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Beta-endorphin levels in both painful and painless diabetic peripheral neuropathy and its relations to pain characters and severity

ABSTRACT

Introduction. In the peripheral nervous system (PNS), β-endorphins produce analgesia by binding to opioid receptors (particularly of the mu subtype) at both pre- and post-synaptic nerve terminals, primarily exerting their effect through presynaptic binding.

Aim was to study serum β-endorphin levels in diabetic patients with and without diabetic peripheral neuropathy and its relations to characters and severity of pain in patients with painful diabetic peripheral neuropathy.

Material and methods. The study was a case control study including 88 participants; 73 diabetics and 15 age and sex matched healthy subjects. For all subjects, levels of HbA_{1c}, serum creatinine, total cholesterol, triglycerides, HDL and LDL as well as serum levels of β-endorphin were measured. Pain severity was detected by using visual analogue pain scale.

Results. Serum β-endorphin shows no significant difference between diabetic neuropathic, diabetic non neuropathic and control groups ($p = 0.275$). Serum β-endorphin shows negative correlation with age ($p = 0.049$) and HbA_{1c} ($p = 0.048$). While it was not correlated with pain severity ($p = 0.371$), NDS: total score ($p = 0.803$), BMI ($p = 0.801$), serum creatinine ($p = 0.074$) or DM duration ($p = 0.607$). Serum β-endorphin shows no significant difference between painful and painless neuropathy subgroups ($p = 0.701$).

Conclusion. In our study serum β-endorphin levels showed no significant difference between patients with painless diabetic peripheral neuropathy and those with painful diabetic peripheral neuropathy with different characters of pain. Also, serum β-endorphin levels was not correlated with pain severity. (Clin Diabetol 2017; 6, 5: 159–171)

Key words: endorphin, diabetes, neuropathy

Introduction

Diabetic peripheral neuropathy (DPN) is a common, distressing and debilitating complication that develops in up to 30–50% of diabetic patients. Distal symmetric polyneuropathy (DSP) is the commonest type of neuropathy complicating diabetes [1]. Pain is the most agonizing symptom of DPN [2].

The pathogenesis of DPN is not completely understood, however vascular and metabolic factors are incriminated [3].

Magnetic resonance imaging (MRI) detected shrinkage of the spinal cord in patients with DPN [4], and also dysregulations of the somatosensory afferent pathways, thalamic neuronal dysfunction, and perfusion abnormalities, which reports a significant involvement of the CNS in patients with DPN [3].

Beta-endorphins are neuropeptides that have morphine like effects [5]. They are synthesized and stored in the anterior pituitary gland from their precursor protein ProOpioMelanoCortin (POMC), that is synthesized in response to a signal from the hypothalamus;

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which is corticotrophic-releasing hormone (CRH), released in response to physiologic stress as pain, and postoperative [6].

Beta-endorphins produce analgesia in the peripheral nervous system (PNS), by binding to opioid receptors (particularly of the mu subtype) at both pre- and post-synaptic nerve terminals, resulting in inhibition of the release of tachykinins, particularly substance P, preventing the transmission of pain [7].

In the CNS, beta-endorphins similarly bind mu-opioid receptors and exert their primary action at presynaptic nerve terminals, they exert their analgesic effect by inhibiting the release of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, resulting in excess production of dopamine, which is associated with pleasure [8],and patients with chronic neuropathic pain were found to have low levels of β-endorphin in the cerebrospinal fluid (CSF),which indicates a defective down modulation of pain in chronic neuropathic pain [9].

The aim of this work was to study serum β-endorphin levels in diabetic patients with and without diabetic peripheral neuropathy and to study the possible differences between patients with painful and painless diabetic peripheral neuropathy. We also aimed to study serum β-endorphin levels relations to characters and severity of pain in patients with painful diabetic peripheral neuropathy.

Material and methods

The study included 88 participants, 73 of them were diabetics (cases) recruited from Mansoura Specialized Medical Hospital (diabetes outpatient clinics) from February 2015 to December 2015, and 15 participants were age and sex matched healthy subjects (control group). Diabetic state was confirmed or excluded according to the revised American Diabetes Association criteria [10]. Ethical approval was obtained and each subject gave a written informed consent. The patients were divided into three groups Group (1); 57 diabetic subject with DPN which were further subdivided into 2 subgroups according to presence or abscence of pain. Visual analogue pain scale was used to assess the severity of pain. Group (2); 16 diabetic subjects without peripheral neuropathy. Group (3); control group consists of 15 healthy subjects.

Diagnosis of DPN was based on modified neuropathy disability score. We use score $\geq$ 6 as a cut point for diagnosis of DPN. Presence of pain in the legs was known from history and its severity was graded according to visual analogue pain scale. The following findings is considered as exclusion criteria: patients with serum creatinine > 1.4 mg/dL, liver cell failure, neuropathy due to causes other than diabetes mellitus, CNS disorders.

HbA_{1c} %, serum creatinine, total cholesterol, triglycerides, HDL and LDL levels were measured. Serum β-endorphin was assayed by ELISA supplied by Elabscience (USA). The study design was case control study.

Statistical analysis

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 22.0 for Windows. Spearman correlation coefficient® test was used correlating different parameters. P value < 0.05 was considered statistically significant in all analyses.

Results

The study included 57 diabetic subjects with diabetic peripheral neuropathy, 16 diabetic subjects without peripheral nerve dysfunction and 15 healthy control subjects.

