Original Research Article Medicine

International Journal of Life science and Pharma Research

ISSN 2250-0480

HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN TYPE 2 DIABETES PATIENTS WITH PAINFUL NEUROPATHY BEFORE AND AFTER 6 WEEKS PREGABALIN THERAPY.

INTESSAR SULTAN[1*], OLFAT ABOZED[2], NASHWA ALKHOULY[3], EMAN NAGUIB OSMAN [4], HASSAN ALDUHAILIB[5]AND MEES ALOTAIBI[5]

[1]Department of Medicine, College of Medicine, IbnSina National College for Medical Studies, Saudi Arabia.
[2] Department of Medicine, College of Medicine, Taibah University, Saudi Arabia.
[3] Department of Medicine, College of Medicine, Al-Azhar University, Egypt.
[4] Department of Medicine, College of Medicine, Ain Shams University.
[5] Medical Interns, IbnSina National College for Medical Studies, Saudi Arabia.

ABSTRACT

Painful Diabetic Neuropathy (PDN) is associated with a significant reduction in health-related quality of life (HRQOL). Glycemic control and improving HRQoL are now recognized as the main goals of patient-centered diabetes care. This pre-post quasi study aimed to assess HRQoL in type 2 diabetic patients with PDN before and after pregabalin therapy from October 2017 to April 2018. Adult Saudis outpatients (N=103) with PDN, under no specific therapy, were selected from three private hospitals in Jeddah, Saudi Arabia. Neuropathy Symptom Score, Numeric Rating Scale (NRS-11), neurological examination, 10 gm monofilament, and Ewing's reflex tests were used for assessment. All enrolled patients received pregabalin 75 mg once for 1 week followed by twice daily; then higher doses were used based on response (median dose 150 mg for 6 weeks). Weekly follow up was performed for patient's severity using NRS-11 and for drug side effects. HRQOL was assessed before and 6 weeks after pregabalin therapy using the Arabic version of The RAND 36-item Health Survey. Patients had severe PDN (median of 7), poor metabolic control (median A1C of 9.1) and disabling both mental (36.71) and physical summary scores (32.50) of HRQoL (both below 50). Higher baseline A1C was significantly associated with higher pain severity (r=0.467, p=0.000) and lower pain score-QoL (r=-0.267, p=0.006). After 6 weeks of therapy, significant improvements were detected in pain severity, metabolic control and all sub-parameters of HRQoL (p=0.000 for all). The major side effect was dose-dependent somnolence (18%). Uncontrolled type 2 adult Saudi patients with severe PDN have disabling HRQoL. Six weeks of pregabalin therapy was safe and effective and was associated with the improvement of physical and mental parameters of HRQoL. Given its recent restrictions in Saudi Arabia, risk of misuse and dependency, other therapeutic modalities for these patients should be similarly investigated.

KEYWORDS: ***Painful diabetic neuropathy; health-related quality of life; Pregabalin***,

INTESSAR SULTAN*
Department of Medicine, College of Medicine, IbnSina National College for Medical Studies, Saudi Arabia

Received on: 14/01/2019
Revised and Accepted on: 07/02/2019
DOI: http://dx.doi.org/10.22376/ijpbs/lpr.2019.9.1.P65-72

