SHORT COMMUNICATION

Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results

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Diabetes mellitus (DM) is the main cause of small-fibre neuropathy (SFN) in developed countries (1, 2). Notably, one of the possible manifestations of SFN is itch (3–9). The aim of this study was to assess SFN as a potential cause of itch in DM, as well as other factors that may contribute to itch in DM, such as glycaemic control and skin xerosis (10, 11).

MATERIALS AND METHODS

This prospective study evaluated itch among 23 patients with diabetes mellitus type 2 (DM2). Itch intensity was assessed with the Numerical Rating Scale (NRS) and the 4-Item Itch Questionnaire (4IIQ). Skin dryness was evaluated clinically and by non-invasive assessment of epidermis moisturizing. Neuropathy was assessed using clinical Katzenwadel neuropathy scale and SFN was assessed with intraepidermal nerve fibre density (IENFD). Patients' characteristics, study design and methods are shown in Appendix S1.

RESULTS

Twelve patients experienced itch during the study period, with the mean itch intensity assessed on a numerical rating scale (NRS_{max}) over a period of 3 days rated as 8 ± 2 points (range 5–10 points, median 8 points), indicating severe itch. Mean itch NRS_{max} in the previous 24 h was 6.4 ± 2.5 points (range 1–10 points, median 6 points), while the mean result of the 4 Item Itch Questionnaire (4IIQ) was 6 ± 2.6 points (range 3–13 points, median 5.5 points). Itch was usually localized, affecting mainly the lower extremities (58.3%, $n=7$). Two subjects reported generalized itch (16.7%). Regarding neuropathy, there was a visible trend, although this was not statistically significant, for more pronounced neuropathy assessed clinically in patients with itch ($p=0.091$). In addition, a positive trend between itch intensity assessed with the 4IIQ and neuropathy assessment on the Katzenwadel scale was revealed ($R=0.5$, $p=0.08$) (Table SI). The possibility of clinically relevant neuropathy was diagnosed in approximately 66.7% of itchy patients (possible neuropathy in 41.7%, $n=4$, clinically overt neuropathy in 25%, $n=3$), while in the non-itchy group it was diagnosed in approximately one-quarter (possible neuropathy in 27.3%, $n=3$, no patients had clinically overt neuropathy) (**Table I**). More than 80% of patients with itch (83.3%, $n=10$) reported other sensations (tingling, numbness, pain, stinging, burning, hyperaesthesia, hypoaesthesia) clinically connected to polyneuropathy, while it was only approximately 50% in the non-itchy group (54.5%, $n=6$), with significant differences in experienced tingling or numbness ($p=0.022$ and $p=0.043$, respectively). The possibility of clinically relevant polyneuropathy (total score) correlated positively with the HbA1c values ($p=0.02$); however, there were no significant differences regarding glycaemic control (fasting plasma glucose and glycated haemoglobin) between itchy and non-itchy subjects (Table SII). Moreover, our analysis revealed that the total score on the Katzenwadel scale correlated negatively with skin dryness assessed with corneometry in the forearm and abdominal area ($R=-0.5$, $p=0.032$ and $R=-0.5$, $p=0.022$, respectively), as well as there being a tendency to drier skin on the lower legs ($R=-0.4$, $p=0.093$) and skin dryness assessed clinically ($r=0.4$, $p=0.074$) (Table SIII). Furthermore, itchy subjects had significantly drier skin measured with corneometry in the abdominal area ($p=0.016$), as well as on the lower leg; however, this only had marginal significance ($p=0.056$). Skin dryness assessed with corneometry in the area of the forearm correlated negatively with disease duration ($R=-0.5$, $p=0.022$).

Table I. Studied aetiopathogenetic factors contributing to itch in diabetes mellitus and dependencies on itch: neuropathy

	With itch ($n=12$)	Without itch ($n=11$)	p-value*
Katzenwadel scale (points), mean ± SD	3.2 ± 1.7	1.2 ± 1.1	0.091[b]
Median (range)	4 (0–5)	1 (0–3)	
IENFD (fibers/mm) mean ± SD	2.7 ± 1.6	3.7 ± 2.0	NS[b]
Median (range)	2.8 (0–5.2)	3.4 (1.2–6.4)	
Other symptoms linked to diabetic polyneuropathy, *n* (%)			
Numbness	8 (66.7)	2 (18.2)	0.022[c]
Tingling	9 (75)	3 (27.3)	0.036[c]
Pain	3 (25)	2 (18.2)	NS[c]
Stinging	2 (16.7)	1 (9.1)	NS[c]
Burning	5 (41.7)	2 (18.2)	NS[a]
Hyperaesthesia	4 (33.3)	1 (9.1)	NS[c]
Hypoaesthesia	1 (8.3)	0 (0)	NS[c]

[a]χ^2 test, [b]Mann–Whitney *U* test, [c]Fisher's exact test.
SD: standard deviation; NS: not significant; IENFD: intraepidermal nerve fibre density. *Group with itch vs group without itch.