The mean age of patients in the neuropathic group (53.91 ± 5.53 years) was not significantly different from either the diabetic or control groups (50.37 ± 7.56 and 50.93 ± 5.65 years, respectively) (p = 0.053).

Male and female number and percentage ratio in the diabetic neuropathic group was 26 (45.6%)/31 (54.4%), in the diabetic non neuropathic group 8 (50%)/8 (50%) and in the control group 8 (53.3%)/7 (46.7%) in male and feme respectively. The difference between all groups regarding gender was statistically insignificant (p = 0.850).

There was no significant difference between diabetic neuropathic, diabetic non neuropathic and control groups as regard body mass index (p = 0.489). BMI in the studied groups was [32.29 (28.1–38.3), 35.62 (27.675––40.8) and 31.88 (25.95–35.78) kg/m^2, respectively].

Systolic BP wasn't significantly different (p < 0.084) between diabetic neuropathic, diabetic non neuropathic and control groups [130 (120–140), 120 (120–130) and 120 (110–130) mm Hg, respectively], also there was no significant difference regarding diastolic BP between the studied groups [80 (70–90), 70 (70–80) and 80 (70–80) mm Hg respectively] (p < 0.336).

All subjects of the control group were normotensive, while most of the patients in the diabetic neuropathic and diabetic non neuropathic groups were hypertensive. There were 40 hypertensive patients (70.2%) in the diabetic neuropathic group, and 9 patients (56.2%) in the diabetic non neuropathic group. There was no significant difference between the two groups regarding the number of patients with hypertension (p = 0.295).The duration of hypertension was significantly longer in the diabetic neuropathic versus diabetic non neuropathic groups [5 (0–15) and 0.5 (0–4) years respectively] (p < 0.001).

There was no significant difference between diabetic neuropathic and diabetic non neuropathic groups as regard the anti-hypertensive drugs (p = 0.028). In diabetic neuropathic and diabetic non neuropathic groups there were following number of patients receiving ACEIs: 14 (24.6%) and 6 (37.5%) respectively, patients receiving BBs: 2 (3.5%) and 1 (6.3%) respectively, patients receiving CCBs: 3 (5.3%) and 1 (6.3%) respectively and patients receiving combinations of more than one antihypertensive drugs: 21 (36.9%) and 1 (6.3%) respectively.

Duration of diabetes was significantly longer in diabetic neuropathic group than in diabetic non neuropathic group [14 (8.5–20) *versus* 4 (1.125–9.5) years, respectively] (p < 0.001). Drug therapy for DM shows no significant difference among both diabetic neuropathic and diabetic non neuropathic groups (p = 0.058). Insulin was used by 19.3% (11 patients) of the diabetic neuropathic group *versus* 50% (8 patients) of the diabetic non neuropathic group, insulin + metformin was used by 54.4% (31 patients) of the diabetic neuropathic group *versus* 0% (0 patients) of the diabetic non neuropathic group, SU was used by 14% (11 patients) of the diabetic neuropathic group versus 25% (4 patients) of the diabetic non neuropathic group and SU + metformin was used by 14% (11 patients) of the diabetic neuropathic group *versus* 25% (4 patients) of the diabetic non neuropathic group.

Painful and painless neuropathy subgroups were matched for age (53.709 ± 6.414, 54.153 ± 4.378 years respectively) (p = 0.766) and sex; in the painful neuropathy subgroup [11 males (35.5%) and 20 females (64.5%)] and in the painless neuropathy subgroup [15 males (57.7%) and 11 females (42.3%)] (p = 0.094). BMI shows no significant difference between both subgroups (34.69 ± 7.03 and 31.79 ± 6.15 kg/m^2 respectively) (p = 0.107).

Table 1. Demographic and clinical data of the studied groups

Data		Groups			p
		Diabetic neuropathy present	Diabetic neuropathy absent	Control	
Age (years)	Mean	53.912	50.375	50.933	0.053
	± SD	5.536	7.562	5.65	
Gender (N/%)	Male	26 (45.6%)	8 (50%)	8 (53.3%)	0.850
	Female	31 (54.4%)	8 (50%)	7 (46.7%)	
BMI [kg/m^2]	Median	32.29	35.62	31.88	0.489
	Range	28.1–38.3	27.675–40.8	25.95–35.78	
SBP [mm Hg]	Median	130	120	120	0.084
	Range	120–140	120–130	110–130	
DBP [mm Hg]	Median	80	70	80	0.336
	Range	70–90	70–80	70–80	
Hypertension (N/%)	Yes	40 (70.2%)	9 (56.2%)		< 0.295
	No	17 (29.8%)	7 (43.8%)		
Hypertension duration	Median	5	0.5		< 0.001
(years)	Range	0–15	0–4		
Hypertension treatment	ACEIs	14 (24.6%)	6 (37.5%)		0.028
(N/%)	BBs	2 (3.5%)	1 (6.3%)		
	CCBs	3 (5.3%)	1 (6.3%)		
	Combination	21 (36.9%)	1 (6.3%)		
	No	17 (29.8%)	7 (43.8%)		
DM duration (years)	Median	14	4		< 0.001
	Range	8.5–20	1.125–9.5		
DM treatment (N/%)	SU	8 (14%)	4 (25%)		< 0.058
	Insulin	11 (19.3%)	8 (50%)		
	Insulin + metformin	31 (54.4%)	0 (0%)		
	SU + metformin	7 (12.3%)	4 (25%)		

