RESEARCH ARTICLE

A Comparison of Neuropathy Quality of Life Tools: Norfolk QOL-DN, PN-QOL-97, and NeuroQOL-28

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Abstract

Aims To explore the effectiveness of the Norfolk QOL-DN (QOL-DN), PN-QOL-97, and NeuroQOL-28 as tools for early detection of diabetic peripheral neuropathy in overweight, obese, and inactive (OOI), prediabetes (PD), and type 2 diabetes (T2D) individuals.

Methods Thirty-four adults were divided by A1C [(10 OOI, 13 PD, and 11 T2D] and the sural nerves were tested bilaterally via NC-Stat DPN Check, conducting a sural nerve conduction study (NCS). Participants were individually timed, filling out questionnaires (QOL-DN, NeuroQOL-28, and PN-QOL-97) at a self-selected pace. Data were analyzed and compared to NCS findings to determine the best instrument for early neuropathy detection, usability in screening settings, and application for individuals with OOI, PD, and T2D.

Results Abnormal NCS results were obtained from 27 individuals, of which 25 were bilateral and symmetrical. Confirmed DSPN criteria were met for 24, and 1 case met criteria for subclinical neuropathy. Normal NCS findings, reported symptoms, and reduced bilateral sensation were found in 7 cases. The QOL-DN and NeuroQOL-28 significantly predict neuropathy criteria in OOI, PD, and T2D subjects. Analyses revealed the QOL-DN as the quickest for completion (M=5.17; SD=1.83), followed by the NeuroQOL-28 (M=5.58; SD=3.56), and the PN-QOL-97 (M=13.23; SD=3.606).

Conclusions The QOL-DN and NeuroQOL-28 are valid early screening measures for DPN detection. Time completion studies revealed that the QOL-DN and NeuroQOL-28 may be used as excellent short screening measures, completed in approximately 6 minutes or less, with reasonable scoring for both. The NeuroQOL-28 is a better fit for immediate feedback, time constraints, or limited staff. Future investigations should evaluate these tools for detection in DPN-prone individuals and in subclinical populations screenings.

Keywords: Quality of Life; QOL-DN; PN-QOL-97; NeuroQOL-28; Overweight Obese Inactive

1. Introduction

Diabetes can be an overwhelming chronic disease that places significant physical and mental demands on individuals, often leading to distress and degradation of consistent self-care behaviors [1,2,3]. Such stressors and inconsistent monitoring behaviors may lead to physical damage and health complications caused by extended or acute hyperglycemia [4]. Hyperglycemia promotes early microvascular complications related to diabetic neuropathy (DN), including altered eyesight, kidney damage, and impaired psychosocial functioning, all of which may bring significant health impacts [5, 6]. Recently, the International Prevalence and Treatment of Diabetes and Depression Study (INTERPRET-DD) was undertaken in 14 countries and found that among 2,733 participant aged 18–65 years with type 2 diabetes (T2D), the overall prevalence of diabetic peripheral neuropathy [1] was 26.71%

(95% CI: 25.08–28.40), emphasizing that this health issue is commonplace in this population [7, 8].

An individual's outlook on life, how he or she experiences it, interacts with others, and chooses activities may be affected by a DN diagnosis and individual symptomology. Such adverse outcomes on an individual, the ability to perform tasks, and psychosocial functioning is referred to as health-related quality of life (HRQOL) [9]. HRQOL is an important concept within diabetes care management, particularly due to the rising impact of the disease itself. Globally, as of 2019, more than 463 million people (9.3% of the world's population) were living with some type of diabetes, and the International Diabetes Federation estimates that number will rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [10, 11], and as many as half of these individuals currently with diabetes have not been diagnosed.

Research over the past several decades has made great strides in developing several HRQOL assessments that specialize in assessing DN-related measures and address HRQOL as a significant factor [12-15]. Within the realm of HRQOL, DN has been of particular interest, with individuals dedicating significant research effort to the validation of neuropathy-specific measures. Individuals at risk for or who are experiencing DN should be promptly screened to facilitate optimal health outcomes [16].

