Pruritus in diabetes mellitus (DM) and its pathophysiology-based treatment

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ABSTRACT

Pruritus is a common complaint of diabetic patients with a substantial impact on financial and health status, but the pathophysiology is unclear and treatment with antihistamines has mostly been unsuccessful. To date, we still do not have guidelines to help us treat pruritus in diabetes mellitus, so we felt the need to review the existing literature to explore possible ways to treat these patients. We collected 85 pieces of literature from various sources such as PubMed and Google Scholar, and independently extracted these data to make this review. While the pathophysiology behind pruritus in diabetes mellitus remains largely unknown, some trials have found a few pharmacological treatments to be effective in alleviating itch in these patients.

ABSTRAK

Pruritus merupakan keluhan umum yang mempunyai dampak yang besar baik secara finansial maupun pada kesehatan pasien diabetes melitus, namun patofisiologinya masih belum jelas dan pengobatan dengan antihistamin seringkali tidak berhasil. Sampai saat ini, pedoman tatalaksana untuk pruritus pada pasien diabetes mellitus masih belum ada, sehingga kami merasa perlu untuk mempelajari literatur yang ada untuk mencari alternatif untuk mengobati pasien diabetes mellitus dengan pruritus. Kami mengumpulkan 85 literatur dari berbagai sumber seperti PubMed dan Google Scholar, dan mengekstraksi data dari literatur-literatur tersebut secara independen untuk membuat tinjauan pustaka ini. Meskipun patofisiologi pruritus pada diabetes mellitus masih belum dimengerti, beberapa penelitian menemukan beberapa pengobatan farmakologik yang efektif.

INTRODUCTION

Pruritus, or commonly known as itch, is a disturbing stimulus that causes the desire to scratch the affected skin area. Pruritus is classified based on its location and its duration. Location-wise, pruritus is classified into generalized and localized pruritus. It is categorized as acute pruritus if it is experienced for up to six weeks. Meanwhile, if it lasts longer than six weeks, it is categorized as chronic.[1,2] Recent epidemiological studies show that chronic pruritus occurs in 22–27% of the population.[1,3]

The International Forum for the Study of Itch (IFSI) classified chronic pruritus into 6 categories: (1) dermatologic, (2) systemic, (3) neurologic, (4) psychogenic/psychosomatic, (5) mixed, and (6) others.[4] Diabetes mellitus (DM), a health issue that has reached pandemic proportions and is also a health problem of dire proportions in Indonesia,[4–6] is one of the systemic disorders that is commonly linked to pruritus.[2] However,

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some authors suggest pruritus in DM as mixed pruritus with the additional role of both dermatologic and neurologic components.[4]

A study conducted on 106 DM patients by Al Mutairi *et al.*[7] reported pruritus as the second most common cutaneous manifestation, affecting 49% of patients. Specific studies on pruritus in DM are limited and hard to compare due to non-homogenous methodology. Most studies did not specify if their results were the point prevalence, life-time prevalence or incidence, of pruritus. In their literature review, Stefaniak *et al.*[4] concluded that pruritus might be experienced in about 18.4% to 27.5% of patients with type 2 DM (T2DM).

Patients with chronic pruritus generally have lower quality of life (QoL).[1,2,4,8,9] The QoL regression in pruritic patients is similar to that in chronic pain patients.[8,10] It has a remarkable impact on the medical and economic condition of the patients. In the United States of America, patients with pruritus have an expenditure ratio of 1.64 times more than the average population. About $90 billion extra per year needs to be spent for treating pruritus.[10] The impact of chronic pruritus is also magnified in diabetic patients. Intense scratching due to pruritus can cause wounds that might lead to diabetic foot ulcers (DFU) and sleep disturbance. DFU is a chronic and devastating complication of diabetes, and around 5–24% of DFU cases will end in loss of limb, usually by means of amputation.[11,12] Long term sleep disturbance has substantial adverse effects on metabolism, disruption in circadian rhythms, and pro-inflammatory responses, and therefore it will further exacerbate the complications of diabetes mellitus.[13] All of the consequences of DFU and sleep

disturbance caused by pruritus greatly reduce the QoL of diabetic patients and consequently increase the mortality rate.

Treating pruritus in diabetes should be done to improve the QoL but unfortunately it remains a challenge. There is no proposed mechanism that can accurately explain the pathophysiology of pruritus in diabetes. Underlying pathophysiology of diabetes, the course of the disease, coexisting comorbidities, and medications complicate the issue and tend to make diabetic patients more susceptible to developing pruritus.[4] Pruritus in diabetic patients does not always respond well to the use of antihistamine. Therefore, it is assumed that histamine is not the only pathway that plays a part in pruritus in diabetic patients.[4,14]

Pruritus is a common complaint amongst diabetic patients with a substantial impact on financial and health problems, but the pathophysiology is not clear and treatment with antihistamines has mostly been unsuccessful in many diabetic patients with pruritus. In light of this issue, we would like to understand it better by doing this literature review. We aimed to gather current knowledge of the pathophysiology of pruritus in DM and the possible use of various pathophysiology-based managements, other than antihistamines, in diabetic patients.

MATERIALS AND METHODS

Literature searches were performed on Google Scholar and PubMed without any time restrictions, using the keywords: pruritus, dermatology, DM, and itch. The last search was done on 1st of October 2021. Results from the initial search are reviewed by reading the abstract, discussion, and conclusion to see if they

are relevant to the inclusion criteria, which are as follows 1) Discussing various forms of chronic pruritus related to DM; 2) Talks about the pathophysiology of DM related to the dermatological aspect of it.

Case series, case controls, cross-sectional studies, review articles, systematic reviews, web pages, books, book reviews, reports, editorials, position statements, commentaries, exploratory studies, open-label studies, experimental studies, randomized controlled trials, prospective cohorts, and retrospective cohorts were included in our review. The literature which passed the initial screening underwent a more thorough assessment and independent extraction by all four authors.

A total of 132 articles from Google Scholar and 110 from PubMed were obtained at the start of the search. Seventy-one articles were deleted after manual double checking. A screening was then carried out in which we each independently reviewed the abstracts and conclusions of each literature. Sixty-five literatures were excluded, leaving 106 at hand. A more in-depth review of the literature excluded another 21 and we ended up with 85 literatures.

Among the 85 papers, there is one case series, three case controls, seven cross-sectional studies, 45 review articles, two systematic reviews, one web page, three books, and one book section. The others are one book review, two reports, one editorial, one position statement, one commentary, one exploratory study, two open-label studies, nine experimental studies, one randomized controlled trial, two prospective cohorts, and one retrospective cohort.