P — probability; SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACEIs — angiotensine converting enzyme inhibitors; BBs — beta-blockers; CCBs — calcium channel blockers; SU — sulphonylurea

Table 2. Demographic and clinical data of the neuropathic group

Data		Subgroups		p
		Painful neuropathy	Painless neuropathy	
Age (years)	Mean	53.709	54.153	0.766
	± SD	6.414	4.378	
Gender (N/%)	Male	11 (35.5%)	15 (57.7%)	0.094
	Female	20 (64.5%)	11 (42.3%)	
BMI [kg/m^2]	Mean	34.69	31.79	0.107
	± SD	7.03	6.15	
SBP [mm Hg]	Mean	125.16	136.5	0.026
	± SD	15.464	19.815	
DBP [mm Hg]	Mean	77.42	83.46	0.049
	± SD	10.318	11.981	
Hypertension (N/%)	Yes	21 (67.7%)	19 (73.1%)	0.774
	No	10 (32.3%)	7 (26.9%)	
Hypertension duration (years)	Median	2	6	0.411
	Range	0–20	0–21	
Hypertension treatment (N/%)	ACEIs	8 (25.8%)	6 (23.1%)	0.853
	BBs	1 (3.2%)	1 (3.8%)	
	CCBs	2 (6.5%)	1 (3.8%)	
	Combination	10 (32.3%)	11 (42.3%)	
	No	10 (32.3%)	7 (26.9%)	
DM duration (years)	Median	15	11.5	0.146
	Range	2–25	3.5–25	
DM treatment (N/%)	SU	3 (9.7%)	5 (19.2%)	0.443
	Insulin	17 (54.8 %)	14 (53.5%)	
	Insulin + metformin	8 (25.8%)	3 (11.5%)	
	SU + metformin	3 (9.7%)	4 (15.4%)	

P — probability; SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACEIs — angiotensine converting enzyme inhibitors; BBs — beta-blockers; CCBs — calcium channel blockers; SU — sulphonylurea

Table 3. Clinical characteristics of pain in the painful neuropathy subgroup

Data		(N/%)
Pain character (N/%)	Pricking	3 (9.7%)
	Deep aching	4 (12.9%)
	Coldness	2 (6.5%)
	Tingling	20 (64.5%)
	Burning	2 (6.5%)
Pain severity (VAS)	Median	7
	Range	5–8
Pain therapy	No treatment	26 (83.9%)
	Carbamazepine	2 (6.5%)
	Gabapentin	2 (6.5%)
	Pregabalin	1 (3.2%)
Other pains	No	20 (64.5%)
	OA	8 (25.8%)
	Frozen shoulder	1 (3.2%)
	Trauma	0 (0%)
	Back pain	2 (6.5%)

VAS — visual analogue scale; OA — osteoarthritis

Table 4. NDS of the studied groups

Data		Groups			p
		Diabetic neuropathy present	Diabetic neuropathy absent	Control	
NDS: total score	Median	8	2	0	< 0.001
	Range	6–10	0–4	0–0	
Vibration perception (RT)	Median	1	0	0	< 0.001
	Range	1–1	0–1	0–0	
Vibration perception (LT)	Median	1	0	0	< 0.001
	Range	1–1	0–1	0–0	
Temperature perception (RT)	Median	1	0	0	< 0.001
	Range	0–1	0–0	0–0	
Temperature perception (LT)	Median	1	0	0	< 0.001
	Range	0–1	0–0	0–0	
Pin prick (RT)	Median	1	0	0	< 0.001
	Range	1–1	0–0	0–0	
Pin prick (LT)	Median	1	0	0	< 0.001
	Range	1–1	0–0	0–0	
Achilles reflex (RT)	Median	2	0	0	< 0.001
	Range	1–2	0–0	0–0	
Achilles reflex (LT)	Median	2	0	0	< 0.001
	Range	2–2	0–0	0–0	

P — probability; NDS — neuropathy disability score; RT — right foot; LT — left foot

Table 5. NDS of the neuropathic group

Data		Subgroups		p
		Painful neuropathy	Painless neuropathy	
NDS: total score	Mean	8.48	8.15	0.440
	± SD	1.568	1.617	
Vibration perception (RT)	Mean	0.97	0.96	0.902
	± SD	0.180	0.196	
Vibration perception (LT)	Mean	0.97	0.85	0.133
	± SD	0.180	0.368	
Temperature perception (RT)	Median	1	1	0.312
	Range	0–1	0–1	
Temperature perception (LT)	Median	1	1	0.437
	Range	0–1	0–1	
Pin prick (RT)	Median	1	1	0.437
	Range	0–1	0–1	
Pin prick (LT)	Median	1	1	0.054
	Range	0–1	0–1	
Achilles reflex (RT)	Mean	1.71	1.81	0.475
	± SD	0.529	0.491	
Achilles reflex (LT)	Mean	1.71	1.88	0.182
	± SD	0.588	0.326	

P — probability; SD — standard deviation; NDS — neuropathy disability score; RT — right; foot; LT — left foot

