

The Prevalence, Severity, and Impact of Painful Diabetic Peripheral Neuropathy in Type 2 Diabetes

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OBJECTIVE— To determine the prevalence of painful diabetic peripheral neuropathy (PDPN) in a population-based sample and to estimate its severity and impact.

RESEARCH DESIGN AND METHODS— A cross-sectional descriptive study consisting of two phases: phase 1, a postal survey to patients with type 2 diabetes (an initial screening questionnaire including one question about pain); phase 2, neurological history and examination using the Toronto Clinical Scoring System. Subjects with PDPN or mixed (PDPN and nonneuropathic) pain completed the Neuropathic Pain Scale and Neuroqol to assess severity and nature of the pain and impact on quality of life. Those without PDPN completed the Neuroqol only.

RESULTS— In phase 1, there was a 92.7% response ($n = 326$), with 208 (63.8%) subjects reporting pain. In phase 2, 269 (82.5%) subjects attended and 51 (19.0%) were found to have PDPN: 99 (36.8%) nonneuropathic pain, 20 (7.4%) mixed pain, and 99 (36.8%) no pain (PDPN prevalence 26.4%). Of those with PDPN, 80% stated that their pain was moderate or severe. Those affected had poorer quality of life than those with no pain (difference in mean scores 3.6 [95% CI 2.5–4.6%]) compared with those with nonneuropathic pain (1.7 [0.4–2.9%]). Both pain and neuropathy score were independently associated with quality of life, and subjects with PDPN had significantly higher neuropathy scores.

CONCLUSIONS— Our study showed a prevalence of PDPN of 26.4%. Having PDPN has a significant negative effect on quality of life, and increasing neuropathy is associated with an increasing risk of developing PDPN.

Diabetes Care 29:1518–1522, 2006

Peripheral neuropathy is one of the most common complications of both type 1 and type 2 diabetes. In a population-based study (1), 22% of the diabetic cohort had peripheral neuropathy that was graded as either moderate or severe. Long-standing peripheral neuropathic pain associated with peripheral neuropathy occurs in one of six diabetic subjects (2).

Peripheral neuropathy (or diabetic polyneuropathy) can present as a loss of

sensation that can lead to neuropathic ulcers, and it is a leading cause of amputation (3,4). It is the most common type of neuropathy in people with diabetes (5,6), though reported prevalence estimates vary, in part as a result of different sampling methods and differing diagnostic criteria.

Peripheral neuropathy may be asymptomatic. When symptoms are present, they may be negative or positive. Negative symptoms include loss of sensa-

tion and loss of strength, while positive symptoms include pricking or pain (6). One of the most distressing symptoms that people can suffer from is neuropathic pain and paresthesia (3). Chronic painful diabetic peripheral neuropathy (PDPN) can cause symptoms that last for years and severely impair quality of life (7).

It was noted in a recent review (8) that knowledge of the epidemiology of PDPN “is compromised by the lack of large population-based studies and by the lack of agreement by authorities on diagnostic criteria, precise definitions and grading of severity of PDPN. These problems can lead to potentially important sampling biases and measurement error.”

The recent study by Daousi et al. (2) investigated the prevalence, severity, and current treatment of “chronic painful neuropathy” in a community sample selected from primary care practices in Liverpool, U.K. They compared the prevalence in people with diabetes (type not specified) with that in a sample of people free from diabetes selected from the same practices. The prevalences in these two samples were 16.2% (95% CI 6.8–16%) and 4.9% (2.6–7.2%), respectively, which is a convincingly significant difference. They assessed neuropathic disability and symptom severity using the same instruments as Young et al. (9). They concluded that chronic painful peripheral neuropathy was “common, often severe but frequently unreported and inadequately treated.”

This current study aimed to determine the prevalence of PDPN in a population-based sample derived from one U.K. general practice and to estimate the severity and impact of PDPN on affected individuals.

RESEARCH DESIGN AND METHODS

This is a cross-sectional descriptive study of diabetic polyneuropathy and PDPN in a complete population-based sample in an urban community in South Wales, U.K. In the U.K., each resident is entitled to primary care that is free at the point of access and, except in cases requiring immediate care (e.g., accidents and injuries), is delivered by the primary

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Received for publication 15 November 2005 and accepted in revised form 20 March 2006.