DISCUSSION

Diabetes mellitus is a disease characterized by high blood glucose levels resulting from defects in insulin secretion and/or insulin action.[15] Pruritus is often cited as a common manifestation in diabetic patients.[16] There are various conditions associated with the onset of pruritus in diabetic patients, such as skin disorders, diabetic neuropathy, end-stage renal disease, and iatrogenic or secondary to anti-diabetic therapy.[15,16] The prevalence of skin disorders in DM ranges from 30% to 97% in various regions worldwide, but not all of them have pruritus as their symptom.[4,15,17] Pruritus can be experienced by diabetic patients with non-infectious (such as dry skin, prurigo nodularis, lichen planus) or infectious (such as dermatophytosis, candidiasis) skin disorders.[15] Pruritus can also be experienced by diabetic patients for no apparent reason.[18]

Pathophysiology of pruritus in DM is not fully understood. The connection between blood glucose level and pruritus is inconclusive.[16] Ko *et al.*[19] found a connection between high postprandial glucose levels and generalized pruritus in patients with DM. Hillson *et al.*[20] also found a connection between fasting plasma glucose levels and generalized pruritus in both newly diagnosed and untreated DM. Researches with HbA1c have a more mixed result. Neilly *et al.*[21] found no correlation between HbA1c and pruritus, and this finding is echoed by Ko *et al.*[19] as well. However, at the other end of the spectrum, a study by Afsar and Elsurer found that visual analogue scale (VAS) itch score on diabetic patients is strongly related to HbA1c.[22]

Since there are various conditions associated with the onset of pruritus in diabetic patients, it follows that there should be various mediators or pathways in the pathophysiology of pruritus in DM. Before we dive deeper

into the pathophysiology of pruritus in DM, we will first take a look at the pathophysiology of pruritus in general.

Pathophysiology of pruritus in general

Pruritus is a unique sensation. It is encoded by genetically distinct neurons both in the peripheral and central nervous systems. Characteristically, it triggers scratching. Although specific neurons for pruritus have been detected, it is not clear whether all the neurons signal pruritus and only pruritus. Yet, pruritus also interacts with the other sensory modalities (pain, temperature, and mechanical force) at multiple locations, from a particular dermatome to the brain.[23,24] This review summarized our current understanding of the molecular and neural mechanisms of pruritus.

Pruritus is sensed by cutaneous nerve fibers called pruriceptors. Unmyelinated C-fibers, mostly, and thin myelinated Aδ-fibers are responsible for sensing pruritus.[23] Branching terminal fibers of these sensory afferent neurons are found at the epidermal-dermal junction.[14] Some of them reach the uppermost viable layer of epidermis.[23] Sensory nerves are part of an interactive milieu with a plethora of mediators generated from the sensory neurons themselves, neighboring cells, keratinocytes, and the microbiome. There are multidirectional communications between the nervous and immune systems within the skin, perhaps directed against components of the microbiota, which can evoke pruritus.[23,24] Currently known mediators of pruritus, which play different roles in different pruritus conditions, include histamine, serotonin/5-hydroxytryptamine (5-HT), proteases,

cytokines-interleukins, peptides (bradykinin, substance P, calcitonin gene related peptide, neurotrophin, opioid peptides), and phospholipid metabolites (cannabinoids, eicosanoids, platelet-activating factor). These mediators are key contributors to and exacerbate pruritus by activating cognate receptors on sensory neurons.[14]

The binding of those mediators with their cognate receptors activates a series of signal transduction systems. Currently, two signal pathways of pruritus have been identified, namely histamine-dependent (histaminergic) signaling pathway and histamine-independent (non-histaminergic) signaling pathway.[14] In the histaminergic pathway, binding of histamine to its cognate receptors, particularly H1 receptor and H4 receptor, promotes activation of phospholipase C (PLC) β3, enhances calcium levels, and irritates lipoxygenase (LOX) and phospholipase A (PLA). These further induce the activation of downstream target transient receptor potential cation channel vanilloid 1 (TRPV1). Pruritus signals through this pathway are relayed via mechanically insensitive C-fibers (CMi), which nerve endings mainly distribute in the dermo-epidermal junction, to their cell bodies in dorsal root or trigeminal ganglia followed by synapsing with second-order neurons in the dorsal horn of the spinal cord.[14,23]

The other signaling pathway, nonhistaminergic, seems to be involved in pruritus which is resistant to antihistamine, such as chronic pruritus.[14,25] Many pruritogens can stimulate this pathway. Binding of pruritogens with their cognate receptors stimulates either protease-activated receptor 2 (PAR-2) or Mas-related G protein-coupled receptors (Mrgprs).

Activation of PAR2 sensitizes PLC, then the downstream targets including TRPV1 and transient receptor potential cation channel ankyrin 1 (TRPA1) are activated. Activated Mrgprs, is then coupled to G beta-gamma protein complex (Gβγ) or PLC or other; then they promote TRPA1/TRPV1 activation. This non-histaminergic signaling pathway is usually mediated by a class of mechanically sensitive C-type fibers (CMHs), which nerve endings mainly distribute in the epidermis. These CMHs also synapses with second-order neurons in the dorsal horn of the spinal cord.[14,23]

Peripheral pruritus nerves synapse with interneurons as the second-order neurons in the dorsal horn of the spinal cord. Interneurons are the gate-keepers of neuronal activity. They have excitatory or inhibitory function to modulate afferent input carried to the projection neurons to the brain. Gastrin-releasing peptide (GRP)+ interneurons and tertiary GRP receptor (GRPR)+ neurons are key to stimulating pruritus circuits in the spinal cord. Binding of GRP to GRPR evokes scratching reaction.[14,23,26] Spinal pruritus signals transmitting process is also elicited by binding of B-type natriuretic peptide (BNP) to its transmembrane natriuretic peptide receptor A (NPRA). BNP-NPRA may serve as the upstream of the GRP-GRPR system to regulate neurotransmission of pruritus in the spinal cord. BNP and glutamate released from primary sensory neurons activate secondary neurons expressing NPRA in the dorsal horn. Then the secondary neurons secrete GRP and activate GRPR of a third neuron and ultimately lead to pruritus perception.[14,23,24]

Complementary to the excitatory circuits, there are numerous interneuron populations in the spinal cord that have an inhibitory function in the pruritus process. For example, inhibitory basic helix loop helix 5 interneurons (B5-I) and somatostatin (SOM) interneurons. Inhibitory interneurons express γ-aminobutyric acid (GABA), as the major neurotransmitter, besides neuropeptide Y (NPY), dynorphin (DYN, a kappa-opioid agonist), and galanin. B5-I inhibits GRP+ and GRPR+ neuron signaling of pruritus. Loss of inhibition, either by depletion of inhibitory interneurons or the inhibitory neurotransmitters results in intensified pruritus.[23,24,26]

