patients with DSPN from those patients without DSPN with an accuracy of 66%. The cutoff point which has the highest sensitivity (61%) and specificity (62%) was 33.3 ng/ml (Fig. 1). Serum level of sFas showed a positive significant correlation with the electrophysiological severity of DSPN ( $r_s=0.359$  at *P*=0.020). On the contrary, its level lacked significant correlation with clinical severity assessed by TCNS (Table 3). In addition, there were no significant correlations between serum levels of sFasL with either clinical or electrophysiological severity of DSPN (Table 3). Serum level of sFas showed a significant positive correlation with HbA1c level among group A patients ( $r_s=0.325$  at

**Table 1 Correlation between clinical and electrophysiological severity of distal symmetrical polyneuropathy with diabetes duration, and glycated hemoglobin, among group A patients**

Group A (DM +DSPN)	Electrophysiologically assessed severity score	Toronto
DM duration (years)	$r_s=0.592$	$r_s=0.745$
	<i>P</i> =0.000*	<i>P</i> =0.000*
HbA1c%	$r_s=0.514$	$r_s=0.553$
	<i>P</i> =0.001*	<i>P</i> =0.000*

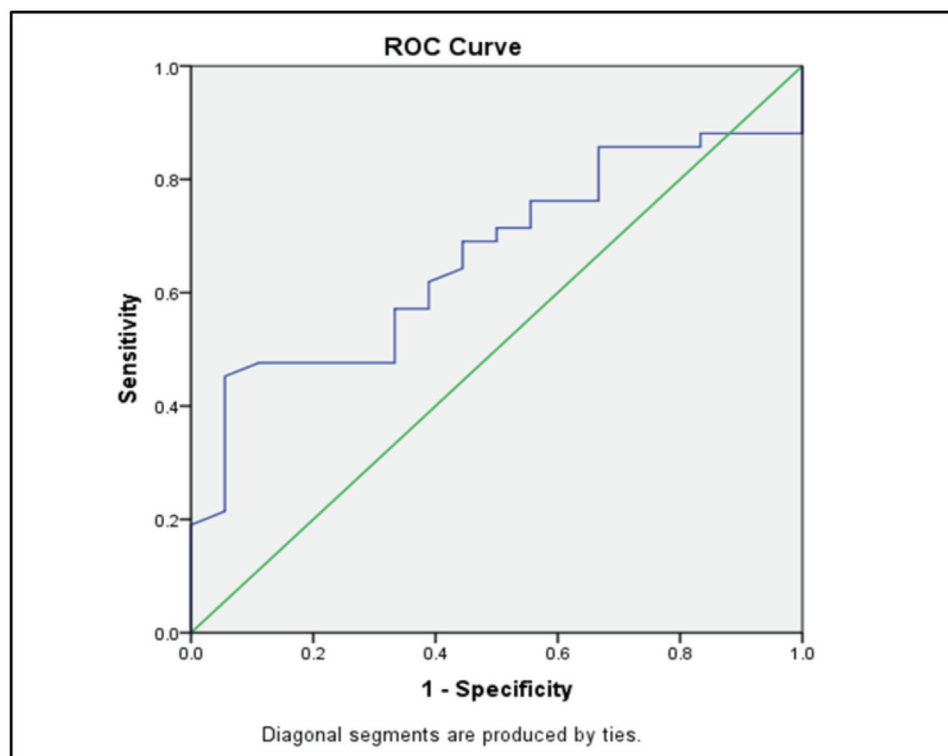
DM, diabetes mellitus; DSPN, distal symmetrical polyneuropathy; HbA1c, glycated hemoglobin;  $r_s$ , Spearman's  $\rho$  test. \**P*≤0.05, statistically significant.

**Table 2 Analysis of variance of serum levels of soluble Fas and soluble Fas ligand Serum level among the studied groups**

	Group A DM +PN (n=42)	Group B DM-PN (n=18)	Group C control (n=30)	<i>F</i>	<i>P</i>	Post hoc	<i>P</i>
						In-between group comparison	
sFas (ng/ml)							
Minimum–maximum	10.75–69.12	17.31–56.74	3.91–22.5	53	0.001*	A and BA and CB and C	0.029*0.000*0.000*
Mean±SD	40.96±17.7	31.12±10.73	13.14±6.7				
sFasL (ng/ml)							
Minimum–maximum	0.04–0.2	0.03–0.17	0.04–0.17	0.054	0.94		
Mean±SD	0.10±0.045	0.098±0.046	0.097±0.042				

DM, diabetes mellitus; PN, peripheral neuropathy; *F*, one-way analysis of variance post hoc Games–Howell test; sFas, soluble Fas; sFasL, soluble Fas ligand. \**P*≤0.05, statistically significant.

Fig. 1



ROC curve of soluble Fas serum level.

**Table 3 Correlation between clinical and electrophysiological severities of distal symmetrical polyneuropathy with soluble Fas and soluble Fas ligand**

Group A	Electrophysiologically-assessed severity score		TCNS	
	$r_s$	$P$	$r_s$	$P$
sFas	0.359	0.020*	0.194	0.218
sFasL	-0.189	0.230	0.252	0.107

$r_s$ , Spearman's  $\rho$  test; sFas, soluble Fas; sFasL; soluble Fas ligand; TCNS, Toronto Clinical Neuropathy Score. \* $P \leq 0.05$ , statistically significant.