Diabetic neuropathy is the most common chronic complication experienced in T2D [17] with over half of those with diabetes experiencing neuropathy and diabetic peripheral neuropathy [1,18]. This complication mimics other conditions and it is therefore diagnosed by a process of excluding other factors [4]. Individuals with prediabetes (PD) have been found to have abnormal nerve conduction study (NCS) results [19], raising questions as to when DN develops [16, 20] and how soon it affects QOL. Various types of diabetic neuropathy may be experienced, but generally fall into four areas including peripheral, autonomic, proximal, and focal neuropathies [4]. Within these types of diabetic neuropathies, the term distal symmetric poly neuropathy (DSPN) is extremely common, and attributable to ongoing micro vessel damage from recurring hyperglycemia [21]. Furthermore, current research indicates that having overweight, obese, or inactive status [19, 22] places an individual at increased risk for disease, including potential progression to PD and T2D and other forms of physiological dysfunction, yet sparse research is available relating to how these individuals may experience DN [23]. Neuropathy screening is considered a standard of care for individuals diagnosed with T2D, but not for overweight, obese and inactive (OOI) individuals. Therefore, the purpose of this study was to compare three measures of QOL, the NQOL–DN, the PN-QOL-97, and the NeuroQOL-28, in adults with OOI, PD, and T2D to determine which instrument may be the most effective at detecting DPN at various stages compared to a criteria standard, the NC–Stat DPN Check (NeuroMetrix, Waltham, MA).

2. Subjects

This study included a total of 34 adults of both sexes and varying ethnicities, divided into three groups: 10 overweight, obese, and inactive normoglycemic (OOI) individuals 22 (6 females, 4 males; 59.6±13.0 years), 13 individuals with prediabetes (PD) (11 females, 2 males; 56.4±12.2 years), and 11 individuals with T2D (7 females, 4 males; 59.6±12.1 years). Individuals with T1D, active tobacco use, presence of hepatitis B, hepatitis C, HIV, pregnancy, damage to the lower extremities, history of nerve disease

(other than neuropathy), history of peripheral arterial disease, lower limb amputations, or foot ulcers were excluded from participation. Participants were recruited by flyers, email, word of mouth and university announcements. Subjects were screened by phone for exclusionary factors prior to reporting for testing. This research was approved by the University Institutional Research Board of Old Dominion University and subjects participated in informed, signed consent procedures before participating.

3. Materials and Methods

3.1 Procedures

Questionnaires were filled out after individuals were screened and consented into the study and prior to other data collection measures. Completion times were tracked for each instrument, allowing a comparison of the time investment needed to utilize each chosen method. Individuals were placed in a quiet room with a volunteer research assistant who timed their completion of each instrument in minutes and seconds. Questionnaires were checked by volunteer research assistants and investigators for completeness before proceeding to A1C testing. Incomplete questionnaires were completed before proceeding with the study.

3.2 Quality of Life Instruments

Norfolk Quality of Life Diabetic Neuropathy Tool. The Norfolk Quality-of Life Diabetic Neuropathy tool (QOL-DN) has been found to be reliable across many different populations [24-26]. This comprehensive tool has demonstrated sensitivity to both small and large fiber impairment while also detecting improvements in neuropathy.[24-26].

PN-QOL-97. This instrument has been identified as a validated measure for identifying DPN and successfully used in research [14, 27, 28]. It is a PN-specific HRQOL measure offering multiple psychometric properties to be considered [13, 14].

NeuroQOL-28. The NeuroQOL-28 questionnaire instrument has been validated as a neuropathy and foot ulcer specific QOL tool, and subsequently utilized in a myriad of studies evaluating key QOL factors involved in the DPN experience [15, 29].

3.3 A1C Testing and Subject Categorization

Sterile techniques were used to collect blood samples and perform A1C testing. Hemoglobin A1C (A1C) fingerstick testing was performed with a Siemens DCA Vantage 2000 Analyzer [30] and DCA Vantage A1C test kits following standardized protocols from Lenters-Westra and Slingerland [30] and Selvin et al. [31]. Individuals were instructed prior to their appointment to drink several glasses of water within 2–3 hours before arriving for the study to avoid errors on the test, such as high total hemoglobin errors. Individuals were also instructed to stay well hydrated for the 24-hour period beforehand. Assignment to groups was based on current A1C testing values obtained onsite during study procedures, and subjects were categorized as follows: OOI: 4.0–5.6%, PD: 5.7–6.4%, T2D: 6.5% and above [31-33].