INTRODUCTION

The American diabetes association (ADA) in 2019 recommended that primary care providers should give attention to both glycemic control as well as quality of life. [1] For diabetic neuropathy, ADA recommended assessment and treatment of patients to reduce neuropathic pain, autonomic dysfunction symptoms and to improve quality of life. [1]There isagrowing evidence that diabetes mellitus has a negative impact onthe health-related quality of life (HRQoL). [2, 3] Evidence also points to diabetic complications as the main determinant factor of poor HRQoL. [2-4] Painful diabetic neuropathy (PDN) is one of the most common long-term debilitating and distressing complications of diabetes. It is the main initiating factor for foot ulceration, Charcot neuroarthropathy, and lower-extremity amputation. [5,6] PDN is a small fiber disease that is associated not only with significant reduction in HRQoL[7-12] but also with increased mortality. [7] Mechanism behind this poor HRQoL may involve pain, mood, mental state, disturbed sleep, and daily activities. [8,9] Unlikeother diabetic vascular complications, the impact of PDN on HRQoLhas not been extensively studied. [7-12] several different classes of medications have been used to treat PDN with varying degrees of success. Clinical guidelines consistently recommend pregabalin, a α2δ ligand gabapentinoids as a first-line monotherapy for PDN based on its efficacy, tolerability and safety[1] despite recent restrictions on pregabalin off-label use. Pregabalin has been shown to improve pain intensity and HRQoL in neuropathic patients. [13, 14]In Saudi Arabia, a country with a high prevalence of type 2 diabetes[15]; the reported studies of PDN are scarce in particular, on focus with HRQoL. A study[4] found that HRQoL was significantly associated with the presence of diabetic complications. Some studies[4, 16, 17] conducted in Riyadh region reported poor HRQoL in Saudi patients with type 2 diabetes. However, these studies did not restrict inclusion to PDN patients or evaluate the effect of any therapeutic modalities. Therefore, this study aimed to assess HRQoL and its response to pregabalin therapy in type 2 adult Saudi patients with PDN.

METHODOLOGY

This quasi experimental pretest-posttest design study was conducted in three private hospitals (IbnSina College Hospital, New Al-Jedani hospital, and Al-JedaniAlsafa Hospital). The three hospitals are related to IbnSina National College for Medical Studies in Jeddah, Saudi Arabia. Ethical approval for research was obtained from IbnSina National Collegeethical committee. Written informed consent was taken from all patients before participation.Eligible participants included type 2 diabetes adult Saudi patients of any gender who were seeking diabetes care at outpatient clinics and found to have PDN. Patients who were already on therapy for PDN or for any psychiatric illnesses, patients with nephropathy, pregnant women, inpatients, and severely ill patients were excluded. Patients with asymmetrical, motor, or mono-neuropathy, cranial neuropathy, progressive neuropathy, or upper limbs neuropathywere excluded. Moreover, exclusion criteria also included patients with other cause for neuropathy (malignancy, chronic inflammatory demyelinating polyneuropathy, paraproteinemia, etc…). Demographic (age, gender, occupation) and clinical data (duration of diabetes, diabetic complications, smoking, and other comorbidities) were collected from the patients in the outpatient clinics between September 2017 and April 2018. All participants were selected by non-randomized convenient sampling consecutively to obtain the required sample size ≥ 100 within the time frame.

Diagnosis of PPN

A- Neuropathy Symptom Score[18] consists of five criteria: 1. Burning, numbness and tingling (2 points) or Fatigue, cramping and aching (1 point) feelings in the lower extremity. 2. The feelings (symptoms) are present in the feet (2 points) or calf (1 point). 3. There are nocturnal exacerbations of the symptoms (2 points) or they are equally present during the day and night (1points). 4. The feelings (symptoms) wake the patient up from sleep (1 point). 5. Walking (2 points) or standing (1 point) maneuvers reduce symptoms. The total symptom score of 3-4 points was considered "mild symptoms", 5-6 points "moderate" and 7-9 points "severe" symptoms. Severity of pain before and after therapy was evaluated separately by the Numeric Rating Scale (NRS-11)[19] which is an 11–point scale for patient self-reporting of pain (0: no pain, 1 – 3: mild pain, 4 – 6: moderate pain, 7 – 10: severe pain). B- Clinical examination: both feet were examined for neuropathy using the Semmes-Weinstein 5.07 (10 gm) monofilament testand testing the pain prick, touch and vibration sensation. Autonomic neuropathy was diagnosed if a patient had 2 positive tests out of the following: changes in heart rate during deep inspiration and expiration, Valsalva maneuver or standing up, and

blood pressure fluctuations during standing up and handgrip.

