Corneal Sensitivity as a Potential Marker of Diabetic Neuropathy

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ABSTRAK

Diabetes mellitus (DM) adalah kelainan metabolik kompleks dan kronis yang menyebabkan banyak komplikasi. Salah satu komplikasi DM yang paling umum adalah neuropati diabetes. Ada banyak penelitian yang mengeksplorasi sensitivitas kornea sebagai penanda potensial neuropati diabetes. Artikel ini bertujuan untuk mengeksplorasi hubungan antara sensitivitas kornea dan neuropati diabetes. Pada neuropati diabetes, sensitivitas kornea terganggu akibat rendahnya tingkat faktor trofik saraf kornea, serabut saraf sensorik terganggu, dan kehilangan komunikasi sel dendtritik. Pada pasien diabetes, kondisi ini dapat dinilai dengan beberapa teknik, seperti estetika Cochet Bonnet, aesthesiometri kornea non-kontak, dan mikroskop konfokal. Beberapa target terapeutik yang menjanjikan untuk sensitivitas kornea terganggu meliputi terapi faktor sel induk dan pertumbuhan yang dapat digunakan untuk mencegah komplikasi pada pasien dengan keratopati neurotropika diabetes. Sensitivitas kornea yang terganggu berperan sebagai penanda potensial neuropati diabetes. Dokter, dokter mata dan ahli penyakit dalam, harus mengantisipasi kemungkinan untuk mengamati perubahan berikut pada pasien diabetes dengan neuropati dengan menggunakan uji penilaian sensitivitas kornea.

Kata kunci: *diabetes melitus, diabetik neuropati, sensitivitas kornea, uji penilaian.*

ABSTRACT

Diabetes mellitus (DM) is a complex and chronic metabolic disorder leading to many complications. One of the most common complications of DM is diabetic neuropathy. There are many studies exploring corneal sensitivity as a potential marker of diabetic neuropathy. This review aims to explore association between corneal sensitivity and diabetic neuropathy. In diabetic neuropathy, corneal sensitivity is impaired due to low level of corneal nerve trophic factors, impaired sensory nerve fibers, and lost communication of dendtritic cell. In diabetic patients, this condition can be assessed by several techniques, such as Cochet Bonnet aesthesiometry, non-contact corneal aesthesiometry, and confocal microscopy. Few promising therapeutic targets for impaired corneal sensitivity include stem cell and growth factor therapy that can be used to prevent complication in patient with diabetic neurotrophic keratopathy. Impaired corneal sensitivity serve as a potential marker of diabetic neuropathy. Doctors, opthalmologists and internists, should anticipate the possibility of observing the following changes in diabetic patients with neuropathy by using corneal sensitivity assessment test.

Keywords: *diabetes mellitus, diabetic neuropathy, corneal sensitivity, assessment test.*

INTRODUCTION

Diabetes mellitus (DM) is a complex and chronic metabolic disorder that can lead to death if not managed properly. It is estimated that 415 million (8.8%) adults in the world are living with diabetes in 2015 and this prevalence is predicted to grow to 642 million in the next 25 years.[1]

DM can lead to many debilitating acute and chronic complications, which include neuropathy, retinopathy, nephropathy, stroke, and myocardial infarction.[2] Diabetic neuropathy (DN) is the most common complication of DM, affecting 50% patients.[1] Early diagnosis of neuropathy in diabetic patient is important for risks evaluation and therapeutic management thus preventing complications. Recently, there are many studies exploring corneal sensitivity as a potential marker of diabetic neuropathy.[3,4] Corneal innervation has higher density than skin or others and the assesment are not invasive nor difficult. This review aims to explore recent studies about association between corneal sensitivity and diabetic peripheral neuropathy.