All patients included in the study, had a decreased intraepidermal nerve fibre density (IENFD) (3.2 ± 1.8; median 3.0, range 0–6.2 fibers/mm, $n=23$) in comparison with normative values for the distal leg at the innervation site of the sural nerve (12). The mean value of IENFD for the itchy group was lower than for the non-itchy subjects (2.7 ± 1.6; median 2.8, range 0–5.2 fibers/mm and 3.7 ± 2.0;

median 3.4, range 0–6.4 fibers/mm, respectively); however, this difference did not reach statistical significance. In the whole group studied no subject score was inside the normal range (12).

The IENFD did not correlate with itch intensity assessed by NRS and 4IIQ (detailed data not shown), nor with age, disease duration or glycaemic control.

Females had a higher IENFD (4.0 ± 1.8 [0–4.6] fibers/mm) compared with males (2.9 ± 1.6 [2.0–6.4] fibers/mm; $p=0.016$), while there was a visible trend to drier skin assessed with corneometry (chest area) in patients with lower IENFD ($R=0.4$, $p=0.088$). Patients with lower IENFD have a higher possibility of neuropathy on Katzenwadel neuropathy scale ($R=-0.4$, $p=0.053$).

Patients with severely reduced IENFD (<30% of the normative cut-off value (12)) did not differ according to itching sensations experienced, age, duration of disease, glycaemic control, skin dryness or clinical possibility of neuropathy. A total of 11 patients (47.8%; 6 out of the itchy group and 5 out of non-itchy group) had severely reduced IENFD (Fig. S1). Although not significant, the current study indicates that severely reduced IENFD occurred more frequently in males ($p=0.058$), patients who reported alcohol usage ($p=0.068$) and those experiencing stinging sensations ($p=0.093$).

DISCUSSION

To the best of our knowledge, this is the first study to assess IENFD as a factor contributing to itch in patients with DM. The aim of this study was to determine potential pathogenetic factors in this entity.

In 2005 Brenaut et al. (7) showed that itch might be a symptom of SFN, present in approximately 68% of affected subjects. Recently, in 2020, Pereira et al. (5) proposed diagnostic criteria for chronic generalized itch arising from SFN, and they constitute 3 obligatory criteria: (*i*) presence of chronic itch (CI); (*ii*) symptom begins on normal-appearing skin; and (*iii*) reduced IENFD as per normative values. In addition, several facultative criteria, such as alleviation of itch characteristics (burning, tingling and sensation, such as needle pricks, itch occurring in attacks, moderate to severe itch intensity, daily and long-lasting occurrence) with cold/ice or emollient application and aggregation with warmth and calmness have been proposed. SFN-related itch is a subtype of neuropathic itch with peripheral nerve damage (3, 6). CI arising from neuropathic conditions typically begins on normal-appearing skin, or if scratching behaviour has ensued, patients may also present with chronic scratch lesions. In the study group all itchy patients fulfilled the above-mentioned criteria, CI on non-lesioned skin lasting longer than 6 weeks was diagnosed, and all patients had reduced IENFD compared with normative values (12). The mean itch intensity in the current study group was assessed as 8 ± 2 points, indicating severe itch. Clinically, the vast majority of patients reported pruralgia, with only 2 patients (16.7%) reporting itch exclusively. In addition, patients in the itchy group significantly more frequently experienced tingling or numbness sensations, compared with the non-itchy population (Table I).

Similarly, as in other studies (5, 8), in the current study cohort of patients itch intensity was not correlated with the IENFD values. In our previous study (13) we proposed a pathogenetic model in which prolonged poorly controlled DM resulting in diabetic polyneuropathy contributes to skin dryness and, subsequently, causes itch. Also, in this study subjects with drier skin had lower IENFD, while itchy subjects had significantly drier skin.

All of the aforementioned observations require a cautious approach in the clinical decision-making process, as the groups of patients were relatively small; however, other studies assessing SFN were completed with a similar number of biopsies. In addition, the morphology of the nerve fibres was not assessed. Nevertheless, our experience demonstrates that patients with CI in DM will benefit from a holistic and interdisciplinary approach, taking all possible factors: neuropathy, skin xerosis, but, mainly, glycaemic control, into consideration.

In conclusion, although there was no difference in IENFD between itchy and non-itchy subjects, SFN should be considered as a possible origin of itch in patients with DM, as this may affect further management of itch in diabetes.

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