Medical record and Anthropometrics

Medical record files were reviewed for metabolic control (the latest glycated hemoglobin (HbA1c) results), drug therapy, hypothyroidism, hypertension, obesity, other micro vascular and macro vascular complications, and a history of diabetic foot. Anthropometric measurements (weight, height, waist circumference) were measured on the same day of interview using standard measurements and body mass index (BMI) was then calculated.

Assessment of health-related quality of life (HRQoL)

HRQoL was assessed using the Arabic version of The RAND 36-item Health Survey 1.0. [6,20,21] The SF-36 has 8 multi-item scales assessing physical function (10 items), physical role-limitation (4 items), bodily pain (2 items), general health (5 items), energy (4 items), social function (2 items), emotional role-limitation (3 items) and emotional well-being (5 items). [20,21]In this study, the physical and mental function summary scores[22]were computed from the 8 items scales. Based on item response theory for scale scoring, the eight item scales were scored from 0 to 100 scales according to the response of each question. All questions are equally weighted within each item scale. Physical health summary score was the mean of the physical function, physical role-limitation, bodily pain, general health scores. Mental health summary score was the mean of emotional well-being, emotional role-limitation, social function, and energy scores. The score of 50 or above was considered normal andlower than 50 were considered a disability. The lower the score the higher the disability (a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).[23]

Pregabalin therapy (Lyrica® Pfizer, New York, USA)

At time of implementation of the study, pregabalin prescription was restricted to hospitals. The drug was available at the local internal pharmacy and all patients received their prescription through the local health information system. Treatment was initiated after neuropathy diagnosis and continued for 6 weeks if tolerable. All enrolled patients received pregabalin 75 mg once(daily for 1 week followed by twice daily then higher doses were used based on response and tolerability. Patients were examined every week to identify if they developedsideeffects. The primary efficacy measure was end point median neuropathic pain score using the NRS-1119 derived during the follow up visits every week to guide dose of drug escalation. Safety measures were ensured during each visit and included incidence of adverse events, physical and neurologic examinations, and 12-lead electrocardiogram. Patients continued their same antidiabetic medications and received their usual diabetes care. HRQoL was reassessed 6 weeks after therapy using the same Arabic version of The RAND 36-item Health Survey.

STATISTICAL ANALYSIS

All the study data were analyzed using the SPSS 23 software for Windows. Continuous abnormally distributed variables and scores were summarized as median (range) and categorical variables as frequency and percentages. Computed variables were used to compute the summary scores. The non-parametric testrelated samples was used to compare variables before and after therapy. Pearson's correlation was used to test different associations. SPSS legacy dialogue was used to construct scatter plot graphs (1&2). Excel was used to construct figures (3-5). For all statistics, a two-sided p-value <0.05 was considered as statistically significant.

RESULTS

This study included 103 type 2 Saudi patients with PDN (32% males and 68% females) with median age of 55 years and median duration of diabetes of 14 years. Their demographic and clinical characteristics were shown in Table-I. Their median neuropathy symptom score was severe (median of 7) with severe pain (median of 8). Retinopathy was found in 35%, cardiovascular disease in 17.5%, previous stroke in 6.8%, and peripheral vascular disease in 6.8%. Past history of diabetic foot was found in 18.4% of the patients. A substantial number of the patients had hypertension (71.8%), and overweight/obesity (57.3%). Only 12.6% of the patients were metabolically controlled with high median HA1c of 9.1 (Table 1). Patients had disabling both mental (median of 36.71) and physical summary scores (median of 32.50) of HRQoL (both medians were below 50). Within the physical and mental functions, the role-limitation physical and emotional scores (median score of 0 for both) were the most disabling followed by social health scores (median score of 25). Higher baseline A1C was associated with significantly higher pain severity ($r=0.467$, $p=0.000$) (Figure 1)