M.D. has received an honorarium from Napp. A.T. has received honoraria from Napp, Pfizer, and Janssen-Cilag.

Abbreviations: NPS, Neuropathic Pain Scale; PDPN, painful diabetic peripheral neuropathy; TCSS, Toronto Clinical Scoring System.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc05-2228

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care team. The primary care physician acts as the “gate keeper” for referral to specialist care. Every person registered with the U.K. National Health Service (>90% of the population) has one, and only one, primary care practice to which they look for first-line care for conditions such as diabetes. The number of people registered with any one practice is known as its “list size.”

All people registered with the practice in which this research took place (total list size 8,531), aged >18 years and known to have type 2 diabetes, were potentially eligible for inclusion in the study. The source for identification of subjects was the computerized diabetes register, which is well established and has been operational for over 10 years. The total number of people with diabetes (both type 1 and 2) included on the register (as of 1 March 2004) was 385 (a prevalence of diabetes of 4.5%). Excluding those with type 1 ($n = 28$) gives a prevalence of type 2 diabetes of 4.2%. Most of these potential subjects (>95%) were Caucasian.

Power calculation

The existing literature suggests a likely prevalence of PDPN of up to 25 or 30%. The likely response of the total sample of people with type 2 diabetes was estimated to be ~80%. At this range of prevalence and level of response, the precision of a prevalence based on ~300 responders (at 95% CI) is within $\pm 5\%$ (absolute), which is a level of precision judged to be adequate (10). The study was confined to people with type 2 diabetes, since the number of those with type 1 in the population (28 people) was judged inadequate to provide an acceptably precise estimate of the prevalence of neuropathy.

Phase 1: postal survey

All eligible subjects were sent an information sheet and screening questionnaire. The latter included the question, “Do you have a burning, aching or tenderness in your legs or feet?” This was taken from the Diabetic Neuropathy Symptom Score (11). Subjects were also asked the year of diagnosis of diabetes (this method was thought to be more accurate than data derived from the primary care records).

Phase 2: clinical examination and further assessment

Those responding to phase 1 of the study were enrolled in the second phase, in which a clinical neurological history and examination were carried out by one ob-

Table 1—Basic details of study participants, prevalence of pain, and prevalence of PDPN

Population break down	n (%)
Practice population (“list size”)	
Total	8,531
Diabetes register	
Total	385
Known to have type 1 diabetes	28
Known to have type 2 diabetes	354
Found not to have diabetes	3
Deceased	1
Study sample (phase 1)	
Potentially eligible	353
Nonresponders (25) and those unable to respond (2)	27
Responders	326 (92.7)
Reported pain	208 (63.8)
Did not report pain	118 (36.2)
Study sample (phase 2)	
Eligible	326
Attended for assessment	269 (82.5)
Neuropathic pain	51 (19.0)
Nonneuropathic pain	99 (36.8)
Mixed pain	20 (7.4)
No pain	99 (36.8)

server (M.D.) who assessed the presence and severity of PDPN. Peripheral neuropathy was assessed using the validated Toronto Clinical Scoring System (TCSS) (12,13). The TCSS produces a score derived from a clinical assessment of six symptoms, five sensory tests, and lower-limb reflexes, giving a maximal score of 19. The degree of neuropathy was based on the TCSS score and used in a previous study (13); a score ≤ 5 was recorded as showing no neuropathy, 6–8 mild, 9–11 moderate, and >11 equated to severe neuropathy.

The clinical examination allowed the subjects to be categorized into those with PDPN, with nonneuropathic pain, mixed pain (elements of both neuropathic and nonneuropathic pain), and those with no pain. The diagnosis of PDPN was made if the pain was bilateral, below the knees, often worse at night, not related to exertion, and not caused by other conditions known to be present such as arthritis, sciatica, and peripheral vascular disease. Those with PDPN or mixed pain completed the Neuropathic Pain Scale (NPS) (14) and the recently developed Neuroqol (15). Those with nonneuropathic pain or no pain completed the Neuroqol only. The NPS is a validated 10-item questionnaire used to quantify different pain qualities using a 0- to 10-point scale. The Neuroqol is a validated 35-item score as-

sessing quality of life for a person with neuropathy. Following personal communication with the primary author of the Neuroqol, the quality-of-life score was calculated using all 35 items combined into separate domains. The means of the different domains were used to give a single QoL score. Those with PDPN or mixed pain were asked to make an assessment of the severity of their pain by responding to the question, “Over the last week, when your pain has been present, would you rate this as mild, moderate or severe?”