GRPR+ neurons, as the third-order neurons in the dorsal horn of the spinal cord, decussate anteriorly before traveling rostrally along the contralateral spinothalamic and spinobrachial tracts. GRPR+ neurons synapse with thalamic neurons that communicate with various brain regions, including the sensory cortex, insula, and motor cortex, to produce pruritus perception and a strong motor response to pruritus – the scratch.[24,26] In addition to these peripheral inputs, higher-level brain regions provide descending control to spinal cord pruritus neurons. Pruritus is potentiated by serotoninergic neurons from the nucleus raphe magnus (NRM) that directly connect with GRPR+ neurons. Inhibitory interneuron activity in the spinal cord is modulated by noradrenergic neurons in the locus coeruleus modulate. The mid-brain periaqueductal gray (PAG) is activated during scratching and was considered as a pruritus suppressing brain area. GABAergic and dopaminergic (DA) neurons in the ventral tegmental area (VTA) play a role in the central reward processing of pruritus. In general, DA neurons are key neuronal elements in motivation and reward systems, whereas GABA neurons are believed to drive aversion and disrupt reward processes.[23]
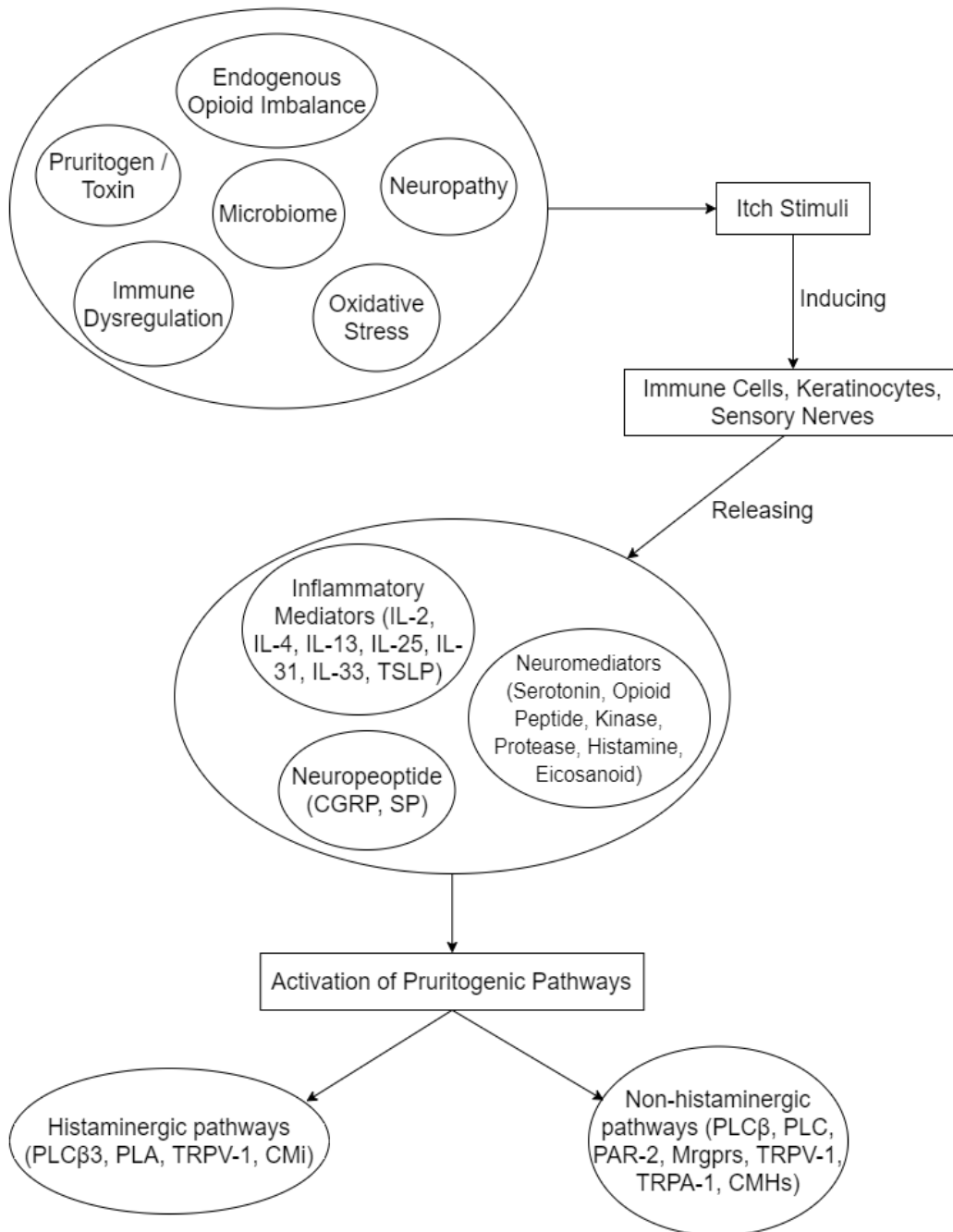
FIGURE 1. Chronic pruritus signaling pathways. **(**IL-2: interleukin-2, IL-4: interleukin-4, IL-13: interleukin-13, IL-25: interleukin-25, IL-31: interleukin-31, IL-33: interleukin 33, TSLP: thymic stromal lymphopoitein, PLCβ3: phospholipase C beta 3, PLA: phospolipase A, TRPV-1: transient receptor potential cation channel subfamily V member 1/vanilloid receptor 1, CMi: mechano-insensitive C nerves, PLCβ: phospholipase C beta, PLC: phospolipase C, PAR-2: protease activated receptor 2, Mrgprs: mas-related G protein-coupled receptors, TRPA-1: transient receptor potential cation channel subfamily A member 1, CMHs: mechanically sensitive C-type fibers)

Another mechanism that might play a role in the pruritogenic pathway would be opioid receptor signaling. Many studies concluded that there is a significant overlap between pain and pruritus neuronal pathways. It is believed that the nociceptive neurons are tasked to create a constant tonus of inhibition of the pruriceptive neurons. Due to this, we experience an urge to scratch every time we feel a pruritus, replacing the pruritus signal with local pain induced by the scratching. Similarly, when pain is reduced pharmacologically, for example by administration of morphine, pruritus often sets in at the area with reduced pain transmission. This mechanism is likely fueled by inhibitory interneurons in the dorsal horn of the spinal cord. This theory is supported by genetic experiment study on mice. When the gene that controls the transcription factors for these inhibitory interneurons was deleted, the mice suffer from severe chronic pruritus.[27,28]

The mechanism of opioid receptors in pruritus is thought to involve upregulations of the central mu-opioid receptors which give rise to feelings of pruritus, while suppressing the peripheral kappa-opioid receptors that reduce pruritus perception. Morphine, which is a mu-opioid receptor agonist, can induce pruritus in humans, while naloxone, a mu-opioid receptor antagonist, can inhibit pruritus instead. Activation of the kappa-opioid receptor system in mice has also been shown to reduce scratching activity induced by substance P, histamine, and morphine. Nalfurafine, a kappa-opioid receptor agonist, has been studied in Japan to treat pruritus in patients with chronic kidney disease (CKD) and chronic liver disease (CLD). The result showed that there is a partial decrease in pruritus intensity without any severe adverse reactions.[27,28]

Pathophysiology of pruritus in DM

The pathophysiology of pruritus in DM is not fully understood, as mentioned before. It seems that the pathophysiology is complex and interconnected. Researchers nowadays believe that dry skin (xerosis cutis) and diabetic peripheral neuropathy are the two main factors associated with pruritus in DM.[4] Disruption of skin barrier underlies the occurrence of dry skin.[29] Therefore, we will focus on the role of skin barrier disruption and diabetic peripheral neuropathy in the pathophysiology of pruritus in DM. Moreover, we will highlight the role of oxidative stress in causing pruritus in DM, as it is believed that oxidative stress plays an important role in the development of complications in DM.[30] At the end, we will discuss about pruritus in diabetic patients with CKD and pruritus secondary to anti-diabetic therapy.