and lower pain score-QoL (r=-0.267, p=0.006) (Figure 2). Ofall the patients who received and continued their drug therapy, only the major side effect was dose-dependent somnolence in 18% of patients. The median dose of pregabalin was 150 mg per day (therapeutic range) with maximal dose of 600 mg daily received by 20% of patients. After 6 weeks of therapy, significant improvements were detected in pain severity, metabolic control (Figure 3) and all sub-parameters of HRQoL (p=0.000 for all) (Figure 4 and 5). During Post therapy, there were no significant correlations between A1C, severity of pain, doses of pregabalin or parameters of HRQoL.

Table 1
Characteristics of type 2 diabetes patients with PDN painful Diabetic neuropathy (N=103).

	Frequency (%)/ Median (range)*
Gender: Male	33 (32%)
Female	70 (68%)
Age: years	55 (71)
Employment	26 (25.2%)
Duration of diabetes: years	14 (34)
Smoking	5 (4.5%)
Hypothyroidism	22 (21.4%)
Hypertension	74 (71.8%)
Overweight/Obesity	59 (57.3%)
Retinopathy	36 (35%)
CVD	18 (17.5%)
Previous CVA	7 (6.8%)
PVD	7 (6.8%)
Previous diabetic foot:	19 (18.4%)
Anti-diabetic oral drugs	57 (55.3%)
Insulin injections	61 (59.2%)
Waist Circumference: cm	95 (120)
Glycated hemoglobin (HbA1c): %	9.10 (8.1)
Metabolic control:	13 (12.6%)
Neuropathy Symptom Score	7 (5)
Autonomic neuropathy	5 (4.9%)
Severity of pain (NRS-11)	8 (6)
Moderate	14 (13.6%)
Severe	89 (86.4%)

Median was used for continuous variables with abnormal distribution.

CVD: cardiovascular disease, CVA: cerebrovascular disease, PVD: peripheral vascular disease, WC: waist circumference, HbA1c: glycosylated hemoglobin. OAD: oral anti-diabetic drugs.

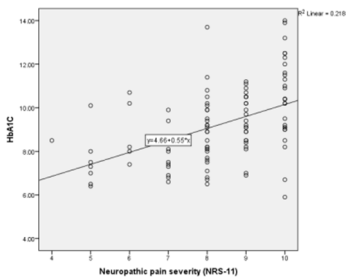


Figure 1
Significant correlation between baseline A1C and baseline Neuropathic pain severity (r=0.467, p=0.000).