**Table 4 Correlation between serum level of soluble Fas with diabetes duration and glycated hemoglobin among group A patients**

Group A (DM+DSPN)	DM duration (years)	HbA1c%
sFas	$r_s=0.190$	$r_s=0.325$
$P$	0.228	0.035*

DM, diabetes mellitus; DSPN, distal symmetrical polyneuropathy; HbA1c, glycated hemoglobin;  $r_s$ , Spearman's  $\rho$  test; sFas, soluble Fas. \* $P \leq 0.05$ , statistically significant.

$P=0.035$ ); however, it did not show significant correlation with diabetes duration (Table 4).

## Discussion

The role of Fas-mediated apoptosis in the development of DSPN was suggested previously in the literature. The aim of this study was to evaluate this role and further

analyze the possible connection between this pathway and both clinical parameters and the electrophysiological profile of DSPN in patients with type 2 DM, as well as with different diabetic factors.

In this study, diabetic patients with DSPN had statistically significant longer diabetes duration, and higher HbA1c level than those without DSPN. These results run in accordance with many of the DSPN prevalence studies carried out across the world, in which poor glycemic control and longer duration of diabetes were identified as risk factors for DPN [22–24]. Moreover, there were significant positive correlations between both diabetes duration and HbA1c level with clinical severity, assessed by TCNS, and electrophysiologic severity of DSPN ( $P < 0.000$ ). These detected correlation adds more importance on the duration of diabetic illness and the glycemic control over years for the development of DSPN. Similar results were reported by Kamel *et al.* [25] and Kovac *et al.* [26].

This study revealed a significant increase in the mean value of sFas serum level in diabetic patients with DSPN compared with diabetic patients without DSPN ( $P=0.028$ ) and control group ( $P=0.000$ ). Increased serum concentrations of sFas are considered to reflect activation of the Fas/FasL system, which is an important inducer of apoptosis. Moreover, the significant increase

of sFas serum level in diabetic peripheral neuropathy patients indicates that Fas-mediated apoptosis may have a role in the etiopathogenesis of DSPN. Our findings were similar to those reported by previous studies [12,27]. Furthermore, we demonstrated in our study by ROC curve analysis that sFas was statistically significant in discriminating between diabetic patients with DSPN from those patients without DSPN, with an accuracy of 66%. The cutoff point that has the highest sensitivity (61%) and specificity (62%) was 33.3 ng/ml. This result suggests the use of serum sFas level as a laboratory marker in the detection of DSPN. The present study showed a positive significant correlation between serum level of sFas and electrophysiological assessed severity score ( $P=0.020$ ), supporting the involvement of sFas in the advancement of DPN [13]. Our findings agree with the findings of Zakareia [27] and Al-Rouq [12], who reported a significant correlation between serum level of sFas with deterioration of different electrophysiological parameters. On the contrary, we found insignificant correlation between sFas serum level and clinical severity of DSPN assessed by TCNS ( $P=0.218$ ). This discrepancy between clinical findings and electrophysiological results with the serum sFas could be explained by the symptomatic part of the TCNS making its total score partially subjective compared with the accurate results of NCS. To the best of our knowledge, no previous study assessed the correlation between serum level of sFas and the clinical severity.

Despite the significant difference of serum level of sFas we found between our studied groups, the mean value of sFasL serum levels did not show any statistically significant difference between all the studied groups ( $P=0.94$ ), running with previously reported studies [12,21], which was explained by a-sFasL might be cross-linked with Fas or sFas, and consequently, its free soluble form not available in the serum [21]. The antibodies used for detection of sFasL might not recognize the sFasL epitope present in the sera from diabetic patients and normal controls. Criticism about the detection of cell surface FasL suggests that antibodies used to recognize FasL were not always appropriate for the detection of this protein [28]. c-Fas-mediated apoptosis might be independent from the Fas-FasL interaction, as observed in hepatocytes where it has been reported that bile salts induce apoptosis via direct activation of Fas [29]. Accordingly, no significant correlation between serum level of sFasL with neither clinical or electrophysiological severity could be found in this study as its level was normal in the three studied groups ( $P=0.107$  and  $0.230$ , respectively).

Contrary to our results, Mondal *et al.* [30] reported highly significant decrease in sFasL level in patients with DSPN compared with diabetic patients without DSPN and healthy controls. Moreover, they reported a significant negative correlation between serum level of sFasL and clinical severity of DSPN assessed using vibration perception threshold. They suggested that the enhanced apoptotic activity in DSPN may be owing to increased interaction between upregulated sFas with overexpressed membrane-bound FasL at conserved cleavage site with a lesser cleavage to generate sFasL, which may explain the decrease of serum level of sFasL in patients with DSPN.

In this study, serum level of sFas showed a significant positive correlation with HbA1c level among diabetic patients with DSPN ( $r_s=0.325$  at  $P=0.035$ ); however, it did not show significant correlation with diabetes duration. Similar findings were reported by Hamid *et al.* [31]. Increased glucose concentration was reported to induce apoptosis directly through upregulation of Fas receptors [32]. However, longer diabetes duration does not always reflect uncontrolled hyperglycemia through all this duration. This may explain the absence of significant correlation between serum level of sFas and diabetes duration. In addition, serum level of sFas was significantly elevated in diabetic patients with DSPN, and this duration represents the duration of type 2 DM not the duration of DSPN.

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## Conclusion

Fas-mediated apoptosis has an important role in development of diabetic DSPN and is correlated with its electrophysiological severity.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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