Table 6. Laboratory data of the studied groups

Data		Groups			p
		Diabetic neuropathy present	Diabetic neuropathy absent	Control	
β-endorphin [pg/mL]	Median	293.00	262.50	307.00	0.275
	Range	26.00–1000.00	14.00–700.00	106.00–1000.00	
HbA_{1c} (%)	Mean	8.700	8.206	5.043	< 0.001
	± SD	1.760	1.998	0.397	
Serum creatinine [mg/dL]	Mean	0.815	0.762	0.713	0.103
	± SD	0.179	0.150	0.164	
HDL-cholesterol [mg/dL]	Median	37.00	36.50	37.00	0.998
	Range	25.00–76.00	29.00–103.00	32.00–52.00	
Total cholesterol [mg/dL]	Median	215.00	244.50	218.00	0.453
	Range	118.00–491.00	128.00–376.00	172.00–359.00	
Triglycerides [mg/dL]	Median	155.00	132.50	130.00	0.769
	Range	66.00–546.00	73.00–232.00	71.00–238.00	
LDL-cholesterol [mg/dL]	Median	150.00	165.00	149.60	0.341
	Range	52.00–399.00	87.40–307.00	104.00–275.00	

P — probability; SD — standard deviation; HbA_{1c} — glycosylated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein

Table 7. Laboratory data of the neuropathic group

Data		Subgroups		p
		Painful neuropathy	Painless neuropathy	
β-endorphin [pg/mL]	Median	200	303	0.701
	Range	26–1000	39–800	
HbA_{1c} (%)	Mean	9.061	8.269	0.091
	± SD	1.904	1.493	
Serum creatinine [mg/dL]	Mean	0.787	0.850	0.196
	± SD	0.164	0.192	
HDL-cholesterol [mg/dL]	Mean	40.548	38.461	0.466
	± SD	10.859	10.485	
Total cholesterol [mg/dL]	Mean	240.483	214.080	0.196
	± SD	74.955	76.652	
Triglycerides [mg/dL]	Median	154	158	0.749
	Range	69–277	66–546	
LDL-cholesterol [mg/dL]	Median	174	129.7	0.062
	Range	72–310	52–399	

P — probability; SD — standard deviation; HbA_{1c} — glycosylated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein

Table 8. Serum β-endorphin in patients using treatment for neuropathic pain *versus* non-users

Data	Pain treatment				p
	Non users		Users		
	Median	Range	Median	Range	
β-endorphin [pg/mL]	307	14–1000	104	53–451	0.117

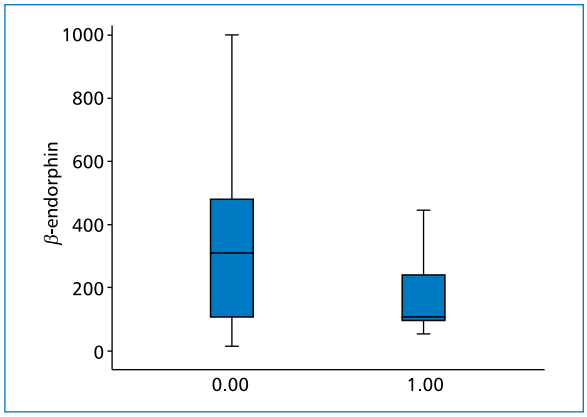

Figure 1. 0.00: patients not using treatment for neuropathic pain; 1.00: patients using treatment for neuropathic pain

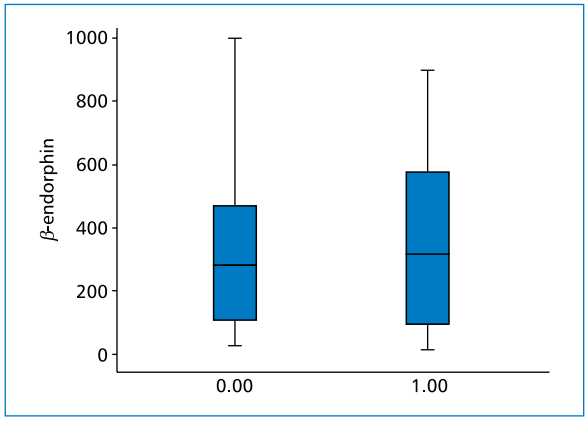

Figure 2. 0.00: patients without associated pain; 1.00: patients with associated pain

Table 9. Serum β-endorphin in patients presenting with pain *versus* those without pain

Data	Associated pain				p
	Absent		Present		
	Median	Range	Median	Range	
β-endorphin [pg/mL]	283	26–1000	315	14–950	0.974

Table 10. Serum β-endorphin in patients having different characters of pain

Data		Character of pain					p
		Pricking	Deep aching	Coldness	Numbness	Burning	
β-endorphin [pg/ml]	Median	104	142	60.5	330.5	436	0.176
	Range	49–680	51.7–399	26–95	53.1–1000	397–475	

SBP and DBP were significantly lower in the painful than painless neuropathy subgroup, (125.16 ± 15.46 and 136.5 ± 19.81 mm Hg) (p = 0.026) and (77.42 ± 10.31 and 83.46 ± 11.98 mm Hg) (p = 0.049) respectively. History of hypertension (HTN) wasn't significantly different between both subgroups, in painful neuropathy subgroup; 21 patients (67.7%) were hypertensive while in painless neuropathy subgroup; 19 patients (73.1%) were hypertensive (p = 0.774). As regard duration of HTN, there was no significant difference between painful and painless neuropathy subgroups [2 (0–20) and 6 (0–21) years respectively] (p = 0.411). Treatment of HTN also shows no significant difference; in painful neuropathy subgroup ACEIs were used in 8 patients (25.8%), BBs in 1 patient (3.2%), CCBs in 2 patients (6.5%) and combinations of more than one antihypertensive in 10 patients (32.3%) while in painless neuropathy subgroup ACEIs were used in 6 patients (23.1%), BBs in 1 patient (3.8%), CCBs in 1 patient (3.8%) and combinations of more than one antihypertensive in 11 patients (42.3%) (p = 0.853).