3.4 NC-Stat DPN Check

NC-Stat DPN Check (DPN-Check, NeuroMetrix Inc., Waltham, MA) procedures followed previously outlined methods as performed by Lee et al. [34]. The point of care device (POCD) test method involved a bilateral examination of the lower extremities to obtain sural nerve amplitude potential (SNAP) and conduction velocity (SNCV) [34, 35]. The device allows for these evaluations by nonclinical personnel assisting in DPN detection at a significantly earlier stage when compared to bedside tests [36-39]. The unit

utilized biosensor technology paired with 2 probes applied directly to the skin posterior to the lateral malleolus. A single press of a button distributed 100 mA of current, which was detected by a single-use disposable biosensor. A built-in thermometer accounted for variances in temperature between 23°C and 30°C and notified the operator if skin temperatures were too cold for testing. SNCV and SNAP values were attempted for each leg with up to 5 attempts to collect the trials. Device errors were not recorded; however, zero readings were recorded by hand and re-attempts we made up to the 5-trial limit, as individuals permitted. The validity and effectiveness of the NC-Stat DPN Check system has been confirmed in prior research [35, 37]. This test served as a criterion standard for the study and all other testing was compared to this measure.

3.5 Data Analyses

Questionnaires were considered valid if complete biographic information, including age and sex was provided [40]. Summary statistics, in the form of continuous data is presented with means and standard deviations. Pertinent Spearman's partial correlations are presented. NC-Stat DPN Check, measuring (3 trials) the right sided sural nerve amplitude potential (RSNAP) served as the comparable criterion standard, determining confirmed distal symmetric polyneuropathy (DSPN) or subclinical DSPN.

Multiple regressions were run to attempt to predict the right SNAP criterion through modeling accounting for A1C, age, body mass index, and selected correlated predictor variables from each questionnaire. Comparisons involved running separate multiple regression analyses with limited covariate and predictor variables with the aim to predict DPN. Covariates and predictors were entered at once, including accounting for known factors such as A1C, age, and BMI as a substitute measure for weight and height, in order to best preserve the regression model degrees of freedom (DOF) [41]. Selected neuropathy-related components were entered into regression models based on potential relationships presented in Spearman's partial correlations with appropriate choices meeting the assumptions of regression, avoiding multicollinearity. Linearity, homoscedasticity, independence of observations (research design and Durbin-Watson), linear relationships, outliers ($\pm$3 SD), influential leverage cases, and multi-collinearity components (correlations, tolerance, variance inflation factor values) were evaluated and addressed for each model independently. All analyses were performed using SPSS Version 22.0 and significance was set at the $p<0.05$ level.

4. Results

4.1 Population Characteristics

Our population included 10 males and 24 females of Caucasian (64.7%) and African American (35.3%) ethnicity, with A1C ranges from 4.4–14.0% for all subjects (Table 1). Fifteen of 34 individuals reported no prior diagnosis or knowledge of T2D, or PD. Five of 15 individuals had PD A1C values and were grouped accordingly. A total of 33 out of 34 individuals were overweight or obese. Twenty-eight individuals reported having no prior neuropathy diagnosis or knowledge. Medication usage varied, with 10 of 34 participants reporting T2D specific medication usage as part of their personal medical plan. Two individuals with T2D reported a combination of T2D and neuropathy medication.

4.2 Sural Nerve Conduction Amplitude and Velocity Results

Overall group means for SNAP and SNCV characteristics did not significantly vary by A1C level (Table 2). Kruskal-Wallis-H testing revealed no significant differences among OOI, PD and T2D groups for SNAP and SNCV values (SNAP: R, $H(2)=1.460$, $p=0.482$; L, $H(2)=2.369$, $p=0.30$; SNCV: R, $H(2)=1.874$, $p=0.392$, L, $H(2)=1.880$, $p=0.39$). Raw data means and standard deviations are presented. Twenty-seven individuals obtained confirmed, individualized, abnormal NCS results, of which 25 were bilateral and symmetrical (Table 3). Twenty-four participants presented with combinations of abnormal distal signs bilaterally, meeting criteria for confirmed DSPN, and one case presented with no signs or symptoms, indicating the presence of subclinical neuropathy. Seven cases presented with normal NCS findings, but in the presence reported symptoms and reduced bilateral distal sensation.