Skin barrier disruption

Skin barrier (SB) is exerted by the epidermis, especially stratum corneum (SC).[29] It protects humans from their surroundings. SB prevents the entry of potential pruritogens like infectious agents and allergens, provides protection against ultraviolet light and oxidative stress, and plays a role in homeostasis, such as humidity of SC.[2,29,31] SB consists of cellular and non-cellular structures.[32] Impaired skin barrier integrity causes excessive water loss and leads to skin dryness. Transepidermal water loss (TEWL), SC hydration, and pH are some of the parameters usually measured to assess skin barrier function.[29]

SB's functions and integrity are disrupted in DM.[4,17,29] A study on physiological changes in the skin of obese, diabetic Japanese men by Ai *et al.*[33] found that there is a significantly higher TEWL and a markedly lower stratum corneum hydration level compared to controls, indicative of dry skin. Skin hydration in diabetic patients is found to be 38% lower when compared to non-diabetic patients.[34] A case-control study

conducted on 52 patients with T2DM by Kim *et al.*[35] also found that SC hydration was significantly lower than their age- and sex- matched non-diabetic control. Moreover, they found a significant decrease of ceramides, free fatty acids, and cholesterol in the SC of DM patients. Triglycerides replaced ceramides as the most substantial SC lipids. Changes in the amount and composition of SC lipids, functioning as a water barrier, leading to skin dryness.[29,36] Decreased sebaceous gland activity is also observed in DM patients and will exacerbate skin dryness.[29]

Dry skin is characterized by a scaly, rough, cracked, and fissured surface.[29,37] In diabetic mice models, impaired epidermal integrity is caused by a certain kind of protein related to tight junction structure, named ZO-1, which was found to be more widely and diffusely expressed, causing hypoplasia and misalignment of the epidermal basal layer.[35,38] Typically, when a dye called lucifer yellow (LY) is applied to normal mice's ears, the stain's distribution would be limited to hair follicles and outer areas of the SC. In diabetic mice, LY stains a wider area of the SC. The quantity of LY positive signals was found 2.7 ± 0.4-fold greater in diabetic mice than in controls.[38] The diameter size of LY dye spots can reach up to 10 μm or more. Epidermal integrity impairment makes the diabetic skin more vulnerable to external substances, such as infectious pathogens and chemical damage. Fungus can easily infiltrate the skin of diabetic patients because their hypha size is about 6–12 μm, smaller than the size of the dye spots.[35,38,39]

The entry of pathogens or chemical agents through the disrupted skin barrier and the skin barrier disruption itself may trigger inflammatory reaction.[40,41] Skin cells, immune cells, and the microbiome can release pruritus mediators that can activate their cognate pruriceptors on the nerve endings. In an inflammatory environment, either histaminergic or nonhistaminergic pathway can be activated, depending on the mediators present. Histamine, released from mast cells, activates CMi that are different to CMHs which are activated with the other pruritogens, as described in the section on the pathophysiology of pruritus in general. The potential action that is formed in the afferent sensory nerves will be conducted to dorsal horn of spinal cord, then projected to thalamus and finally to the somatosensory cortex in the brain, including the motor cortex, to induce perception of pruritus and scratching. The pruritus-scratch cycle can perpetuate skin barrier damage and pruritus. Severe scratch-induced epidermal injury also injures sensory nerve endings that may be rendered hyperexcitable upon regeneration.[29,40]

Diabetic peripheral neuropathy

Diabetic neuropathy is the most prevalent chronic complication of diabetes.[42] It is a diagnosis of exclusion. It will be diagnosed as diabetic neuropathy if no additional causes of neuropathy other than diabetes is found.[42,43] Patients with prediabetes may also develop neuropathies that are similar to diabetic neuropathies.[42] The most common form of diabetic neuropathy is diabetic peripheral neuropathy.[42,44] Risk factors for diabetic peripheral neuropathy include age, male gender, duration of diabetes, uncontrolled glycemia, height, overweight and obesity, and insulin treatment.[45] It is characterized by neurodegeneration of peripheral nerve systems that preferentially targets sensory and autonomic neurons.[46] Among the peripheral nerve fibers, small nerve fibers (e.g., Aδ and C) are the most vulnerable structures. Damage to small nerve fibers is responsible for the development of small fiber neuropathy (SFN) in DM.[47]

A multifactorial pathogenesis of

diabetic peripheral neuropathy is suggested by experimental studies, but the causes remain unknown. A prevailing view of the pathogenesis is that oxidative and inflammatory stress may, in the context of mitochondrial dysfunction and hyperglycemia, damage nerve cells.[42,45,47] Moreover, hyperglycemia is associated with decreased expression of CB_1 receptors in dorsal root ganglia. A decline in CB_1 receptor expression may contribute to the loss of neuroprotective effect of cannabinoids and the neurodegenerative process observed in DM.[1,48] Neurovascular impairment with poor repair processes and endothelial dysfunction also have been implicated in the neurodegenerative process.[44,49] The entire neuron, from the perikaryon (cell bodies) to the terminal, is targeted by diabetes.[46] Biopsy findings reflect a loss of multifocal and focal proximal nerve fibers, but a more severe damage is visible in distal fibers.[45] Degeneration of intraepidermal small nerve fibers and depletion of small nerve fibers surrounding sweat glands were identified.[47,50] Axonal degeneration and segmental demyelination are the main pathological characteristics of neuropathic damage induced by hyperglycemia.[45,46]

Depletion of small nerve fibers surrounding sweat glands cause sudomotor dysfunction. Sudomotor dysfunction is a common feature of diabetic autonomic neuropathy. Autonomic supplies in the skin and subcutaneous tissue have an essential role in blood flow, nutritional delivery, and lubrication modulated by the sudomotor function (sweat gland).[51] Sudomotor dysfunction decreases sweat production. Lower sweat production has a strong positive correlation with the hydration status of the surface of the skin. Lower hydration status will lead to dry skin.[29,42,44,50] Furthermore, pruritus can occur based on the skin barrier disruption caused by dry skin.[52,53]

Meanwhile, damage to the pruriceptive small nerve fibers can result in neuropathic pruritus. Neuropathic pruritus is generally understood as pruritus resulting from neuronal or glial damage without skin alterations.[26] Injured sensory neurons normally have reduced sensation, but in some people, a paradoxical compensatory mechanism may occur. Hyperexcitability may develop in the injured sensory neurons and their surrounding network, generating action potentials in the absence of a stimulus and altering stimulus-response function.[46,54]