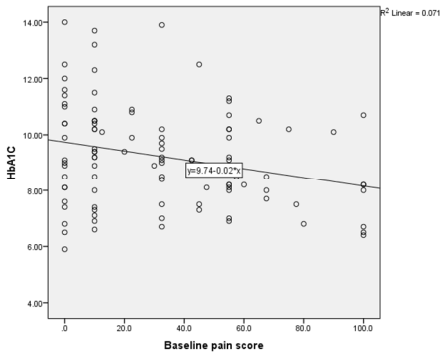
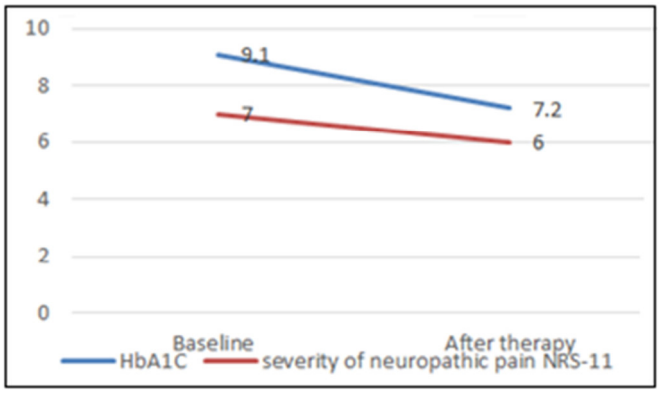
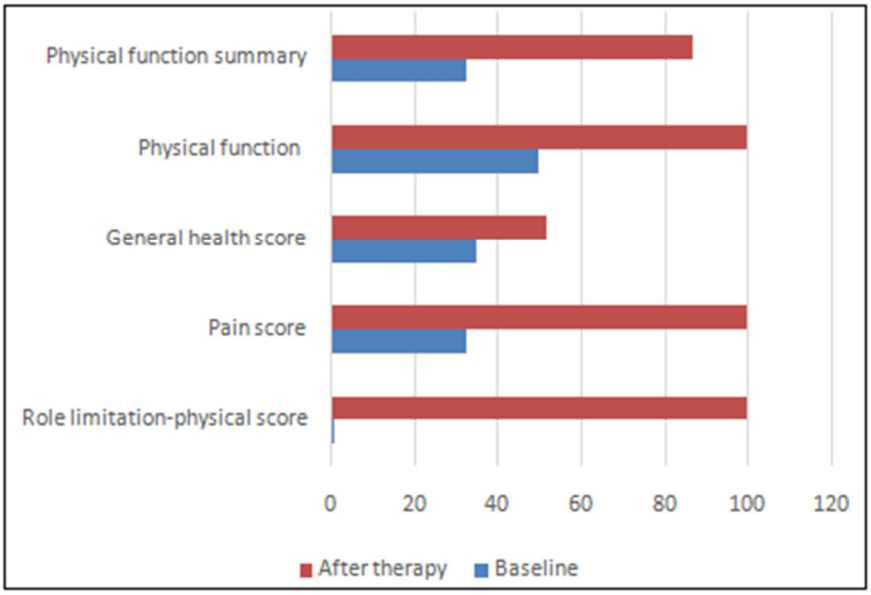


Figure 2
Significant correlation between baseline A1C and baseline pain score-QoL (r=-0.267, p=0.006).



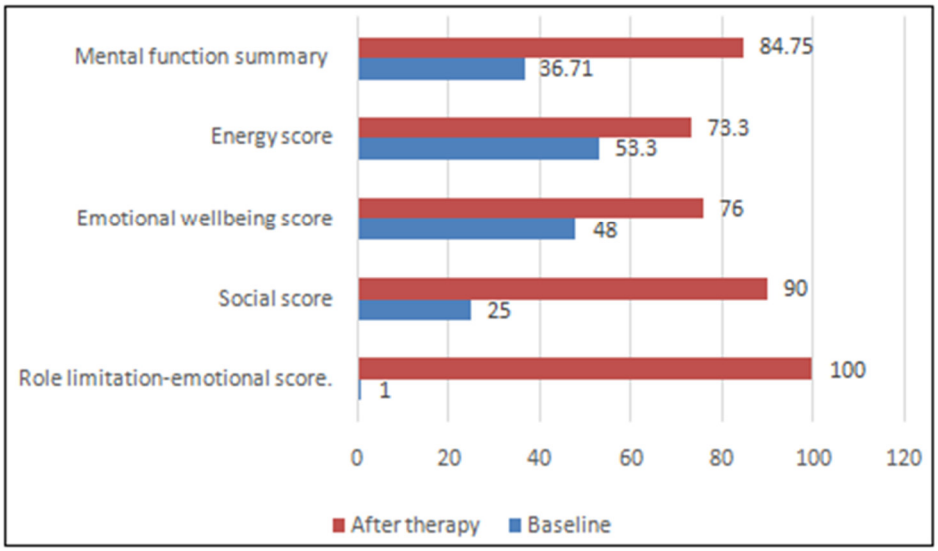
P=0.000

Figure 3
Improvement of metabolic control (HbA1C) and severity of neuropathic pain 6 weeks after pregabalin therapy.