To compare continuous data, *t* tests and ANOVA were used, and Spearman's rank correlation and χ^2 tests were used to compare categorical data. SPSS version 12.0 was used in all analysis.

RESULTS— Table 1 gives the basic details of study participants, the prevalence of pain in those who responded to phase 1, and the prevalence of PDPN in those who attended for phase 2. The characteristics of responders are as follows: phase 1: age 67.1 ± 11.5 years, time from diagnosis 8.04 ± 6.9 years, male sex 55.8%; phase 2: age 66.7 ± 10.9 years, time from diagnosis 8.03 ± 6.8 years, male sex 58.1%.

Of the responders to phase 1 ($n = 326$), 208 (63.8%) reported pain and, of those assessed in phase 2 ($n = 269$), 51 (19.0%) were found to have PDPN, 99

Table 2—Assessment of type of pain and other clinical data in relation to neuropathy

Degree of neuropathy assessed by the TCSS	n (%)	n (%) with PDPN or mixed pain	A1C (%) (means ± SD)	Duration of diabetes (years) (means ± SD)
No neuropathy (0–5)	107 (39.8)	8 (7.4)	6.89 ± 1.3	6.09 ± 5.6
Mild neuropathy (6–8)	98 (36.4)	20 (20.1)	7.26 ± 1.3	8.79 ± 6.5
Moderate neuropathy (9–11)	37 (13.8)	24 (64.9)	7.49 ± 1.3	9.08 ± 8.5
Severe neuropathy (12+)	28 (10.0)	19 (67.9)	8.13 ± 1.9	11.60 ± 8.4
Total	269 (100)	71 (26.4)	7.26 ± 1.43	8.03 ± 6.9

(36.8%) had nonneuropathic pain, 20 (7.4%) had mixed (PDPN and nonneuropathic) pain, and the remaining 99 (36.8%) had no pain. This gives an overall prevalence of PDPN of 26.4% ([51 + 20]/269) in those who attended for assessment.

Table 2 shows the relationship between the presence of neuropathy and PDPN. The odds ratio (OR) for having PDPN or mixed pain (i.e., neuropathy compared with no neuropathy) was 7.9 (95% CI 3.5–17.2), the OR for having pain for those with mild neuropathy compared with no neuropathy was 3.4 (1.4–8.0), and OR for having pain for those with mild neuropathy compared with moderate/severe neuropathy was 15.6 (6.8–35.5). Ordinal regression analysis showed that degree of neuropathy is associated with degree of blood glucose control (as assessed by HbA_{1c} [A1C]) and duration of diabetes. The OR for A1C was 1.28 (95% CI 1.08–1.52; $P = 0.004$), and the OR for disease duration was 1.06 (1.02–1.1; $P = 0.019$).

Fifty-eight subjects did not take part in phase 2 because 25 were inappropriate for assessment (e.g., terminal or psychiatric illness), 12 declined, 7 were no longer

registered with the practice, 8 had died, and 6 were unable to be contacted. For those with nonneuropathic pain ($n = 99$), the main causes of pain recorded were arthritis (39), intermittent claudication (17), cramps (17), and sciatica (12).

Quality-of-life (NeuroQol) scores for those assessed in phase 2 were 5.4 ± 4.6 for PDPN ($n = 51$), 7.8 ± 5.6 for mixed pain ($n = 20$), 3.7 ± 3.3 for nonneuropathic pain ($n = 99$), and 1.8 ± 2.0 for no pain ($n = 99$). Those with PDPN had significantly poorer quality of life compared with those with no pain (difference in mean scores 3.6 [95% CI 2.5–4.6]) compared with those with nonneuropathic pain (1.7 [0.4–2.9]). The difference between those with PDPN and those with mixed pain was not statistically significant (-2.4 [–5.1–0.25]).

Table 3 shows the results (NPS) from the PDPN group in relation to their initial assessment as to the severity of the pain (mild, moderate, or severe). In general, PDPN is rated as unpleasant and sharp (the categories with the highest mean scores). The severe and moderate groups rated the pain as a deep pain, and the mild group reported it as surface pain. The lat-

ter group reported a single type of pain that was felt occasionally, whereas the severe and moderate group report a constant background pain with occasional breakthrough flare-up pain. Participants' self assessment of the severity of their pain correlates well with their assessment of average pain intensity level ($R = 0.678$, $P = 0.001$).