Ion channel expression, trafficking, and phosphorylation status within sensory neurons are critical determinants of excitability.[46,54,55] Channels within the injured sensory neurons and the surrounding network can be directly activated independently from receptor recruitment, to excite afferent neurons and produce neuropathic pruritus. For example, voltage-gated sodium channels (Na_v) which are expressed in small-diameter sensory neurons of the dorsal root ganglia, trigeminal ganglia, and sympathetic ganglia. These channels regulate neuronal excitability and action potential propagation by altering resting membrane potential and inactivation thresholds.[26,54] Methylglyoxal, one of the increased reactive metabolites in DM, can post-translationally modify $Na_v1.8$ and TRPA1, which leads to sensory neuron hyperexcitability.[46] Numerous gain-of-function mutations serving to increase neuronal excitability have also been identified as the cause of neuropathic pruritus in patients.[26] Hyperpolarization-activated cyclic nucleotide-gated channels which are important for repetitive firing also act to regulate neuronal excitability, whereas potassium channels act as important breaks on excitability.[46]

Peripheral nerve damage also affects non-neuronal cell types in the

spinal cord. Astrocytes and microglia undergo proliferation, upregulation of cytokine production and release, and morphologic changes called reactive gliosis. Reactive gliosis in both cell types play a role in neuropathic pain by releasing pro-inflammatory cytokines and chemokines, which sensitize pain-coding spinal cord neurons to be more responsive to peripheral stimuli. A similar mechanism whereby gliosis modulates pruritus circuits to promote pruritus perception may be present in neuropathic pruritus.[26,46]

Oxidative stress

Oxidative stress is defined as a disequilibrium status between oxidants (free radicals, reactive oxygen and nitrogen species, reactive metabolites) and antioxidants in cells with the advantage of oxidants. Oxidative stress is linked with DM.[56] Increased glucose levels in DM leads to a failure of oxidative phosphorylation in mitochondria, loss of ATP production, and overproduction of reactive oxygen species (ROS) by mitochondrial electron transport chain. Excessive ROS will damage the nuclear DNA chain. DNA damage activates poly(ADP-ribose) polymerase (PARP). PARP then causes a decrease in glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Decreased GAPDH activity causes an increase in glycolytic metabolites (glyceraldehyde 3-phosphate, fructose 6-phosphate, and glucose) that will activate major mechanisms, namely an increase in glucose metabolism through the polyol pathway, an increase in methylglyoxal which will induce advanced glycation end products (AGEs) formation and AGEs receptor (RAGE) expression, activation of protein kinase C (PKC) isoform β, γ, dan δ, and an increase in hexosamine pathway activity. These mechanisms mediate additional ROS accumulation and inflammation, leading to damage

in cells' structures and functions and ultimately DM complications such as skin barrier disruption and neuropathy.[46,56,57] Skin barrier disruption and neuropathy then induce pruritus in DM through the pathophysiological mechanisms that we have described above.

Oxidative stress itself also plays a critical role in both acute and chronic pruritus. Different oxidants induce profound scratching behavior in mice via activation of TRPA1. Oxidative stress-induced pruritus response is largely independent of histamine, consistent with the clinical observation that chronic pruritus associated with oxidative stress is resistant to antihistamine treatment.[58] Another study by *Zhou et al.*[59] also found that oxidative stress plays a critical role in acute and chronic pruritus in the periphery and spinal cord. They suggest that acrolein, which is both a product and initiator of lipid peroxidation, may be a novel endogenous pruritogen during oxidative stress. It has been identified as an endogenous TRPA1 agonist. The role of oxidative stress in inducing chronic pruritus was supported by their result that antioxidants are effective in alleviating chronic pruritus in their mouse model. They also found that antioxidant can scavenge the intracellular ROS, thus interrupting the intracellular pruritus signal transduction in primary pruriceptive sensory neurons.[59]

Pruritus in diabetic patients with CKD

Approximately one-third of DM patients develop complications such as CKD.[60,61] The prevalence of pruritus in CKD patients ranges from 10 – 77%, with an estimated overall prevalence of 55% among patients undergoing dialysis. This phenomenon is known as CKD-associated pruritus (CKD-aP).[62–64] The pathophysiology of CKD-aP is still not well understood at this time, with a lot of conflicting studies. The relation of CKD-aP and DM is not limited to just

being comorbidities. While skin xerosis (which is also a complication of DM itself as we have iterated above) has been traditionally seen as a causative factor in CKD-aP. recent studies have disproved this. Skin xerosis is now believed to be an exacerbating factor instead. Lastly, histamine was also considered the primary pathway for pruritus in CKD-aP, but this too has been disproved and newer studies have shown that CKD-aP is mediated by a nonhistaminergic pathway because it does not have histamine-specific changes like wheals.[27,64]

There are lots of theories out there regarding how the pruritus perception happened, but four of the more popular theories, described by Verduzco *et. al.*[27] are: toxin deposition, peripheral neuropathy, immune system dysregulation, and opioid imbalance. We shall discuss all four theories briefly and compare notes from some studies on them. The first theory, toxin deposition, implicated toxins in CKD patients that accumulate under the skin act as potential pruritogens. Uremic toxins, calcium, vitamin A, phosphate, magnesium, and aluminum have been put forward as potential toxins. It has also been postulated that parathyroid hormone (PTH) levels have something to do with it, because in some patients, parathyroidectomy alleviates the pruritus.[27] However, while this theory has not been fully disproved, there are some researches that refuted this theory. These researches found that the levels of the potential toxins were not consistently related to the presence of CKD-aP, and dialysis or toxin removal did not always alleviate the pruritus.[27,64]

The second theory, peripheral neuropathy, believes that the neuropathy in patients with CKD and DM results in neuropathic pruritus, which happens when diseased primary afferent sensory neurons or diseased interneurons are activated out of proportion to or independent of any pruritogens.[27,46]

Neuropathy is common in CKD patients, and it is found that dialysis patients with other neuropathic issues such as restless leg syndrome and paresthesia often have CKD-aP as well.[27]

The third theory, immune system dysregulation, is a lot more complex and involves a lot more pathways and receptors. This theory suggests that microinflammation happens in the skin of CKD patients and possibly also systemically, and the inflammation stimulates pruritus. Supporting this hypothesis would be the high levels of inflammatory markers seen in CKD patients, which includes white blood cell count, T-helper 1 (Th1) cells, C-reactive protein and IL-2.[27] It is noted that in CKD-aP, there is a prominent shift of uncommitted Th lymphocytes into Th1 lymphocytes. This is followed by an increase in cytokines produced by Th1 lymphocytes, such as IL-6, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). The release of TNF-α further enhances the expression of Th1 lymphocytes, while IL-6 sets off a cascade known as the TO IL-6/phosphorylated-Bruton's agammaglobulinemia tyrosine kinase (pBTK)/phosphorylated-extracellular signal regulated kinase (p-ERK) signaling-induced pruritus. Moreover, there is also an increase in IL-31, which is a pruritogenic cytokine released by Th2 lymphocytes. On another front, there is indirect evidence that a highly pruritogenic cytokine called leukotriene B4 is also heightened in patients with CKD-aP. Lastly, increased concentration of another pruritogen called β2-microglobin is also found in the serum and skin of patients suffering from CKD.[64]