DIABETES MELLITUS

DM is a metabolic disorder which is caused by multiple etiologies. The main characteristic of DM is chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism due to inadequate insulin secretion, action, or both.[4] Microvascular and macrovascular complications are the pathologic hallmark of DM. It provokes changes in blood vessels by affecting the capillary basement membrane including arterioles in the glomeruli, retina, skin, muscle, myocardium.[1] Several complications that are included as acute complications are diabetic ketoacidosis, hyperosmolar hyperglycemic states, lactic acidosis, and hypoglycemia. If they are not treated immediately, death can occur.[2] Chronic complications of DM include diabetic nephropathy, atherosclerosis, diabetic retinopathy, and DN. As an organ with rich vascularization, the eyes are also one of the targets of these DM complications.[1,2,5]

DM and its associated ocular diseases encompass a complicated disorder with multiple etiologies, both genetic and environmental factors. Diabetic retinopathy is the most common ocular diseases related to DM, affecting around 30% patient with DM worldwide. Earliest change seen in diabetic retinopathy is the retinal blood barrier damage. This microvascular abnormality can lead to capillary occlusion and leakage. Furthermore, retinal hypoxia, edema, and hemorrhage can occur.[6] In this review, we will focus more in diabetic neurothropic keratopathy (DNK).

DIABETIC PERIPHERAL NEUROPATHY (DPN)

One of the neurologic disorders for DM, DPN affects 50% of all diabetics patient.4 Unfortunately, this complication is often recognized in later stage. There are several theories proposed to explain the pathogenesis of DPN including polyol pathway, accumulation of advanced glycosylation end-products (AGEs), low levels of growth factors, free radical-oxidative stress, and immunologic factors.[4,7]

Well-known pathogenesis of DPN is increased polyol pathway flux. Hyperglycemia induces activation of intracellular polyol pathway causing accumulation of sorbitol. This results in decreasing level of protein kinase C and Na/K-ATPase activity, thus cellular water, electrolyte imbalance and oxidative injury can occur.[8]

Another well-known theory of DM pathogenesis is AGEs; products of protein cross-linking causing damage in cellular structure and functions. These byproducts reduce the elasticity and increase permeability of blood vessels. Furthermore, modified plasma proteins bind to receptors for AGEs on cells by inducing the production of reactive oxygen species (ROS). It might activate several factors causing pathologic alteration in gene expression.[9]

Singh et al[10] reported that accumulation of AGEs can cause fiber loss in peripheral nerve of diabetic human. The formation and accumulation of AGEs in peripheral nerve take a major role in the development of diabetic neuropathy by affecting structural and functional proteins as well as indirectly activating receptors for AGEs.[10] AGEs accumulation is responsible for the progression of diabetic keratopathy, but it's not well understood. Shi Long et al[11] found that AGEs induce apoptosis in retinal pericytes and corneal epithelium as suggested by corneal

epithelium apoptosis in diabetic rats with AGEs accumulation.

ROS also plays important role in DN by mediating cellular responses to AGEs. Excessive ROS found in DM patients causes retinal pericyte apoptosis. Shi Long et al[11] hypothesized that interaction between AGEs and receptor for AGEs (RAGE) might induce intracellular ROS generation and activate C-jun N terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK), which play an important role for corneal epithelium apoptosis.

There are several growth factors which undergo deficiency in diabetes. Nerve growth factor, neurotrophins[3-5], keratocyte growth factor, and transforming growth factor are found in corneal epithelium and stroma keratocytes. Those factors are necessary for epithelial regeneration and repairing the damaged peripheral nerves. Diabetes can inhibit neuron regeneration by detracting these neurotrophic factors.[3]

Hyperglycemia also induce the expression of inflammatory cytokines of the innate immune system, such as IL-1β and TNF-α which have an important role in lacrimal gland and cornea reepithelization impairment thus their expression may lead to corneal nerve alterations and cause neurotrophic lesion and dysfunction of feedback mechanism that controls tear secretion which results in diabetic dry eye.[12]