Table 1: NCS Results by Group

NC-Stat DPN Check - Sural Nerve						
	N	Min	Max	Mean	Std. Err	Std. Dev
SNAP-R (μV)						
OOI	10	2.0	14.3	6.631	1.444	4.567
PD	13	2.0	24.7	7.691	1.674	6.037
T2D	11	2.0	25.0	9.875	2.133	7.076
SNAP-L (μV)						
OOI	10	2.3	21.7	7.129	1.834	5.798
PD	13	3.0	21.7	7.277	1.186	4.277
T2D	11	3.0	21.7	10.572	2.064	6.847
SNCV-R (μV)						
OOI	10	35.3	55.7	46.2	1.902	6.016
PD	13	30.0	57.0	48.2	1.871	6.747
T2D	11	35.3	57.0	45.5	1.816	6.022
SNCV-L (μV)						
OOI	10	41.3	55.0	47.265	1.519	4.803
PD	13	43.0	55.0	49.637	1.072	3.865
T2D	11	37.3	57.0	46.876	1.946	6.455

*Displayed in untransformed form, as raw data

Table 2: Sural NCS, Signs and Symptoms

	Variable	Total	Group OOI	PD	T2D
Sural NCS *N* = 34	Normal	7	1	3	3
	Abnormal*	27	10	9	8
Signs *N* = 34	Tuning Fork				
	Normal	14	3	6	5
	Abnormal*	20	7	7	6
	Monofilaments				
	1-g				
	Normal	3	1	0	2
	Abnormal*	31	9	13	9
	10-g				
	Normal	3	1	0	2
	Abnormal*	31	9	13	9
Symptoms *N* = 34	None Reported	11	6	1	4
	Reported**	23	4	12	7
Autonomic *N* =34	None Reported	21	7	8	6
	Reported**	13	3	5	5
ADLS *N* = 34	None Reported	26	8	10	8
	Reported**	8	2	3	3
NCS, Sign & Symptom Combinations	AbNCS, Signs & Symptoms	17	3	9	5
	AbNCS, Signs or Symptoms	9	5	1	3
	AbNCS, No Signs or Symptoms	1	1	0	0
	NNCS, Signs & Symptoms	7	1	3	3

*Bilateral testing; abnormal findings on at least one limb; **Self-reported on QOL-DN
AbNCS = Abnormal nerve conduction study; NNCS = Normal nerve conduction study

Table 3: Spearman Partial Correlations

		RSNAP	LSNAP	RSNCV	LSNCV
QOL-DN		*N*=34	*N*=34	*N*=34	*N*=34
Total Score	Corr.	-0.289	-0.352	-0.004	-0.242
	Sig.	0.128	0.061	0.985	0.205
Large Fiber	Corr.	-0.275	-0.322	-0.058	-0.290
	Sig.	0.149	0.088	0.765	0.127
Small Fiber	Corr.	-0.251	-0.185	-0.340	-0.361
	Sig.	0.189	0.336	0.071	0.054
Symptoms	Corr.	-0.291	*-0.417	0.047	-0.102
	Sig.	0.126	0.024	0.808	0.597
ADLS	Corr.	-0.331	-0.260	0.066	-0.074
	Sig.	0.079	0.164	0.734	0.701
Autonomic	Corr.	-0.188	-0.297	-0.091	-0.188
	Sig.	0.328	0.117	0.638	0.329
PN-QOL-97		*N*=34	*N*=34	*N*=34	*N*=34
Physical	Corr.	0.350	*0.399	0.107	0.166
	Sig.	0.063	0.032	0.579	0.389
Mental	Corr.	*0.505	*0.479	0.052	-0.101
	Sig.	0.005	0.009	0.791	0.603
NeuroQOL-28		*N*=34	*N*=34	*N*=34	*N*=34
Total Score	Corr.	-0.194	-0.334	-0.288	-0.279
	Sig.	0.314	0.077	0.129	0.142
Neuropathy Specific	Corr.	-0.305	*-0.464	-0.177	-0.204
	Sig.	0.108	0.011	0.358	0.287
Overall QOL Judgement	Corr.	*0.523	*0.426	0.194	0.025
	Sig.	0.004	0.021	0.312	0.897