P=0.000

Figure 4
Improvement of physical function HRQoL sub-parameters 6 weeks After pregabalin therapy



P=0.000

Figure 5
Improvement of mental function HRQoL sub-parameters 6 weeks After pregabalin therapy

DISCUSSION

This 6-week- therapy study with median dose of 150 mg pregabalin reported improved HRQoL and pain intensity in a group of metabolically uncontrolled Saudi patients with severe diabetic neuropathy and severe neuropathic pain. The drug was well tolerated except for somnolence in 18% of patients and showed good response to lowering the dose. Previous studies have shown that patients with PDN had significantly lower HRQOL compared to general population[26,27] as well as diabetic patients not suffering from PDN.[9,22,23]Moreover, astudy[8] with 1111 diabetic patients reported low physical and mental scores in PDN patients, but not in neuropathic patients without pain. Another study[11]reported statistically significant correlation between a measure of health status and pain intensity in PDN patients. However, in one study[22;] the frequency of quality of life impairments was significantly higher in patients with chronic pain with neuropathic characteristics than in those with chronic pain without neuropathic characteristics. In addition, Davies and his coworkers[24] showed that both pain and neuropathy have a statistically significant negative effect on quality of life and that these two variables act independently. Taken together, the pathophysiology of neuropathic pain might be very specific and need recognition by physicians who care for diabetic patients. Pregabalin has been shown to improve HRQoL and pain intensity in PDN[14, 25]in a dose related efficacy but unfortunately with an increase incidence of side effects. Pooled analysis of seven randomized, controlled clinical trials[14] in patients with PDN supported these findings and showed that over the effective dose range, pregabalin reduced pain rapidly and steadily. The most striking findings in the present study were the significant associations between metabolic control and severity of both neuropathic pain and pain score of HRQoL before therapy (Figures 1, 2). The association between chronic hyperglycemia and the development of diabetic neuropathy is well known. In the landmark diabetes control and complications trial (DCCT) [26]metabolic controls was able to slow down the progression of neuropathy after a mean follow up of 6.5 years. After therapy, the glycemic control improved significantly within 6 weeks despite continuation of the same diabetic care. The improvement in neuropathy and HRQoL may explain improvement of glycemic control, but no significant associations between them were found; probably because of the short duration of follow up. On the other hand, the rapid improvement of neuropathic pain and all HRQoL parameters within 6 weeks of therapy may be simply explained by the direct analgesic effect of pregabalin therapy. Results showed that the significant reduction of pain intensity after therapy was not significantly associated with improvement of HRQoL. Similar findings were reported by others who found that pregabalin beneficial effects on sleep quality or HRQoL are poorly correlated with reduction on pain intensity after an 8-week treatment course.[13]in this study, the main side effect of pregabalin was dose-dependent somnolence that was recorded in 18% of patients. Pregabalin has been recently associated with potential abuse charges and overdose mortalities. Fortunately, no studies were recorded on managing patients with overuse or fatal use of any gabapentinoids. In a recent systematic

review[27] of 106 studies, there was no convincing evidence of addiction. The only reported side effects were related to symptoms of relapses. There were four cases with behavioral dependence symptoms in patients without a previous history of drug abuse. Authors recommended that gabapentinoids should be avoided or administered with caution only through therapeutic and prescription monitoring. Based on these findings and others, Saudi Arabia had restricted the pregabalin prescription since February 2018.There are several limitations in this study. First; the pretest-posttest design limits to some extent the conclusions about the cause-and-effect relationships with high degree of certainty. Secondly; the duration of the study is relatively short, more evidence of efficacy and safety could be derived from longer duration of therapy. Third; the SF-36 method is generic rather than specific. It has inherited limitation to detect disease-specific outcomes, and consequently, the results and conclusion reported might not be generalized to other populations.