CORNEA

The cornea is a transparent and avascular connective tissue which serves as a protective membrane which light pass on its way to the retina. Cornea consists of five layers: epithelium, bowman membrane, stroma, descement membrane, and endothelium. Cornea is in constant state of relative dehydration, called deturgesced state.[13,14] The endothelium plays more important role than the epithelium in the mechanism of dehydration. Age, trauma, and inflammation can decrease the number of endothelial cells. Furthermore, endothelial cells have no mitotic activity. Destruction of the endothelial cells causes transient edema of the cornea and loss of transparency which clears when the epithelial cells regenerate.[13,14]

Corneal sensation is essential for optimal eye health. Corneal epithelium is the most densely innervated and sensitive epithelium surface of the body. Cornea is innervated by ophthalmic branch of trigeminal ganglion, while corneal stromal nerves comes from the sclera or ciliary body. Superficial limbal and subconjunctival nerve networks also innervate the epithelium with denser central distribution. These sensory branches are the nasociliary branch of the ophthalmic nerve.[15] Corneal nerves produce a sensation of pain in humans from mechanical, thermal, and chemical stimulation. The corneal nerve functionality is assessed by corneal sensitivity test.[3,16]

CORNEAL SENSITIVITY ASSESSMENT

Recent studies have explored corneal sensitivity as a potential marker of diabetic neuropathy.[17] There are two clinical techniques that may be used to assess corneal sensitivity: Cochet Bonnet (CB) aesthesiometer and non-contact corneal aesthesiometry (NCCA).[18]

CB aesthesiometer has been used as a standard clinical method for measuring corneal sensitivity. The instrument consists of a nylon monofilament of constant diameter which can give pressure based on its length. The length of filament which ellicit a sensation on subject represents the corneal touch threshold. This method is minimally invasive because it causes subclinical microtrauma to the contacted part of cornea.[9]

NCCA is the non-invasive measurement of corneal sensitivity, which procedure uses controlled pulses of air with variable pressure to stimulate the cornea. The corneal nerve sensation threshold is measured to a composite stimulus outcome consisting of air pressure, tear film evaporation, disruption, and cooling.[18,19] Pritchard et al[18] reported that composite scores used to evaluate neuropathy such as the neuropathy disability score (NDS) have been associated with corneal sensitivity when measured using NCCA and previously shown that a NCCA reading of 0.66 millibars or more could be diagnostic of neuropathy in type 2 DM patients.

Bikbova et al[3] reported that confocal microscopy is a non-invasive method for quantifying the damage of corneal sensory

nerves that can be a marker for diabetic neuropathy. In vivo corneal confocal microscopy is an established technique which has been used as a diagnostic tool with a variety of clinical applications in ocular and neurological diseases.[17] Pirchard et al[20] reported that a 4-year incident neuropathy of type 1 diabetic patient that confocal microscope could predict the development of DPN with 63% sensitivity and 74% spesificity.[21,22]

MEASUREMENT OF NEUROPATHY

Neuropathy can be measured by some methods, including diabetic neuropathy symptom score, modified neuropathy disability score (NDS), neuropad, monofilament, electrophysiology, or quantitative sensory testing. The diabetic neuropathy symptom score is usually used in clinical setting, such as four questions regarding steadiness in walking and lower limb symptoms. A score between 0 and 4 are recorded; 0 means there is no neuropathy and 4 means polyneuropathy present. The modified NDS is a clinical scoring system which uses a 128 Hz turning fork, neurotip for pin prick sensation, warm and cold metal rods for temperature perception, and tendon hammer for the presence or absence of ankle reflex. The monofilament test using 10-gram nylon filament can be used by applying the tip of it to three pre-determined points on the sole of the hand and foot. Toronto criteria is used to determine classification of neuropathic status and with either a modified NDS >2 or diabetic neuropathy symptoms score >1 which indicates the presence of diabetic neuropathy.[17,23]

Symptoms of neuropathy have also been shown to be associated with a loss of corneal sensitivity. More recently, the neuropathy symptom score was shown to be significantly associated with corneal sensitivity, such that the greater the symptom score the higher the non-contact corneal aesthesiometric sensation threshold.[18] A direct relationship between corneal sensitivity and a comprehensive inventory of parameters of neuropathy has not been investigated. As the corneal sensation threshold measured using NCCA is being explored as an additional non-invasive tool in diagnosing neuropathy, it is important to understand the relationship between corneal sensitivity and other measurement of neuropathy.