All correlations account for HbA1C, age, height, and weight.
* significance at the 0.05 level

4.3 Correlations

Spearman's partial correlations were run between NC-Stat DPN Check criteria standard variables, which were the right and left SNAP and SNCV values, and all questionnaire data components while accounting for age and A1C values. Significant correlations were identified and are presented in Table 4. The QOL-DN symptom component moderately correlated with the right SNAP criterion [*R*, $r_s(34)$=-0.365, p=0.044]. The PN-QOL-97 physical component score moderately correlated with both the right and left SNAP criteria [*R*, $r_s(34)$=0.375, p=0.038; L, $r_s(34)$=0.366, p=0.043], as did the mental component scores; however, the relationship was considerably stronger [R, $r_s(34)$=0.522, p =0.003; L, $r_s(34$=0.451, p=0.011]. NeuroQOL-28 neuropathy specific components moderately strongly correlated to the left SNAP [$r_s(34)$=-0.426, p=0.017], and the NeuroQOL-28 overall QOL judgment score strongly [RSNAP, $r_s(34)$=0.541, p=0.002], and moderately correlated [LSNAP, $r_s(34)$=0.396, p=0.028] to our criteria SNAP values.

Table 4: Regression Results

QOL-DN Regression Results	Unstd. Coeff.		Std. Coeff.	t	Sig.	95% Conf. Int for B.	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Constant	28.084	7.291		3.852	0.001	13.15	43.018
Age	-0.311	0.066	-0.629	-4.738	0	-0.446	-0.177
A1C	0.262	0.593	0.069	0.441	0.663	-0.954	1.477
BMI	-0.11	0.149	-0.101	-0.741	0.465	-0.416	0.195
Symptoms	3.613	2.523	0.347	1.432	0.163	-1.555	8.78
Total QOL	-2.719	1.096	-0.55	-2.481	0.019	-4.964	-0.474
PN-QOL-97 Regression Results							
Constant	-47.42	43.91		-1.08	0.29	-137.85	43.014
Age	-0.348	0.077	-0.73	-4.525	0	-0.507	-0.19
A1C	2.608	1.09	0.374	2.392	0.025	0.362	4.853
BMI	-0.207	0.156	-0.178	-1.326	0.197	-0.528	0.114
Physical Score	4.47	11.653	0.076	0.384	0.705	-19.529	28.47
Mental Score	12.102	6.456	0.349	1.874	0.073	-1.195	25.399
NeuroQOL-28 Regression Results							
Constant	-0.235	18.513		-0.013	0.99	-38.157	37.688
Age	-0.357	0.067	-0.721	-5.344	0	-0.494	-0.22
A1C	0.918	0.549	0.243	1.671	0.106	-0.207	2.042
BMI	0.036	0.151	0.032	0.236	0.815	-0.273	0.345
Neuropathy Specific	-5.358	6.438	-0.129	-0.832	0.412	-18.545	7.829
Overall QOL Judgement	15.748	6.18	0.422	2.548	0.017	3.089	28.406