Low albumin levels and high ferritin levels are also seen in these patients. Further support for this theory includes the fact that the usage of anti-inflammatory medication in these patients has been reported to reduce pruritus. Allergic response may also

be erroneous in patients with CKD-aP. Higher levels of eosinophils, mast cells and the pruritogens associated with these, i.e. histamine and tryptase, are also present in patients with CKD-aP. However, as previously mentioned, the pruritogenic pathway in CKD-aP is non histaminergic.[27] The mast cell tryptase activates proteinase-activated receptor-2 (PAR-2) on pruriceptive nerve afferent fibers. This activation of PAR-2 sensitizes the TRPV1 ion channels downstream in nerve afferents and the transmission of a pruritus signal to the dorsal root ganglion and onto the dorsal horn in the spinal cord. The sensitization of TRPV1 causes the retrograde release of substance P (SP) from nerve endings. SP, in turn, activates dermal mast cells and keratinocytes to release more cytokines, leading to a vicious, self-perpetuating cycle.[64]

The final theory stated by Verduzco *et al.*[27] is the opioid imbalance theory. This hypothesis builds on the theory that the neuronal circuits which transmit pain and pruritus perception overlap substantially. Opioid is a compound that has a role in both. It blocks pain and is known to cause pruritus. Opioid pathways, which have receptors in the brain, peripheral nerves, immune cells, hair follicles, melanocytes, and keratinocytes have been recognized in their role in modulating pruritus. It is suggested that there is an overstimulation of central mu-opioid receptors, antagonism of peripheral kappa-opioid receptors, and an imbalance of stimulation and antagonism of mu- and kappa-opioid receptors in CKD-aP patients, which lead to the pruritus. Studies have also found that there is an upregulation of kappa-opioid receptors in patients with CKD-aP that has a positive correlation with the severity of the CKD-aP. Kappa-opioid receptors activation triggers an antipruritic effect, while mu-opioid receptors trigger pruritus instead. Both kappa and mu-opioids have receptors

in the peripheral and central nervous system. They appear on the surface of dermal mast cells, keratinocytes, and in the dorsal horn.[64]

Pruritus secondary to anti-diabetic therapy

Pruritus can be caused by adverse reactions to anti-diabetic drugs, such as the first generation of sulfonylureas, biguanide, and SGLT2 inhibitors. Pruritus pathophysiology in drugs other than biguanide is still not understood.[2] Biguanide causes pruritus by way of cholestatic injury to the liver.[65] The mechanism behind cholestatic pruritus is largely unknown, but it is believed that the existence of liver associated pruritogens in the system of patients with hepatic diseases affects the opioid and serotoninergic system.[27,28] The hepatic diseases in question are usually the ones of cholestatic nature, and patients with hepatitis rarely reports pruritus. The proposed pruritogens for this theory includes, but not limited to: bile salts, bilirubin, gut microbiome, and lysophospatidic acid.[28,66,67]

The role of bile salts in cholestatic pruritus is not well understood and is subject to a lot of conflicting evidence since not all patients with a high level of bile salts complain of pruritus and the removal of bile salts doesn't always produce an attenuation of the pruritus perception. However, while bile salts may not be directly responsible for causing pruritus in cholestatic patients, there is evidence that it might play a role in activating bile salts receptors: Takeda G protein coupled receptor 5 (TGR5) and MrgprX4. Both receptors have been recognized as being located on pruritogenic sensory neurons. Another argument against the role of bile salts as the dominant pruritogen in cholestatic pruritus is the fact that pruritus is more often a feature of early cholestatic disease, when the levels of bile salts are

still relatively low. To top it off, pruritus usually goes away on its own when the patients experience liver failure.[28,66,67]

Bilirubin is found to be elevated in many patients with cholestatic pruritus, much like bile salts. It stimulates MrgprX4. Just like bile salts, the role of bilirubin as a dominant pruritogen in cholestatic pruritus is also shadowed by the same issue in which the plasma bilirubin levels have little to no correlation with pruritus intensity, and pruritus is more often a sign of early disease rather than late stage.[28,66,67]

Gut microbiome was considered as a potential pruritogen in cholestatic pruritus when it was found that treatment with rifampicin improves pruritus in cholestatic pruritus. Supporting this theory is another study that found that probiotics have been shown to exhibit antipruritic effects. However, there is also another study that compared gut microbiota of patients with primary biliary cholangitis (PBC) suffering from pruritus, patients with PBC without pruritus, and healthy volunteers which found that there is no significant difference of the three groups' gut microbiota composition.[28,66,67]

Lysophosphatidic acid (LPA) has been implicated as a potential pruritogen for cholestatic pruritus, but the evidence surrounding its role in pruritus is still mixed. Serum LPA levels are increased in patients with cholestatic pruritus, and a study proved that injection of LPA into the skin of mice initiated a scratch response. Lysophosphatidic acid is produced by phospholipase D Autotaxin (ATX). Serum ATX levels are significantly increased in cholestatic patients with pruritus compared to cholestatic patients without pruritus. However, ATX level also serves as a biomarker for liver fibrosis, where patients with hepatitis also have markedly elevated levels of serum ATX but do not suffer from pruritus. This creates a paradox on the role of LPA and ATX in modulating pruritus in cholestatic

pruritus and warrants further studies on their role in it.[28,66,67]

Pathophysiology-based therapy for pruritus in DM

Treatment of chronic pruritus in diabetic patients using antihistamine often does not yield satisfactory results.[14,68] Steroid is also to be avoided in this group due to the unwanted hyperglycemia side effect.[69] Treatment of pruritus in DM must be highly tailored to the individual according to their needs.[40] Conducting a careful history taking and examination, differentiating between localized and generalized pruritus, identifying primary lesions should they exist, and spotting red flag symptoms can help to identify the cause of pruritus and in making treatment choices. Most patients will improve with nonpharmacologic therapy including frequent moisturization, avoiding overbathing, behavioral therapy, and breaking the itch-scratch cycle. If this avenue fails, further investigations are warranted to help guide subsequent treatment with any of the many cause-specific topical and systemic approaches available.[70] In this section, which is divided into nonpharmacologic and pharmacologic therapies, we will discuss some of the therapeutic modalities that have been studied so far.

Nonpharmacologic therapies

Glycemic control

Results from researches to search correlation between glycemic control and pruritus are contradictory. There are some researches that indicates correlation between glycemic control and pruritus (especially with generalized pruritus) as we mentioned above.[19,20,22] However, Neilly *et al.*[19] and Ko *et al.*[21] found no correlation between HbA1c and pruritus.[19,21] Despite the minimal

evidence regarding the connection between hyperglycemia and pruritus in DM, it is still recommended to practice good glycemic control.

