Barely Scratching the Surface

Itching or pruritus is an unpleasant sensation that evokes the desire or reflex to scratch. Itching in people with diabetes for the most part suggests a skin condition such as psoriasis, eczema, sunburn, athlete’s foot, hidradenitis suppurativa, pruritus vulvae from monilial infections, xerosis and diabetic eczema, necrobiosis lipoidica, allergies to medications, drug eruptions, and many other conditions. Most are inflammatory disorders. In addition, there are generalized medical conditions that need to be excluded such as obstructive jaundice (bilirubin is a skin irritant at high concentrations), polycythemia vera that can cause generalized itching, myxedema, hypoparathyroidism, uremia, iron deficiency anemia, and malignancy or systemic internal cancers such as lymphoma or Hodgkin’s disease (1). When all have been considered and excluded, the question that needs to be answered is, Does the itching derive from a peripheral or a central mechanism?

Sensations associated with scratching

Pain and itch have very different behavioral response patterns. Pain evokes a withdrawal reflex that leads to retraction and is therefore a reaction trying to protect an endangered part of the body. Itch creates a scratch reflex that draws one to the affected skin site (2). It has been hypothesized that motivational aspects of scratching include the frontal brain areas of reward and decision making. These aspects might therefore contribute to the compulsive nature of itch and scratching (2). It is clear, therefore, that itching is not skin-deep.

Unmyelinated nerve fibers for itch and pain both originate in the skin; however, information for them is conveyed centrally in two distinct systems that both use the same peripheral nerve bundle and spinothalamic tract (3). It is surprising, then, that no one has reported on itch as a symptom of neuropathy. In this issue of Diabetes Care, Yamaoka et al. (4) report on truncal itching as being a symptom of diabetic neuropathy. A large-scale survey of 2,656 outpatients with diabetes and 499 patients without diabetes was performed. The prevalence of truncal pruritus of unknown origin (TPUO) in diabetic subjects was significantly higher than that in age-matched nondiabetic subjects (11.3 vs. 2.9%; \( P = 0.0001 \)). The prevalence of other forms of pruritus was not different between the two groups. Multiple logistic regression analysis revealed that abnormal sensation and deep tendon areflexia were risk factors for TPUO independent of age, sex, duration of diabetes, and A1C. Only TPUO related to objective measures of neuropathy; the other five categories of itching, such as head and neck pruritus of unknown origin, leg pruritus of unknown origin, pruritus caused by dermatitis, and pruritus due to athlete’s foot, did not relate the presence or absence of neuropathy. More importantly, TPUO was found to correlate with symptoms of neuropathy, loss of deep tendon reflexes, and orhotastic hypotension. The authors speculate that this is, therefore, a dysfunction of the autonomic nervous system, but there are no measures of skin blood flow (5), sudometry, or small nerve fiber function (6,7,8) that might have solidified this speculation. The authors further postulate that pruritus may be due to an increased mast cell number and histamine content, which has been reported in experimental dry skin in mice (9). A second possibility is that the sensory C-fiber damage by diabetic polyneuropathy causes pruritus directly. Superficial skin pain is considered to be caused by abnormal firing of the pain nerve fiber in diabetic polyneuropathy patients (10). Similarly, abnormal firing of the nerve fiber of pruritus may induce TPUO. In fact, hyperplasia of the C-fiber in epidermis has been reported in dermatitis with strong pruritus (11). The unmyelinated C-fiber that transmits pruritus is a similar fiber to the sympathetic nerve ending in the skin. So, a significant association between TPUO and orthostatic intolerance seems to be reasonable. Both of the two etiological factors, dry skin due to sudomotor hypofunction and direct nerve fiber damage by diabetic polyneuropathy, might be involved in TPUO. To know the accurate etiology of TPUO, a skin biopsy and nerve fiber staining with anti-protein gene product 9.5 antibody in patients with TPUO may have helped (12). From the point of view of mechanistic aspects of itching, this report is barely scratching the surface of itching; hereafter, we will probe further than skin-deep. Itch can originate in the peripheral nervous system (dermal or neuropathic) or in the central nervous system (neuropathic, neurogenic, or psychogenic) (13).

Dermal/pruritoceptive

Itch originating in the skin is considered pruritoceptive and can be induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation. The primary afferent neurons responsible for histamine-induced itch are unmyelinated C-fibers. Two major classes of human C-fiber nociceptors exist: mechano-responsive nociceptors and mechano-insensitive nociceptors. Mechano-responsive nociceptors have been shown in studies to respond to mostly pain, whereas mechano-insensitive receptors respond mostly to itch induced by histamine. Mechanically induced itch without a flare reaction does not involve histamine; therefore, it is possible that pruritoceptive nerve fibers have different classes of fibers (2).