CONCLUSION

PDN was associated with substantial impact on HRQoL among uncontrolled type 2 Saudi patients with severe PDN. This was achieved by considerable interference in physical and mental functions with profound physical and emotional role limitations. A six-week pregabalin therapy was safe and effective and was associated with improvement of physical and mental functions irrespective of glycemic control or improvement in the severity of neuropathic pain. Given the recent restrictions of pregabalin drug in Saudi Arabia because of risk of misuse and dependency, other therapeutic modalities for these patients should be similarly investigated.

ACKNOWLEDGEMENTS

Great thanks to all physicians working at IbnSina College Hospital, New Al-Jedani hospital, and Al-JedaniAlsafaHospitalwho helped the team by providing the referral cases and other important tools to conduct this study.

AUTHOR CONTRIBUTION STATEMENT

Intessar Sultan, EmanNaguib, NashwaAlkhouly selected participants from their clinics, initiated treatment with pregabalin and performed the weekly follow up. OlfatAbozed was responsible for neurological examination. Hassan Alduhailib and MeesAlotaibi collected the data and interviewed the patients. All researchers were involved in writing the research proposal, studyingthe review of the literature, collecting and entering the research data, analyzing the research data and drafting publication manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Freinkel N. Standards of Medical Care in Diabetes—2019. Am Diabetes Assoc. 2019;42(1):S1–194. Available from: http://care.diabetesjournals.org/content/diacare/suppl/2018/12/17/42.Supplement_1.DC1/DC_42_S1_Combined_FINAL.pdf
2. Wändell PE. Quality of life of patients with diabetes mellitus An overview of research in primary health care in the Nordic countries. Scand J Prim Health Care. 2005;23(2):68–74. DOI: 10.1080/02813430510015296
3. Abolfotouh MA. Effect of Diabetes Mellitus on Quality of Life: A Review. Ann Saudi Med. 1999;19(6):518–24. DOI: 10.5144/0256-4947.1999.518
4. Abolfotouh MA, Salam M, Alturaif D, Suliman W, Al-Issa H AM. Predictors of Quality of Life and Glycemic Control among Saudi Adults with Diabetes. Int J Med Med Sci. 2013;5731(46):23–9. Available from: https://www.researchgate.net/profile/Mostafa_Abolfotouh/publication/258152488_Predictors_of_Quality_of_Life_and_Glycemic_Control_Among_Saudi_Adults_with_Diabetes/links/0deec52723f67eb350000000.pdf
5. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719–24. DOI: 10.1016/s0140-6736(05)67698-2
6. Singh H, Bradley C. Quality of life in diabetes. Int J Diabetes Dev Ctries. 2006;26(1):7. DOI: 10.4103/0973-3930.26882
7. Hsu W-C, Chiu SY-H, Yen AM-F, Chen L-S, Fann C-Y, Liao C-S, et al. Somatic neuropathy is an independent predictor of all- and diabetes-related mortality in type 2 diabetic patients: a population-based 5-year follow-up study (KCIS No. 29). Eur J Neurol. 2012;19(9):1192–8. DOI: 10.1111/j.1468-1331.2011.03659.x