DM duration shows no significant difference between painful and painless neuropathy subgroups [15 (2–25) and 11.5 (3.5–25) years respectively] (p = 0.146). There was no significant difference regarding DM treatment, in painful neuropathy subgroup; SU were used in 9.7% (3 patients), insulin was used in 54.8% (17 patients), insulin + metformin were used in 25.8% (8 patients) and SU + metformin were used in 9.7% (3 patients) while in painless neuropathy subgroup; SU was used in 19.2% (5 patients), insulin was used in 53.5% (14 patients), insulin + metformin were used in 11.5% (3 patients) and SU + metformin were used in 15.4% (4 patients) (p = 0.443).

The most prevalent pain character was tingling (64.5%), other were deep aching pain (12.9%), pricking pain (9.7%), coldness (6.5%) and burning (6.5%). In addition, pain severity on VAS ranges from 5 to 8. 83.9% of neuropathic patient were not using pain-controlling medications and 64.5%. had no other causes of chronic pain.

The neuropathy disability score (NDS) was used to diagnose peripheral neuropathy, total score ≥ 6

Table 11. Serum β-endorphin [pg/mL] in different modalities of nerve disability

	Modalities of nerve disability			p
	Vibration perception (RT)			
	Intact	Lost		
Median	289	304.5		0.759
Range	14–1000	26–1000		
	Vibration perception (LT)			
	Intact	Lost		
Median	307	284		0.817
Range	14–1000	26–1000		
	Temperature perception (RT)			
	Intact	Lost		
Median	284	316		0.409
Range	14–1000	39–1000		
	Temperature perception (LT)			
	Intact	Lost		
Median	284	316		0.318
Range	14–1000	51.7–1000		
	Pin prick (RT)			
	Intact	Lost		
Median	301.5	239		0.453
Range	14–1000	39–1000		
	Pin prick (LT)			
	Intact	Lost		
Median	307	232		0.293
Range	14–1000	39–1000		
	Achillis reflex (RT)			
	Intact	Intact with reinforcement	Lost	
Median	284	313	304.5	0.731
Range	14–1000	39–1000	26–900	
	Achillis reflex (LT)			
	Intact	Intact with reinforcement	Lost	
Median	296	313	268.5	0.952
Range	14–1000	44–1000	26–900	

p — probability; test used — Mann-Whitney U

was diagnostic for peripheral neuropathy. Total score was significantly higher in diabetic neuropathic versus diabetic non neuropathic and control groups; [8 (6–10) *versus* 2 (0–4) and 0 (0–0%) respectively] ($p < 0.001$).

Vibration perception threshold score was significantly higher in diabetic neuropathic versus diabetic non neuropathic and control groups; at the right foot [1 (1–1) *versus* 0 (0–1) and 0 (0–0) respectively] ($p < 0.001$), at the left foot it was the same respectively ($p < 0.001$). Temperature perception score also was significantly higher in diabetic neuropathic *versus* diabetic non neuropathic and control groups; at the right foot [1 (0–1) *versus* 0 (0–0) and 0 (0–0) respectively] ($p < 0.001$), at the left foot it was the same respectively ($p < 0.001$).

Pin prick sensation score was significantly higher in diabetic neuropathic versus diabetic non neuropathic and control groups; at the right foot, [1 (1–1) *versus* 0 (0–0) and 0 (0–0) respectively] ($p < 0.001$), at the left foot it was the same respectively ($p < 0.001$). Achillis reflex score was significantly higher in diabetic neuropathic *versus* diabetic non neuropathic and control groups; at the right foot, [2 (1–2) *versus* 0 (0–0) and 0 (0–0) respectively] ($p < 0.001$), at the left foot [2 (2–2) *versus* 0 (0–0) and 0 (0–0) respectively] ($p < 0.001$).

In painful and painless neuropathy subgroups, NDS: total score showed no significant difference [8.48 ± 1.56 and 8.15 ± 1.61 respectively] ($p = 0.440$). With regard to vibration perception threshold score

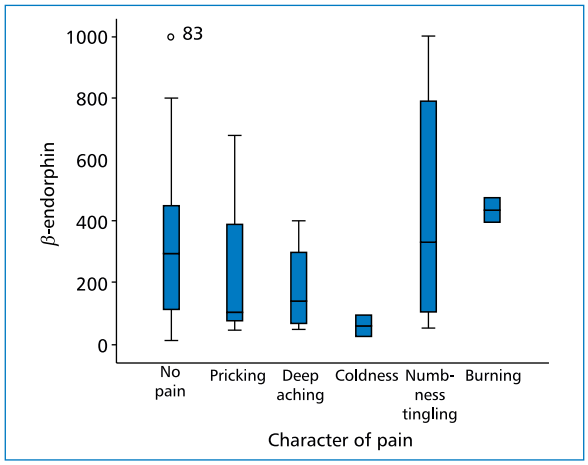

Figure 3. Serum levels of β-endorphins according to type of pain

there was no significant difference between painful and painless neuropathy subgroups; at the right foot it was [0.97 ± 0.18 and 0.96 ± 0.196 respectively] (p = 0.902), at the left foot it was [0.97 ± 0.18 and 0.85 ± 0.368 respectively] (p = 0.133).