Using univariate ANOVA, both pain (NPS score) ($P < 0.0001$) and neuropathy score (TCSS score) ($P < 0.0001$) were independently associated with quality of life ($r^2 = 0.34$); 34% of the variation seen in quality-of-life score could be attributed to the neuropathy and pain scores. Subjects with PDPN had significantly higher neuropathy scores (TCSS 9.3 ± 3.4) than those without PDPN (5.3 ± 3.09), a difference of 3.9 (95% CI 3.0–4.8). There was a statistically significant difference ($P < 0.0001$) between those with mild neuropathy and those with moderate or severe neuropathy.

CONCLUSIONS— The strengths of the study are 1) that it is population based, 2) that it achieved high levels of participation, and 3) that it combined an

Table 3—NPS scores in subjects with PDPN by self-assessed severity of pain

Patients with neuropathic pain	Mild	Moderate	Severe	Total ± SD
n	10 (20%)	24 (47%)	17 (33%)	51
Average pain over last week	3.3	5.1	7.8	5.6 ± 2.5
How sharp is the pain	4.1	5.0	8.2	5.9 ± 3.2
How hot is the pain	1.2	4.9	6.6	4.8 ± 3.4
How dull is the pain	3.2	5.0	5.4	4.8 ± 3.1
How cold is the pain	2	1.5	2.8	2.0 ± 3.3
How sensitive is your skin	3.1	3.8	3.9	3.7 ± 3.4
How itchy is the pain	2.5	1.8	3.8	2.6 ± 3.3
How unpleasant is the pain	3.9	5.3	8.9	6.2 ± 2.7
Intensity of deep pain	2	5.0	7.3	5.2 ± 3.2
Intensity of surface pain	3.3	3.2	4.7	3.7 ± 3.1
Single type of pain sometimes	7 (70%)	10 (42%)	6 (35%)	24 ± 47%
Single type of pain all the time	1 (10%)	1 (4%)	3 (18%)	5 ± 10%
Background pain all the time with breakthrough flare-up pain sometimes	2 (20%)	14 (58%)	8 (47%)	24 ± 47%

initial, questionnaire-based phase with a subsequent in-depth clinical investigation together with validated tools assessing the severity and nature of the pain and its effects on quality of life.

On the other hand, these results are from a geographically circumscribed population in South Wales and not from a nationally representative sample. However, there is no reason to believe that this population is substantially different, in relation to PDPN, from what would be seen on a wider geographical basis except for the issue of ethnic origin of the subjects. This population is almost exclusively Caucasian.

Prevalence

Many previous studies of PDPN have reported a wide range of prevalence estimates from 3% (16) to 32% (17). Many of these are now quite dated, and diabetes care, diagnostic criteria, and the underlying prevalence of diabetes have changed considerably since they were published. Differing prevalence estimates may also be partly explained by differing research design, including differences in sampling and diagnostic criteria for PDPN.

One of the few primary care and, therefore, population-based studies was undertaken in Finland (18). They recruited 144 patients, aged 45–64 years, with newly diagnosed type 2 diabetes and gathered information about pain symptoms at baseline and, for 65% of the cohort, at 10 years after diagnosis. At baseline, 6% had neuropathic pain. At 10 years, 20% of the survivors were affected. In the present study, the average duration of diabetes was ~8 years and the total prevalence 26.4%.

The estimate most closely comparable with that of the present study is that of Daousi et al. (2); however, they studied chronic PDPN (i.e., present for at least 1 year). Their prevalence estimate of 16.2% (95% CI 6.8–16) is based on people with diabetes sampled from general practices in Liverpool, U.K. This compares with 26.4% for the current study. The Liverpool study was a mixed sample of both type 1 and type 2 diabetic subjects, and they recruited 64% of those eligible. The lower prevalence in Liverpool may be the result of chance or the fact that painful neuropathy had to be present for the previous year in order for it to be classified as chronic painful neuropathy. Including those with type 1 diabetes may also have reduced overall prevalence. The diagnosis was reliant on finding a degree of neuropathy,

which may have excluded some with PDPN. In the current study, eight of our subjects were found to have PDPN even though, according to their TCSS, they had no detectable neuropathy.