Lifestyle changes

The American Diabetes Association (ADA) recommends good skin care and lifestyle changes as the main treatment options for skin complications related to diabetes. The do's include: keeping skin clean, keeping house more humid during the winter, wearing loose and soft clothing, using mild shampoos, moisturizing soaps and skin lotion, checking feet every day for sores and cuts, then treating them right away. Patients may also use wet, cooling, fat moist wrapping. What can not be done are: sauna, irritant contact, frequent washing, very hot bath and showers, scratching, bathing in the winter, and using feminine hygiene spray, ice pack, and alkaline cleanser.[70,71]

Emollients

Emollients come highly recommended by ADA as the main part of the lifestyle changes for diabetic patients experiencing pruritus. Because one of the proposed pathophysiologies for pruritus in DM is dry skin, the use of emollients is believed to be beneficial. It can keep the skin moist, flexible, soft, and increases skin barrier function from external disturbance.[72] The lipid layer of the skin, which is useful in keeping skin hydrated, is also normalized by emollients. Sufficient skin hydration can alleviate the pruritus.[4,73] Application of emollients also reduces the number of penetrated intraepidermal nerve fibers and nerve growth factor (NGF) levels in the mouse skin.[29]

There have been quite a few studies on the usage of emollients to treat pruritus in diabetic patients. The most commonly used active ingredient is urea. One study on the usage of emollient containing 5% urea and 0.2% hydroxyethylpiperazine results in significant reduction in TEWL and desquamation. Additionally, skin hydration also improved. Another researcher published two papers on using emollients to treat xerosis. In the first study, 603 patients were enrolled and 179 were diabetic. They were treated using 10% urea cream for 14 days and the results were a decrease in dryness, callosities, and scaling compared to the baseline. The second study enrolled 30 diabetic patients. They were treated in one foot using 10% urea cream (the other foot was used as control). The result was a decrease in scaling, callosities and dryness.[17]

A RCT with 40 T2DM patients, the treatment group received an emollient that is a mix of 5% urea, arginine and carnosine; while the control group received a glycerol-based emollient. The study compared the results after 28 days and the patients in the treatment group experienced an 89% reduction in skin dryness according to dry skin area and severity index (DASI) scale when compared with the control group. Another study conducted on 54 diabetic patients (a mix of type 1 and T2DM) used an emulsion base with 10% glycerin, 5% urea, 1% lactic acid and 8% paraffin for four weeks. The results show a decrease in dryness and skin fissures with an increase in skin hydration compared with the control group. There are more studies like these, and they utilized a mix of 10% urea and 4% lactic acid, another with 10% urea, alpha-hydroxy acid, allantoin, panthenol, oenothera biennis oil, and centella asiatica extract, which have all shown to reduce dryness.[17] One study compared urea formulations with different concentrations, and the results showed that formulations using 6% urea restored adequate skin barrier function, and the 4% urea formula has a longer duration of action.[17] For patients that have contraindications towards

emollients, a study by Ibrahim *et. al.,* found that the diabetic patients treated using topical clove oil treatment showed significant improvement in pruritus relief.[74]

Other topical agents

Usage of topical agents in relieving pruritus is pretty widespread and there is some evidence that it might help with pruritus in diabetic patients. Agents that might be used include, but not limited to, polidocanol, camphor, menthol, and tannin. However, this method might be less useful in controlling generalized pruritus, since it would be challenging to apply a topical agent to the entirety of a patient's body.[17,70]

Pharmacologic therapies

Gabapentin and pregabalin

Gabapentin and pregabalin have a similar form with an inhibitory neurotransmitter named GABA. Pregabalin, which is newer compared to gabapentin, is a prodrug that is usually more well tolerated than gabapentin. These two agents have been successfully used for treating pain with neuropathic origin, such as diabetic neuropathy.[75,76] Due to the significant role that neuropathy seems to play in the pathophysiology of pruritus in DM, a few studies have looked into using treatments for neuropathic pain for this pruritus.

One such study recruited diabetic patients with stage 4 and 5 CKD and some of them are on hemodialysis/peritoneal dialysis. All of them experienced pruritus that did not get better with antihistamine prescription or UV light treatment. Forty-seven out of 71 (66%) of the subjects reported relief with gabapentin. Sixteen out of the 24 subjects that did not report improvements were put on a course of pregabalin. Thirteen subjects (81%) reported relief with pregabalin.

The changes were noticeable fairly quickly, usually after one or two doses or after an increase in dosing. Pregabalin even managed to relieve pruritus in patients that suffer from pre-existing skin condition (pruritus nodularis, chronic eczema and chronic idiopathic urticaria).[64,68]

Antioxidants

Another pathophysiological basis of pruritus in DM that has been proposed is oxidative damage.[4] The role of antioxidants has long been a subject of interest in the care of DM as the state of hyperglycemia promotes auto-oxidation of glucose to form free radicals. Examples of antioxidants that have been studied to this end would be Vitamin C and E, which are believed to lower incidence of T2DM and reduce diabetes complications.[77] Alpha lipoic acid, which plays an essential role in mitochondrial bioenergetic reactions, is believed to modulate and improve insulin sensitivity, as well as protecting insulin receptor from oxidative stress.[77,78] One study used an eight-week course of alpha lipoic acid in diabetic patients with polyneuropathy. They found a significant reduction in pain, burning, numbness and paresthesia since the four-week mark, and an even more significant improvement at eight-weeks.[79] There is also interest in the antioxidant capacities of certain anti-cholesterol drugs like gemfibrozil.[77] Another research utilizing murine models with chronic pruritus conducted by Zhou *et al.*[59] discovered that the systemic administration of N-acetyl-L-cysteine (NAC) and N-tert-butyl-a-phenylnitrone (PBN) significantly alleviates drug induced pruritus, attenuates dry skin related chronic pruritus and suppresses oxidative stress in the skin. However, there is still a lack of studies on the overall safety of these antioxidants.

Cannabinoids

Some clinical studies found that cannabinoids may be beneficial in treating chronic pruritus caused by various skin diseases and systemic conditions. Cannabinoids may have an essential role to play in skin stability as a modulator of the endogenous endocannabinoid system (ECS). ECS is also believed to play a role in some neural mechanisms, including pruritus, pain perception, as well as immunological and inflammatory responses. The ECS modulating function of cannabinoids works on both central and peripheral nervous systems.[80,81] Another study reported that the use of phytocannabinoids in pruritus activates CB1 and Cannabinoid type 2 (CB2) receptors, which have been shown to have antipruritic effects, mediated by inhibiting TRPV-1 receptors.[64]

Cannabinoids are proven to be capable of alleviating pruritus in diseases such as allergic contact dermatitis, asteatotic dermatitis, atopic dermatitis, prurigo nodularis, psoriasis, and even in cholestatic and uremic pruritus. Topical application of physiological lipid cream containing endogenous cannabinoids twice daily reduced pruritus in 38% of patients with uremic pruritus after three weeks. Another study stated that palmitoylethanolamide (PEA) could act as an anandamide (endocannabinoid) activator of CB1 receptors, and when combined with the use of emollients, was found to successfully relieve pruritus in 86.4% patients with prurigo, lichen simplex, and pruritus. A newer study in murine models using peritoneal administration of cannabinoid agonists named WIN 55,212-2 discovered that this agent could ease pruritus induced by high levels of serotonin.[80,81] One RCT that studied the effectiveness of topical cannabinoid oil made from cannabis sativa found that patients treated with the oil showed a significant improvement in pain, cold, and pruritus perception that they experienced after four weeks of treatment.[82] Even though cannabinoids use in DM has been proven to be quite successful in relieving pruritus, more studies should be done, especially studies on a larger population to further determine its efficacy and safety profile.