No significant difference between painful and painless neuropathy subgroups regarding temperature perception score; at the right foot [1 (0–1) and 1 (0–1) respectively] (p = 0.312), at the left foot [1 (0–1) and 1 (0–1) respectively] (p = 0.437). Pin prick sensation score showed no significant difference between painful and painless neuropathy subgroups; at the right foot [1 (0–1) and 1 (0–1) respectively] (p = 0.437), at the left foot [1 (0–1) and 1 (0–1) respectively] (p = 0.054). Achillis reflex score showed no significant difference between painful and painless neuropathy subgroups; at the right foot [1.71 ± 0.529 and 1.81 ± 0.491 respectively] (p = 0.475), at the left foot [1.71 ± 0.588 and 1.88 ± 0.326 respectively] (p = 0.182).

HbA_{1c} levels were higher in the diabetic neuropathic and diabetic non neuropathic groups in comparison to the control group (8.700 ± 1.760, 8.206 ± 1.998 and 5.043 ± 0.397% respectively) (p < 0.001). Serum creatinine levels showed no significant difference among diabetic neuropathic, diabetic non neuropathic and control groups (0.815 ± 0.179, 0.762 ± 0.150, 0.713 ± 0.164 mg/dL respectively) (p = 0.103).

Regarding serum HDL-cholesterol and serum LDL-cholesterol levels there was no significant difference between diabetic neuropathic, diabetic non neuropathic and control groups [37 (25–76), 35.5 (29–103) and 37 (32–52) mg/dL respectively] (p = 0.998) and [150 (52–399), 165 (87.40–307) and 149.60 (104–275) mg/dL respectively] (p = 0.341).

Table 12. Correlation between serum β-endorphin and other variables

Data	β-endorphin	
	r	P
Severity of pain	–0.097	0.371
NDS: total score	0.027	0.803
Age	–0.210	0.049
BMI	0.027	0.801
DM duration	0.056	0.607
HbA_{1c} %	–0.204	0.048
Serum creatinine	0.191	0.074

NDS — neuropathy disability score; BMI — body mass index; HbA_{1c} — glycosylated hemoglobin

There was no significant difference between diabetic neuropathic, diabetic non neuropathic and control regarding serum total cholesterol and triglycerides [215 (118–491), 244.5 (128–376) and 218 (172–359) mg/dL) respectively] (p = 0.453) and [155 (66–546), 132.5 (73–232) and 130 (71–238) mg/dL respectively] (p = 0.769).

Serum β-endorphin levels showed no significant difference between diabetic neuropathic, diabetic non neuropathic and control groups [293 (26–1000), 262.5 (14–700) and 307 (106–1000) pg/mL respectively] (p = 0.275).

HbA_{1c} % showed no significant difference between painful and painless neuropathy subgroups (9.061 ± 1.904 and 8.269 ± 1.493% respectively) (p = 0.091). Painful and painless neuropathy subgroups showed no significant difference regarding serum creatinine (0.787 ± 0.164 and 0.850 ± 0.192 mg/dL respectively) (p = 0.196).

Serum HDL-cholesterol and LDL-cholesterol showed no significant difference between both painful and painless neuropathy subgroups; serum HDL-cholesterol was (40.548 ± 10.859 and 38.461 ± 10.485 mg/dL respectively) (p = 0.466) and serum LDL-cholesterol was [174 (72–310) and 129.7 (52–399) mg/dL respectively] (p = 0.062).

In addition, there was no significant difference between both painful and painless neuropathy subgroups regarding serum total cholesterol and triglycerides (240.483 ± 75 and 214.080 ± 76.652 mg/dL respectively) (p = 0.196) and [154 (69–277) and 158 (66–546) mg/dL respectively] (p = 0.749) respectively.

Serum β-endorphin shows no significant difference between painful and painless neuropathy subgroups [200 (26–1000) and 303 (39–800) pg/mL respectively] (p = 0.701).

Regarding serum β-endorphin there was no significant difference between patients who used pain con-

trolling medications and those who did not use them [104 (53–451) and 307 (14–100) pg/mL respectively] (p = 0.117). There was no significant difference between diabetic neuropathic patients with or without associated pain regarding serum β-endorphin levels [315 (14–950) and 283 (26–1000) pg/mL] (p = 0.974). There were no significant difference in serum β-endorphin levels between patients with different characters of pain (p = 0.176).

There was no significant difference between lost and intact different modalities of nerve disability in either right and left foot as regard serum β-endorphin levels. Difference between intact and lost vibration perception as regard B endorphin in the right foot [289 (14–1000) & 304.5 (26–1000) respectively] (p = 0.759), and in the left foot [307 (14–1000) & 284 (26–1000) respectively] (p = 0.817). Difference between intact and lost temperature perception in the right foot [284 (14–1000) & 316 (39–1000) respectively] (p = 0.409), and in the left foot [284 (14–1000) & 316 (51.7–1000) respectively] (p = 0.318). Difference between intact and lost pin prick sensation in the right foot [301.5 (14–1000) & 239 (39–1000) respectively] (p = 0.453) and in the left foot [307 (14–1000) & 232 (39–1000) respectively] (p = 0.293). Difference between intact achillis reflex, intact achillis reflex with reinforcement and lost achillis reflex in the right foot [284 (14–1000), 313 (39–1000), 304.5 (26–900) respectively] (p = 0.731), andin the left foot [296 (14–1000), 313 (44–1000) and 268.5 (26–900) respectively] (p = 0.952).