Severity

The study by Daousi et al. (2) evaluated pain severity in those with PDPN present for >1 year using a visual analog scale to report maximum pain in the previous 24 h. The mean score was 3.5 (SD 1.5–6.7). The equivalent score, in the current study, is item one of the NPS (the pain intensity score, which reports the average pain over the previous week when pain was present). This value was higher at 5.6. Current pain was also collected in this study and was lower than the average pain intensity score. This probably reflects the fact that most subjects were examined during office hours; the pain of PDPN is characteristically worse at night.

In this study, 20% of those with neuropathic pain (excluding those with mixed pain) described their pain as mild. This grading of pain symptoms correlates well with the pain-intensity scoring. This is in contrast with many other medical conditions that tend to have greater prevalence in those with mild illness compared with more severe categories. This may reflect the nature of neuropathic pain.

In the study by Galer et al. (19), which recorded the pain description of those with PDPN, the subjects had specifically indicated an interest in treatment for the condition. The authors suggested that the cohort used in their study represented a subgroup of the more severely affected PDPN patients. However, the average scores of the NPS showed remarkable similarity with the results from this study, which included all subjects with neuropathic pain. This suggests that the results from Galer et al. were more representative of all subjects with PDPN than previously thought. Another explanation could be that there are cultural differences in pain perception between North Americans and those from the U.K. (20), even though both groups were primarily Caucasian (>90%).

Quality of life

Previous studies have suggested that PDPN has a negative impact on quality of life. Benbow et al. (7) showed that the occurrence of PDPN has an adverse effect on quality of life when compared with a diabetic control group. Galer et al. (19)

revealed statistically significant correlations between a measure of health status and pain intensity.

This study confirms a statistically significant negative effect of PDPN on quality of life when compared with those without pain. It also shows a significant negative effect of PDPN on quality of life when compared with those with nonneuropathic pain, which has not been shown previously.

This study has revealed that PDPN is significantly more likely to occur with increasing neuropathy. By measuring quality of life in this group, a negative effect of diabetic peripheral neuropathy on quality of life could be mediated by pain, other manifestations of peripheral neuropathy, or a combination of both. It could also be explained by those with increased neuropathy having more comorbidities. However, this study shows that both pain and neuropathy have a statistically significant negative effect on quality of life and that these two variables act independently. Pain and neuropathy accounted for one-third of the variation in quality of life.

Relationship between degree of clinical neuropathy and PDPN

Veves et al. (21) suggested that increasingly severe neuropathy is associated with an increased risk of developing PDPN, though their cohort was selective and hospital based and the numbers were small. The study by Sorensen et al. (16), which showed a low prevalence of neuropathy, found that PDPN was far more likely to occur in those with clinically manifested neuropathy than in those without neuropathy. The current study showed that there was a statistically significant difference ($P < 0.0001$) between those with mild neuropathy who have a lower prevalence of PDPN compared with those with moderate or severe neuropathy. Increasing neuropathy is associated with an increased risk of developing PDPN. Deteriorating levels of glycemic control and an increased duration of diabetes are also associated with increasing likelihood of peripheral neuropathy. These comorbidities are so closely interlinked that it is not possible for a cross-sectional study such as this one to disentangle the cause-and-effect relationships.

Eight subjects in this study had PDPN without evidence of neuropathy. These subjects would have been excluded in some previous studies, therefore reducing

the prevalence. We feel it is appropriate to include those with classical pain symptoms even though they have no clinical evidence of neuropathy, as is the case with many other neuropathic pain syndromes that do not require a degree of neuropathy for diagnosis.

It would appear that the pathological processes that initiate neuropathic pain can appear early in the course of neuropathy but become more prevalent with increasing neuropathy.

This study helps to explain the burden that PDPN places on society. If these results can be extrapolated to the diabetic population, then 500,000 subjects in the U.K. have PDPN and 80% of them have moderate or severe pain. The treatment options are limited, which may explain why up to 50% have not requested or received treatment for the condition (2). The development of more effective treatments, with less adverse effects, would appear to be a priority. The finding that increased A1C is correlated with an increased likelihood of developing PDPN is another good reason to promote tighter blood glycaemic control.

Acknowledgments—This study was supported by an educational grant from Pfizer Global Pharmaceuticals.

We are very grateful for the secretarial support provided by Beverley Davies.

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