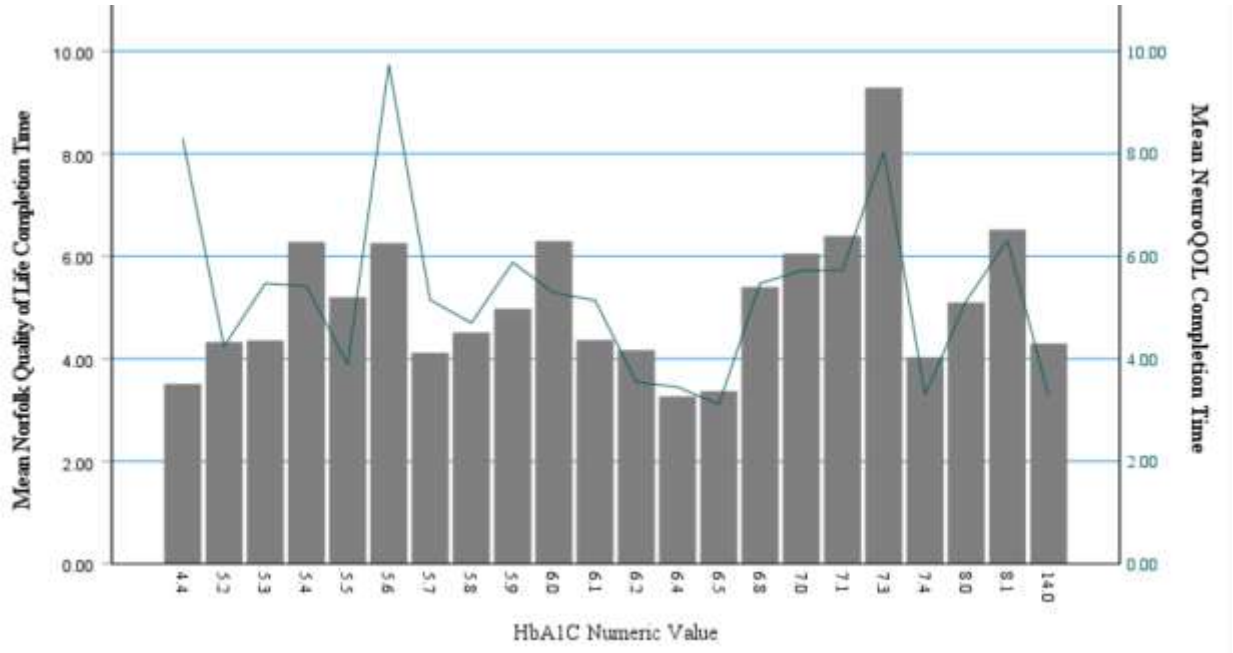
4.4 Completion Times

Completion times analyses revealed that the QOL-DN (*M*=5.17; *SD*=1.83) was the quickest, on average to complete, followed by the NeuroQOL-28 (*M*=5.58; *SD*=3.56) and QOL-97 (*M*=13.23; *SD*=3.61).

4.5 Questionnaires

QOL-DN Questionnaire. A multiple regression was run to attempt to predict the right SNAP criterion with a regression model that accounted for A1C, age, BMI, QOL-DN Symptoms and Total QOL Scores as predictors. The multiple regression model significantly predicted the right SNAP value, $F(5,28)=6.118$, $p<0.001$, adj. $R^2=0.52$. Age ($p=0.000$) and Total QOL ($p=0.019$) significantly added to the prediction. Regression coefficients and standard errors for all three questionnaires are presented in Table 5.

Figure 1. Dual Y Axes with Categorical X Axis Mean of Norfolk Quality of Life Completion Time, Mean of NeuroQOL Completion Time by A1C Numeric Value



PN-QOL-97 Questionnaire. A multiple regression was run to attempt to predict the right SNAP criterion with a regression model that accounted for A1C, age, BMI, and PN-QOL-97 Physical and Mental Scores as predictors. This model significantly predicted the right SNAP value, $F(5,25)=7.465$, $p<0.0005$, adj. $R^2=0.52$. Age ($p=0.000$) and A1C ($p=0.025$) significantly added to the prediction.

NeuroQOL-28 Questionnaire. A multiple regression was run to attempt to predict the right SNAP criterion with a regression model that accounted for A1C, age, BMI, the NeuroQOL-28 Neuropathy Specific Component, and Overall QOL Judgment as predictors. The multiple regression model significantly predicted the right SNAP value, $F(5,28) =7.238$, $p<0.0005$, adj. $R^2=0.49$. Age ($p=0.000$) and Overall QOL Judgment ($p=0.017$) significantly added to the prediction.

5. Discussion

Although the QOL-DN, PN-QOL-97, and NeuroQOL-28 have been validated for use in research as neuropathy instruments to detect DPN, further analysis of these instruments has been recommended [12, 13] . We sought to determine which of three instruments, the QOL-DN [42], the PN-QOL-97, [14] or the NeuroQOL-28 [15] would be the best predictor of neuropathy when compared to our criteria standard measurements in OOI, PD, and T2D populations. The QOL-DN Symptoms component correlated with our LSNAP, but not with the RSNAP, thus regression results revealing a predictor relationship between the Total QOL and RSNAP were not surprising. Examination of bilateral results will be reported elsewhere.