Serum β-endorphin levels showed negative correlation with age (r = –0.210, p = 0.049) and HA_{1c} % (r = –0.204, p = 0.048). However, it did not correlate with pain severity (r = –0.097, p = 0.371), NDS: total score (r = 0.027, p = 0.803), BMI (r = 0.027, p = 0.801), s. creatinine (r = 0.191, p = 0.074) or DM duration (r = 0.056, p = 0.607).

Discussion

The age of our patients ranged from 40–65 years and there was no significant difference regarding age between various groups (p = 0.053). Painful and painless neuropathy subgroups were also matched for age (p = 0.766). Age is a well defined risk factors for diabetic peripheral neuropathy in observational as well as intervention studies [11, 12]. In this work, we couldn't study the effect of age as we selected all our patients from the age of 40 to 65 and we tried to make all groups matched for age.

In our study males constituted 47.7% of the total number of subjects included in the study and females constituted 52.3% and there was no significant difference between the groups regarding gender (p = 0.850). Painful and painless neuropathy subgroups were matched for sex (p = 0.094). Although female gender was associated with painful DPN in some studies [13–15], in our study we have nearly equal distribution between males and females so the effect of gender couldn't be assessed.

DM duration was longer in the neuropathic group [14 (8.2–20) years] versus the diabetic group [4 (1.125––9.5) years] (p < 0.001). Tesfaye et al. (2005) and Shaw et al. (2003) reported that diabetes duration is a well known risk factor for diabetic peripheral neuropathy. However, peripheral neuropathy was documented in cases with prediabetes. The pathogenic mechanisms of prediabetic neuropathy are multiple and not completely understood. Chronic hyperglycemia, dyslipidemia, microangiopathy, and factors of the metabolic syndrome have been implicated [16]. In painful and painless neuropathy subgroups, DM duration showed no significant difference [15 (2–25) and 11.5 (3.5–25) years respectively] (p = 0.146). Diabetes duration was found to be a correlate or predictor for painful DPN in some studies [15, 17] but not in others [18, 19].

There was no significant difference between various groups regarding BMI (p = 0.489). Most of the subjects were obese with BMI > 30 kg/m^2 which constitute 68.42% of the neuropathic group, 75% of the diabetic group and 60% of the control group. In painful and painless neuropathy subgroups, BMI was (34.7 ± ±7 kg/m^2 and 31.8 ± 6 kg/m^2 respectively) (p = 0.107). Ziegler et al. and Jambart et al., reported that obesity (BMI ≥ 30 kg/m^2) was related to painful DPN and have been suggested as a risk marker [15, 18]. Also Maury and Brichard, suggested that obesity represents a risk factor for neuropathic pain as a component of the metabolic syndrome and as a cause of many processes in the pathogenesis of DPN [20].

Hypertension was associated with diabetes in 70.2% of the neuropathic group and 56.2% of the diabetics without neuropathy (p = 0.295). Hypertension was reported as risk factors for diabetic peripheral neuropathy [11]. In our study, regarding to painful and painless neuropathy subgroups: there were 67.7% and 73.1% patients with hypertension respectively (p = 0.774), beside that SBP and DBP were significantly lower in painful neuropathy group when compared to painless neuropathy group (p = 0.026) (p = 0.049). However, hypertension was found as a risk factor for painful DPN in some studies [15, 17].

In our study, the character of pain in the painful neuropathy subgroup was mainly in the form of tingling (64.5%), deep aching (12.9%), pricking in 9.7% coldness in 6.5% and burning in 6.5%. Spallone et al., studied 59 patients with painful DPN and found paresthesia and burning as the most frequent sensory descriptors followed by paroxysmal pain (electric shock

and stabbing), evoked pain (by brushing, pressure and cold), and deep pain (squeezing and pressure) [21]. Baron et al., found that the association between burning, prickling, and numbness was the most common pain sensory profile (26%), followed by the pattern of pain attacks (16%), burning with both prickling and allodynia without numbness (13%), and allodynia with hyperalgesia (9%) [22].

In our study, NDS was significantly higher in neuropathic group in comparison to diabetic and control groups ($p < 0.001$), however, there were no significant differences between painful and painless neuropathy subgroups regarding all items of NDS. Veves et al., suggested that neuropathic pain could be present at any stage of DPN, from subclinical to very late neuropathy [23]. Veves et al., also found that the score of sensory deficits was higher in patients with painful than in those with painless DPN [24]. Another study found that painful DPN patients had worse sensorimotor deficits in comparison to patients with nonpainful DPN [25]. While Boulton et al., reported that painful symptoms improve with the worsening of the sensory loss [26]. Pain in painful DPN would appear to be mainly associated with the impairment of small afferent fibers, however it couldn't be confirmed that there is no small fiber impairment in the absence of pain [27]. Krämer et al., found that those with painful DPN showed no significant difference in vibration perception thresholds and thermal thresholds in comparison to those with painless DPN [28]. Vrethem et al., detected that tactile sensitivity but not thermal sensitivity were more compromised in diabetic patients with painful compared with those with painless DPN [29].

In our study, we found no significant difference regarding serum β-endorphin levels neither between diabetic neuropathic, diabetic non neuropathic and control groups ($p = 0.275$), or between the painful neuropathy subgroup and painless neuropathy subgroup ($p = 0.701$).