Itch receptors are only found in the epidermis and the epidermal/dermal transition layers. Individual itch powder spicules (mucuna pruriens) cause maximal sensitivity when injected into the basal cell layer or the innermost layer of the epidermis. Surgical removal of those skin layers removes the ability for a patient to perceive itch. Itch is never felt in muscle, joints, or inner organs, which shows that deep tissue does not contain an itch-signaling apparatus (14).

Sensitivity to pruritic stimuli is not evenly distributed across the skin and has a random spot distribution with similar densities to that of pain. The same substances that elicit itch upon intracutaneous injection (injection within the skin) elicit only pain when injected subcutaneously (beneath the skin). Itch is readily abolished in skin areas treated with nociceptor excito- toxin capsicain but remains unchanged in skin areas that were rendered insensitive to touch by pretreatment with saponins, an anti-inflammatory agent. Although experimentally induced itch can still be perceived under a complete A-fiber conduction block, it is significantly
findings show that itch is not a subliminal itch state for more than 30 min. These that brief noxious stimuli created an anti-
hibition of pain. In addition, it was found for an extended period of time but no in-
there was a significant inhibition of itch
they induced noxious counter stimuli, such as heat,
stimuli, the reduction of pain and itch
tard oil) in their skin. They found that
histamine) and pain (with topical mus-
nual neuropathy, and nerve irritation (16).
Neurogenic
Neurogenic itch, which is itch induced centrally but with no neural damage, is
often associated with increased accumu-
lation of endogenous opioids and possi-
ably synthetic opioids (14).
Psychogenic
Itch is also associated with some symp-
toms of psychiatric disorders such as
tactile hallucinations, delusions of parasito-
tis, or obsessive-compulsive disorders (as in OCD-related neurotic scratching) (14). Thus, attributing itch to a peripheral neuropathy requires careful exclusion of central causation.

Interactions between itch and pain: pain inhibits itch
Counter-irritation has often been used to
decrease pain perception. It is often used clinically, e.g., the application of capsic-
 which induces pain only to desensitize and relieve it. However, it appears that the
sensation of itch can be reduced by many painful sensations. Ward et al. (17) re-
ported the effects of noxious and nonno-
xious counter stimuli, such as heat, physical vibration, or chemical stimula-
tion on skin, were studied in healthy adults after they had experimentally in-
duced itch (transdermal iontophoresis of
histamine) and pain (with topical mustard oil) in their skin. They found that
when they induced noxious counter stimuli, the reduction of pain and itch
only lasted for up to 20 s. However, when
they induced noxious counter stimuli, there was a significant inhibition of itch
for an extended period of time but no in-
hibition of pain. In addition, it was found that brief noxious stimuli created an anti-
itch state for more than 30 min. These
findings show that itch is not a subliminal
form of pain and that noxious counter-
stimulus is likely to act through a central
mechanism instead of a peripheral one (17). Thus, noxious heat and scratching
have an inhibitory effect on itch (18), but this needs to be demonstrated in diabetic
polyneuropathy.

Mediators of itch
There is a long prodromal period of dia-
abetic polyneuropathy in which there are
increased levels of inflammatory cyto-
kines (5). Inflammatory mediators, such as
bradykinin, serotonin (5-HT), and
prostaglandins, that are released during a
painful or pruritic inflammatory condi-
tion not only activate pruriceptors but
also cause acute sensitization of nocicep-
tors. In addition, expression of nerve
growth factors (NGFs) can cause struc-
tural changes in nociceptors, such as
sprouting. NGF is high in injured or
flamed tissue. Increased NGF is also
found in atopic dermatitis, a hereditary
and noncontagious skin disease with
chronic inflammation (19). NGF is
known to upregulate neuropeptides, es-
pecially substance P. Substance P has
been found to have an important role in
inducing pain. Substance P may contribu-
te to itch by increasing neuronal sensitiz-
aton and affect release of mast cells,
which contain many granules rich in hist-
tamine, during long-term interaction (2).
In those with diabetes, there is a defi-
ciency of NGF and the response to sub-
stance P is impaired; again, one is
surprised that truncal itching occurs in
diabetic polyneuropathy.