Antidepressants

The usage of antidepressants as an antipruritic agent in cases that are resistant to antihistamine and topical agents has been reported for over a decade, especially for patients with uremic, cholestatic, and paraneoplastic pruritus.[83] Like we discussed previously, serotoninergic pathways have a role in pruritogenic signaling, and the release of serotonin from mast cells also induces pruritus. Selective serotonin reuptake inhibitors (SSRIs) inhibit pre-synaptic reuptake of serotonin and might dull transmission of nociceptive stimuli through unmyelinated C-fibers. It has been shown to be effective in treating cholestatic pruritus. SSRIs have been advised as a fourth line treatment when standard therapies did not alleviate pruritus.[28]

The mechanism by which other antidepressants reduce pruritus are still unknown, but it is postulated that these drugs work by attenuating central mechanisms that may aggravate pruritus like mood, stress, and neural sensitization in the brain that are common with chronic pruritus. Chronic pruritus is often associated with psychopathology such as anxiety and depression, so antidepressants may improve pruritus by treating the underlying psychiatric issue. A systematic review in 2017 listed fluoxetine, sertraline, amitriptyline, mirtazapine, fluvoxamine, paroxetine, nortriptyline, and doxepin as antidepressants that have been tested and showed success in reducing chronic pruritus of differing types.[28,83] Fluoxetine is contraindicated in DM, but the other

antidepressants might be able to play a role in treating pruritus in DM.

Capsaicin

Some of the pruritogenic pathways that we have discussed in the previous sections featured TRPV1 ion channels. To recap, the activation of PAR-2 sensitizes TRPV1 downstream in nerve afferents, which then transmits a pruritogenic signal to the dorsal root ganglion and onto the dorsal horn in the spinal cord. The sensitization of TRPV1 also causes the retrograde release of SP from nerve endings which will activate dermal mast cells and release more cytokines. Capsaicin targets TRPV1 channels, depriving it from SP.[64]

A RCT comparing capsaicin 0.03% to placebo found that the patients experienced a significant reduction in pruritus compared with the placebo group. Improvement started right away in the first week of usage. However, there is an issue with treatment adherence because of side effects. Application of topical capsaicin in any of its form is inevitably followed by a transient burning sensation which a lot of patients find intolerable.[64,84]

Mast cell stabilizers

Like we previously mentioned, mast cells seem to have a big role in both pruritogenic pathways. Mast cells release a lot of potential pruritogens, which includes, but not limited to, histamine, tryptase, and serotonin. This leads to some trials utilizing mast cell stabilizers to treat pruritus in DM.[64,85] Cromolyn sodium is a mast cell membrane stabilizer that is available in both topical and oral preparations, and both forms have been shown to be effective in treating patients with pruritus due to refractory CKD-aP. However, another mast cell stabilizer, nicotinamide, has not been shown to be better than placebo.[64]
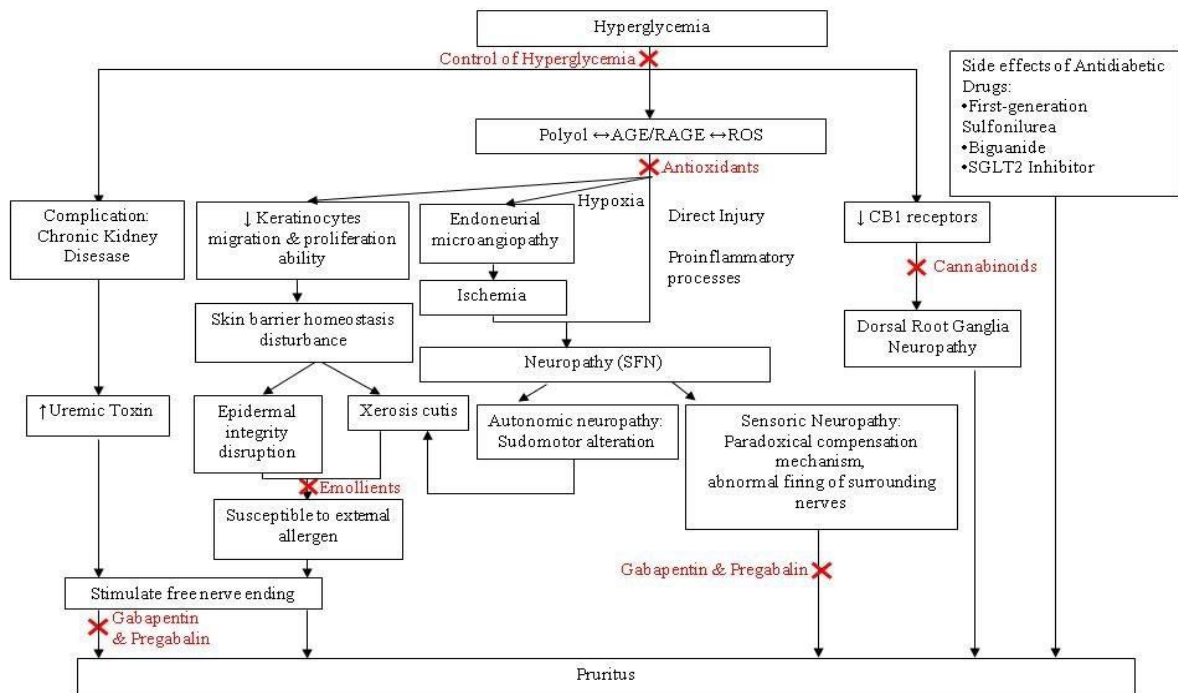

FIGURE 2. Pathophysiology of pruritus in diabetes mellitus and its pathophysiology-based treatment. AGE = advanced glycation end product, RAGE = receptors for AGEs, ROS = reactive oxygen species, CB1 = cannabinoid receptor type 1, SFN = small fiber neuropathy, SGLT2 = sodium-glucose co-transporter-2.

CONCLUSION

The pathophysiology of pruritus in DM is complex and poorly understood. However, a lot of treatment trials have given us more insight on the possible pathologies, while also helping us to understand which treatment might be useful in treating pruritus in DM.

Skin barrier disruption and diabetic peripheral neuropathy are the two main factors associated with pruritus in DM. Oxidative stress, which plays an important role in the development of complications in DM. can also induce pruritus independent of histamine via activation of TRPA1. Meanwhile, pruritus in diabetic patients with CKD and pruritus secondary to anti-diabetic therapy are still not conclusive.

Although there have been no official guidelines regarding the pharmacological treatment for pruritus in DM, we do know that nonpharmacological treatment, such as emollients and lifestyle changes has been the mainstay for treatment and is also recommended by ADA. Some pharmacological treatments have also shown promising results, such as gabapentin, pregabalin, antioxidants, cannabinoids, antidepressants, capsaicin, and mast cell stabilizers. While these treatments have not been fully endorsed by a formal guideline, they might serve us as second line treatment for diabetic patients suffering from pruritus in daily practice. Lastly, further research still needs to be done on a larger population to establish the efficacy and safety of these treatments.

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