In the literature, few studies were found to study β-endorphin level in patients with diabetic neuropathy. Cakir et al., conducted a study on 7 diabetic patients with painful DN, 7 diabetic patients without DN, and 7 healthy control subjects to investigate the efficacy of L-carnitine (LC) in the treatment of painful diabetic neuropathy (DN) and its effects on levels of the endogenous peptide β-endorphin. They found no difference in basal β-endorphin levels between diabetic patients with painful DN and diabetic patients without neuropathy and they also spotted that basal β endorphin levels were significantly lower in the diabetic patients in comparison to the control group [30]. Tsigos et al., reported that β-endorphin concentrations are reduced in the CSF of patients with sensory diabetic polyneuropathy. However the difference wasn't statistically significant between those patients who have painful and those who have painless neuropathy [31]. In our study we found no significant correlation between β-endorphin concentrations and severity of pain ($r = –0.097$, $p = 0.371$). However, β-endorphin levels were significantly negatively correlated with age ($r = –0.210$, $p = 0.049$) and HA_{1c} % ($r = –0.204$, $p = 0.048$). The effect of age on β-endorphin level was previously suggested by Goodwin et al., who described that β-endorphin levels were significantly negatively correlated with age [32].

Serum β-endorphin levels showed no significant difference in our patients how used pain controlling medications versus those who did not use ($p = 0.117$). Bäckryd et al., found no significant correlation between CSF β endorphin level and use of pain medications in patients with chronic neuropathic pain [9]. However, Tramadol which is a drug with mild opiate properties had evidence from randomized controlled trials showing that tramadol is an effective treatment for neuropathic pain [33].

Serum β-endorphin levels in patients with associated pain versus those without showed no significant difference ($p = 0.974$). Serum β-endorphin in patients with different characters of pain showed no significant difference ($p = 0.176$). There was no significant difference between lost and intact different modalities of nerve disability (vibration perception, pain sensation and temperature perception) in either right or left foot as regard serum β-endorphin levels. To our knowledge, no previous studies addressed these topics.

The complex nature of pain pathway involving many pro and anti-nociceptive mediators could explain why β-endorphin concentration doesn't show significant difference in our study. Another explanation can be that central changes may be not reflected peripherally also it may be wise to measure both pro and anti-nociceptive markers at the same time. This explanation is compatible with the study of Veening et al., who observed that peripheral administration of β-endorphin does not necessarily induce the same effects as intra-cerebroventricular administration; this suggests the existence of two functionally different β-endorphin systems, one for the central effects and one for the peripheral effects. They concluded that CSF-levels of β-endorphin are not a reflection of its peripheral levels [34]. Also Bäckryd et al., reported that there are probably two functionally different β-endorphin systems: one peripheral (release of β-endorphin by the pituitary into the systemic circulation) and one central (synthesis in hypothalamic pro-opio-melanocortin (POMC) neurons) [9], with an intact blood-brain barrier (BBB) hinders free exchange of β-endorphin between plasma and CSF [35].

In addition, short half-life of β-endorphin was reported in some studies, which means that spikes for its serum concentration may be missed during the assay. Foley et al., reported that the mean terminal half-life after intravenous administration of 5 or 10 mg of human β-endorphin was 37 min [36]. Veening et al., also reported that half-life values of β-endorphin vary from 20 to 50 min in the human circulation [34]. Butelman et al., reported that full-length β-endorphin was detectable in all subjects up to 5 minutes after intravenous administration [37]. Moreover, Bruehl et al., reported that chronic pain may initially be associated with up-regulation of endogenous opioid analgesic systems, which then may become dysfunctional over time [38].

HbA_{1c} % was significantly higher in diabetic neuropathic and diabetic non neuropathic groups in comparison to control group (8.7 ± 1.8%, 8.2 ± 2% and 5 ± 0.4% respectively) ($p \leq 0.001$), but there was no significant difference between painful and painless neuropathy subgroups (9.061 ± 1.904% and 8.269 ± ± 1.493% respectively) ($p = 0.091$). These finding is in accordance with Tesfaye et al., who reported that poor glycemic control is a risk factor for diabetic peripheral neuropathy [11]. However, Jin et al., reported that the best-known pathogenic factor of DPN is hyperglycemia-induced oxidative stress, and these oxidative stresses are worsened by acute glucose fluctuations [39]. Xu et al., found that glycemic variability assessed by continuous glucose monitoring was significantly independent risk factor for DPN in type 2 diabetes with well-controlled HbA_{1c} % ($HbA_{1c} < 7.0\%$) [40]. Oyibo et al., found that patients with painful neuropathy had greater glycemic excursions and possibly poorer diabetes control, compared with patients with painless neuropathy [41].

In our study lipid profile evaluation showed no significant difference between various groups. Padilla et al, reported that dyslipidemia is linked to diabetic neuropathy, and several underlying mechanisms have been identified, free fatty acids have been shown to directly cause injury to Schwann cells *in vitro*, and also have systemic effects such as promoting inflammatory cytokine release from adipocytes and macrophages [42]. Kassem et al., found that hypertriglyceridemia affects conduction parameters in peripheral nerves in a trend suggestive of early peripheral neuropathy [43].

In Our study, we found no significant differences regarding serum β-endorphin levels neither between diabetic neuropathic, diabetic non neuropathic and control groups, or between painful and painless neuropathy subgroups. There were no significant differences regarding serum β-endorphin levels between patients with different characters of pain and there were no correlations to pain severity. There were no significant differences between lost and intact different modalities of nerve disability with regard to serum β-endorphin levels.

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