8. Van Acker K, Bouhassira D, De Bacquer D, Weiss S, Matthys K, Raemen H. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. Diabetes Metab. 2009;35(3):206–13. DOI:10.1016/j.diabet.2008.11.004
9. Benbow S. Diabetic peripheral neuropathy and quality of life. QJM. 1998;91(11):733–7. DOI: 10.1093/qjmed/91.11.733
10. Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic Peripheral Neuropathic Pain: Clinical and Quality-of-Life Issues. Mayo Clin Proc. 2006;81(4):S3–11. DOI: 10.1016/s0025-6196(11)61474-2
11. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract. 2000;47(2):123–8. DOI: 10.1016/s0168-8227(99)00112-6
12. W. G. Meijer S. M. H. J., J. JT. Quality of life in patients with diabetic foot ulcers. Disabil Rehabil. 2001;23(8):336–40. DOI: 10.1080/09638280010005585
13. Perez-Lloret S, Rojas GM, Menoni MC, Ruiz G, Velásquez C, Rodriguez H. Pregabalin Beneficial Effects on Sleep Quality or Health-Related Quality of Life Are Poorly Correlated With Reduction on Pain Intensity After an 8-Week Treatment Course. Clin Neuropharmacol. 2012;35(1):21–4. DOI: 10.1097/wnf.0b013e31823df2dc
14. Freeman R, Durso-DeCruz E, Emir B. Efficacy, Safety, and Tolerability of Pregabalin Treatment for Painful Diabetic Peripheral Neuropathy: Findings from seven randomized, controlled trials across a range of doses. Diabetes Care. 2008;31(7):1448–54. DOI: 10.2337/dc07-2105
15. Alotaibi A, Perry L, Gholizadeh L, Al-Ganmi A. Incidence and prevalence rates of diabetes mellitus in Saudi Arabia: An overview. J Epidemiol Glob Health. 2017;7(4):211–8. DOI: 10.1016/j.jegh.2017.10.001
16. Al Hayek AA, Robert AA, Al Saeed A, Alzaid AA, Al Sabaan FS. Factors Associated with Health-Related Quality of Life among Saudi Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Survey. Diabetes Metab J. 2014;38(3):220. DOI: 10.4093/dmj.2014.38.3.220
17. Al-Shehri FS. Quality of Life among Saudi Diabetics. J Diabetes Mellit [Internet]. 2014;04(03):225–31. DOI: 10.4236/jdm.2014.43032
18. Ekdahl C, Englund A, Stenstrom Ch. Development and Evaluation of the Index of Muscle Function. Adv Physiother. 1999;1(1):45–53. DOI: 10.1080/140381999443555
19. Anonymous. Pain Intensity Instruments. National Institutes of Health – Warren Grant Magnuson Clinical Center.; 2003. Available from: http://www.scirp.org/(S(i43dyn45teexjx455qlt3d2q))/reference/ReferencesPapers.aspx?ReferenceID=1649098
20. Ware JE. SF-36 Health Survey Update. Spine (Phila Pa 1976). 2000;25(24):3130–9. DOI: 10.1097/00007632-200012150-00008
21. Ware JE, Kosinski M, Turner-Bowker DM GB. How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1).. Lincoln, RI: Quality Metric Incorporated; 2002. 267 p. Available from: https://trove.nla.gov.au/nbdid/24398175
22. Bouhassira D, Letanoux M, Hartemann A. Chronic Pain with Neuropathic Characteristics in Diabetic Patients: A French Cross-Sectional Study. PLoS One. 2013;8(9):e74195. DOI: 10.1371/journal.pone.0074195
23. Tsuji M, Yasuda T, Kaneto H, Matsuoka T, Hirose T, Kawamori R. Painful Diabetic Neuropathy in Japanese Diabetic Patients Is Common but Underrecognized. Pain Res Treat. 2013;2013:1–3. DOI: 10.1155/2013/318352
24. Davies M, Brophy S, Williams R, Taylor A. The Prevalence, Severity, and Impact of Painful Diabetic Peripheral Neuropathy in Type 2 Diabetes. Diabetes Care. 2006;29(7):1518–22. DOI: 10.2337/dc05-2228
25. Radhakrishnan C, Ut A, K S, Manikath N, Cr Rr. Safety and Efficacy of Pregabalin Treatment and Quality of Life in Patients Treated with Pregabalin in Painful Diabetic Peripheral Neuropathy. Diabetes. 2018;67(Supplement 1):2209–PUB. DOI: 10.2337/db18-2209-pub
26. The Effect of Intensive Diabetes Therapy on the Development and Progression of Neuropathy. Ann Intern Med. 1995;122(8):561. DOI: 10.7326/0003-4819-122-8-199504150-00001
27. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol. 2017;27(12):1185–215. DOI: 10.1016/j.euroneuro.2017.08.430