We had anticipated that the QOL-DN would more clearly identify early, or subclinical PN given that the instrument had previously identified 6,000 cases of undisclosed neuropathy amongst individuals with

diabetes in a 25,000 person study in Romania[40]. Our study provides support for this finding through Total QOL-DN (p=0.019) component scores of this instrument. Our results indicate that the QOL-DN, but not the PN-QOL-97, predicted our criterion standard RSNAP value within our regression models, although the PN-QOL-97's Mental Score was relatively close to significance (p=0.073). The NeuroQOL-28 Overall Judgment of QOL (p=0.017) demonstrated significant predictive qualities for early detection, giving further validation to this short questionnaire, yet asymmetry existed in its correlational relationship across the RSNAP and LSNAP variables. Normal variants within our target population could account for such asymmetries. Twenty-six of 34 individuals had abnormal NCS. Of these 26 participants, 24 reported symptoms (recorded via QOL-DN) and the presence of bilateral symmetrical signs as evidenced by 1-g and 10-g monofilaments, 128-Hz tuning fork, and reported symptoms, meeting the requirements for confirmed DSPN [43].

In hypothesizing which instrument would be most effective to detect DPN in our OOI, PD, and T2D populations, we had predicted a correlation of 0.60, or higher between these tools and the NC-Stat DPN Check criteria SNAP and SNCV values. However, our results indicate that all three measures failed to meet this level; although they correlated to our criteria, the association was not as strong as clinically desirable. Correlations revealed significant relationships between the RSNAP and the Neuropathy Overall Judgment QOL (r_s = 0.523), and PN-QOL-97 Mental Scores (r_s = 0.505) for the RSNAP, but not for the QOL-DN.

Early detection is considered critical, yet is difficult to accomplish with currently available methods. Others emphasize the importance of early DPN detection in their research, advising small fiber evaluation as to catch the pathophysiological process in the earliest stages [20, 41, 44]. Clinical exams readily identify small fiber pathology, often using Neurotips (pain and warmth detection), or a cold 128-Hz tuning fork (thermoreceptor evaluation) [4]. Large fiber neuropathy, which is the primary focus of the NC-Stat DPN Check tool, may also be evaluated through hands-on measures (NC-Stat DPN-Check, 1-g, 10-g monofilaments, 128-Hz tuning fork) in clinical or on-site applications to test pressure and large fiber sensitivity changes. Small fiber dysfunction, however, is difficult to detect, often requiring skin biopsy for confirmed status, paired with abnormal QST and clinical exams, requiring clinical appointments. We emphasize the necessity of easy-to-use screening tools that may be utilized in short time commitment community screening efforts. The often-silent beginnings of small fiber dysfunction do not readily lead individuals to seek the clinical assessment necessary to catch the pathology. Unless experiencing symptoms, such as brief pins-and-needles, pricks, or shock sensations, they have little to move them towards clinical evaluation.

Previous research indicated strengths and weaknesses for each instrument prior to the execution of this study; however, it should be noted that each instrument may be more adept at differentiating different components of fiber loss, meaning one may be more able to detect small fiber, another identifies with large fiber loss and another may do well with both or detect autonomic components as well. Our criteria focused on large fiber measurement, and future study designs may need to incorporate multiple means to assess the effectiveness of these QOL tools, ones that address small, large, and autonomic neuropathy components, to better detect the strengths of each instrument. This might include simple bedside tests, such as a cold

tuning fork and Neurotips, to evaluate small fiber components.