Central sensitization
Noxious input to the spinal cord is known
to produce central sensitization, which
consists of allodynia, exaggeration of
pain, and punctate hyperalgesia, which is
extreme sensitivity to pain. Two types of
mechanical hyperalgesia can occur: 1) tou-
ch that is normally painless in the un-
injured surroundings of a cut or tear can
trigger painful sensations (touch-evoked
hyperalgesia) and 2) a slightly painful pin-
prick stimulation is perceived as more
painful around a focused area of inflam-
mation (punctate hyperalgesia). Touch-
evoked hyperalgesia requires continuous
firing of primary afferent nociceptors, and
punctate hyperalgesia does not require
continuous firing, which means it can
persist for hours after a trauma and can be
stronger than normally experienced. In
addition, it was found that in patients
with neuropathic pain, histamine ione-
phoresis resulted in a sensation of burn-
ing pain rather than itch, which would be
induced in normal healthy patients. This
shows that there is spinal hypersensitivity
to C-fiber input in chronic pain (2). Per-
haps the damage to C-fiber in small fiber
polyneuropathies (5) unbridles the central
pruritogenic mechanism causing itching.
Thus, although truncal pruritus may
have drawn attention to a possible rela-
tionship with diabetic polyneuropathy,
this is only scratching the surface of the
complex relationship between itching and
central and peripheral somatic and
autonomic nerve function. The provocat-
ive article in this issue of Diabetes Care
should lead to an interesting probing of
the complexities and depths of itching
and provide new insights into the rela-
tionship between peripheral and central
processing of cognitive function in
diabetes.

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DOI: 10.2337/dc09-2035
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Acknowledgments—No potential conflicts of
interest relevant to this article were reported.

References
1. Botero F. Pruritus as a manifestation of
systemic disorders. Cutis 1978;21:873–
880
2. Ikoma A, Steinhoff M, Ständner S, Yostipo-
vitch G, Schmelz M. The neurobiology of
itch. Nat Rev Neurosci 2006;7:535–547
3. Greaves MW, Khalifa N. Itch: more than
skin deep. Int Arch Allergy Immunol
2004;135:166–172
4. Yamaoka H, Sasaki H, Yamasaki H,
Ogawa K, Ohita T, Furuta H, Nishi M,
Nanjo K. Truncal pruritus of unknown
origin may be a symptom of diabetic
polyneuropathy. Diabetes Care 2010;33:150–155
5. Vinik A, Ullal J, Parson HK, Casellini CM.
Diabetic neuropathies: clinical manifesta-
tions and current treatment options. Nat
Clin Pract Endocrinol Metab 2006;2:
269–281
6. Arora S, Smakowski P, Frykberg RG,
Simeone LR, Freeman R, LoGerfo FW,
Veves A. Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy. Diabetes Care 1998;21:1339–1344

7. Berghoff M, Kilo S, Hilz MJ, Freeman R. Differential impairment of the sudomotor and nociceptor axon-reflex in diabetic peripheral neuropathy. Muscle Nerve 2006;33:494–499

8. Veves A, Akbari CM, Primavera J, Donaghue VM, Zacharoulis D, Chrzan JS, DeGirolami U, LoGerfo FW, Freeman R. Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. Diabetes 1998;47:457–463

9. Ashida Y, Denda M. Dry environment increases mast cell number and histamine content in dermis in hairless mice. Br J Dermatol 2003;149:240–247

10. Pfeiffer EA. Electrical stimulation of sensory nerves with skin electrodes for research, diagnosis, communication and behavioral conditioning: a survey. Med Biol Eng 1968;6:637–651

11. Tobin D, Nabarro G, Baart de la Faille H, van Vloten WA, van der Putte SC, Schuurman HJ. Increased number of immunoreactive nerve fibers in atopic dermatitis. J Allergy Clin Immunol 1992;90:613–622

12. Pittenger GL, Ray M, Burcus NI, McNulty P, Basta B, Vinik AI. Intraepidermal nerve fibers are indicators of small-fiber neuropathy in both diabetic and nondiabetic patients. Diabetes Care 2004;27:1974–1979

13. Yosipovitch G, Greaves MW, Schmelz M. Itch. Lancet 2003;361:690–694

14. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z. Itch: scratching more than the surface. QJM 2003;96:7–26

15. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjörk HE. Specific C-receptors for itch in human skin. J Neurosci 1997;17:8003–8008

16. Bernhard JD. Itch and pruritus: what are they, and how should itches be classified? Dermatol Ther 2005;18:288–291

17. Ward L, Wright E, McMahon SB. A comparison of the effects of noxious and innocuous counterstimuli on experimentally induced itch and pain. Pain 1996;64:129–138

18. Yosipovitch G, Fast K, Bernhard JD. Noxious heat and scratching decrease histamine-induced itch and skin blood flow. J Invest Dermatol 2005;125:1268–1272

19. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. Br J Dermatol 2000;142:1114–1120