The further development of questionnaires to screen for small fiber component dysfunction should be a priority as much of the public does not seek medical attention until symptoms have become obvious. Ultimately, the focus of patient reported outcomes such as the QOL-DN, PN-QOL-97, and the NeuroQOL-28 is DPN screening and detection, thus evaluating these instruments for different facets of the targeted disease population and determining each tool's viability in that subset was a useful objective of the current study. Both the QOL-DN and NeuroQOL-28 likely identified key subjective measures that align well with objective screening measure in early hyperglycemic processes within our small pilot population. The QOL-DN was effectively employed to identify key symptomology necessary for the diagnosis of DPN, aiding and assisting in a patient centered, cumulative approach. These instruments are available in US and UK versions, with the NeuroQOL-28 available in 10 languages and the QOL-DN available in 8 [13], indicating widespread availability for research and screening efforts. Strengths of the QOL-DN are highlighted by Vinik, Hayes, Oglesby, Bastyr, Barlow, Ford-Molvik and Vinik [42], where the QOL-DN demonstrates a well-rounded approach, uncovering multiple neuropathy-related components, including complications, medication use, autonomic factors, fiber specific domains, and validated use for revealing undisclosed neuropathy [40, 42]. Our study showed similar results, disclosing DPN in individuals who were unaware of their deteriorating physiological state, revealing promise for the QOL-DN in revealing disease in diverse population settings. The NeuroQOL-28 focuses on painful symptoms, reduced sensation, ADLS, diffused sensory and motor changes, emotional changes, and overall QOL, which likely explains its usefulness in our study [15]. These facets relate to our research, as the completion of results reflect a strong indication of neuropathy in this population, suggesting that careful screening of individuals at earlier stages may be quite beneficial in the DPN detection process, even prior to acute hyperglycemia diagnosis. Elevated A1C status in such populations is associated with the development of decreased motor and sensory nerve conduction velocities, which may arise out of acute bouts of hyperglycemia experienced though postprandial excursions [45, 46]. Our participants were likely to report a variety of component changes, including psychometric properties that are evaluated and reported by this measure. Currently, each questionnaire has its strengths and should be applied accordingly.

Previous research has reported unknown completion times for the NeuroQOL-28 and QOL-DN [13], making this study the first to document time to completion for all three measures. Our finding that completion times were shorter for the QOL-DN and NeuroQOL-28 suggests that these two would ultimately make better choices for optimizing community screening efforts. Both instruments can be employed within a short time, and the choice between which measure to use in future early DPN investigations is a difficult one as these instruments are typically applied in populations that are likely further along in their disease process than the ones in this pilot work. Quickly completed PROMs provide more leeway for integration into community screenings, as does quick scoring in order to be of immediate use to the individual. Of the 3 measures, scoring is easiest for the NeuroQOL-28, which can be done in less than 5 minutes. The QOL-DN requires additional time to provide feedback and

likely, contact information or a second reporting to disseminate results. The PN-QOL-97 requires elaborate scoring accomplished through Excel.

Limitations that should be considered include that we performed a pilot study and generalizations may not be made to large populations. Lack of random assignment and use of volunteers for subjects created potential selection bias, with clinical population research targeting and low available funding heavily influencing this method. The A1C machine that was used within the study is a validated machine [30], but oral glucose tolerance testing is preferred by some research scientists, particularly for individuals with cardiac autonomic neuropathy (CAN) [47], which we did not screen for and, therefore, we cannot account for unknown discrepancies. The NC-Stat DPN Check device was used solely to test the sural nerve; thus, deficits in nerve function relating to other nerves of the lower leg were not confirmed through this device. Previous research has not investigated the validity of the QOL-DN, PN-QOL-97, and the NeuroQOL-28 within an OOI population and this should be considered when interpreting our findings. Furthermore, each of these instruments detects particular types of neuropathy, and we only assessed large fiber components with our NC-Stat DPN check device.

6. Conclusions

Both the QOL-DN and NeuroQOL-28 significantly predict neuropathy criterion standard components in OOI, PD, and T2D subjects, adding validity to their use as screening measures as early DPN detection tools. The PN-QOL-97 effectively identified multiple DPN-related issues; however, its ability to predict our criteria standards were not statistically significant. Time completion studies revealed that the QOL-DN and NeuroQOL-28 may be used as excellent short screening measures, completed in approximately 6 minutes or less, with reasonable scoring for both. The NeuroQOL-28 is a better fit for immediate feedback, time constraints or limited staff. Consideration should be given to adding fiber specific domains to the NeuroQOL-28 and psychological measures assessing the impact of depression to the QOL-DN, thus adding potential to both instruments to align with different facets potentially experienced by the target population, hopefully increasing the power of their constructs. Asymmetry in NCS findings warrants proposing that future research consider how falls and injuries may contribute to the uneven pathogenesis of SNAP values in subacute and acute hyperglycemic populations and to further explore other options for effective screening for early DPN. Priority should be given to investigations seeking to evaluate the effectiveness of these tools to detect DPN within early, DPN prone, predefined populations, providing new opportunities to increase the effectiveness of these and other instruments in subclinical population screening efforts.

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