ALTERED CORNEAL SENSITIVITY AS A FORM OF DPN

Corneal sensitivity can be impaired by number of ocular and systemic diseases, such as DM. Its impairment is found in nearly 20% of diabetic patients.[23] Pritchard et al[18] reported that corneal sensation threshold was significantly higher for patients with neuropathy compared to those without neuropathy and controls ($p=0.002$). It was measured by several functional measures of neuropathy, such as NCCA, NDS, neuropad, monofilament, DNSS, and others. Patients with neuropathy showed poorer outcome of established neuropathy measures than diabetic patients without neuropathy and control. Komolafe et al4 reported there was a strong, statistically significant negative correlation between corneal sensitivity and vibration pressure threshold (peripheral neuropathy). Corneal sensitivity decreases significantly with the increase in vibration pressure threshold ($p<0.001$).

Many studies have shown that one of the functions of corneal nerve fibers is to maintain a healthy cornea.[3] Besides, nerve-derived trophic factors have functions in regulating the biochemistry of the corneal epithelium and controlling the normal as well as renewal processes in maintaining the corneal epithelial cells. Hence, patients with impaired corneal innervation, such as in diabetic patients, have increased risk of corneal impairment caused by trophic factors deficiency. One of manifestation of diabetic polyneuropathy in cornea is diabetic neurotrophic keratopathy.

Zhou et al[24] discovered that impaired corneal epithelial wound healing in diabetes can be caused by low level of corneal nerve trophic factors. In their study using quantitative PCR and ELISA, the cilliary neurotrophic factor (CNTF) mRNA and protein levels were found to be significantly downregulated in diabetic mice. They found that low level of CNTF causes delayed corneal epithelial wound healing. Supplementation of the exogenous trophic

factors can promote wound healing by activating corneal epithelial stem cells.[24]

Gao et al[25] considered that DM damaged the neural communications of dendritic cells and impaired sensory nerve regeneration resulting in diabetic neuropathy. Diabetic-induced denervation of the cornea, damage the integrity of corneal epithelial cells and their ability to recover from injury. DM decreases the density of sensory nerve fibers and the number of CD IIC-positive cells in the cornea. They found decreased number of dendritic cells is in tune with a decrease nerve fibers density. DM impairs communication between dendritic cells and nerve causing diabetic peripheral neuropathy, delayed cornea wound healing, impairs and reduces number of dendritic cells infiltration. This results in low level of CNTF which has a vital role in corneal innervation.[25]

Diabetic neuropathy may be involved in the progression of lacrimal gland dysfunction leading to dry eye syndrome. Integrity of lacrimal function unit and normal function cornea is maintained by nerve fibers. The result of Schirmer's I Test and corneal sensitivity were worse in diabetic patients with neuropathy compared to patients without neuropathy and control ($P<0.001$).[26]

Delayed epithelial wound healing and lacrimal gland dysfunction may be the cause of recurrent erosions. Reduced corneal sensitivity plays an important role on dry eye, thus predispose to corneal trauma and neurotrophic corneal ulcers. Recurrent epithelial defects and abrasion were also found in intraocular surgeries of diabetic patients. Accumulation of AGEs impairs epithelial basement membrane and causes delayed re-epithelialization. Thus, it causes prolonged and recurrent epithelial defects and predispose the cornea to infection, such as fungal keratitis.[27]

Normal post-cataract surgery patients with impaired corneal sensitivity is associated with impairment of normal blinking and tearing reflexes resulting in corneal epithelium impairment. In addition, inflammatory cytokines produced as a response to corneal incision healing may also decrease corneal sensitivity and cause tear film instability. Sitompul et al[28] reported that temporal site corneal incision may reduce corneal sensitivity in the surgical area because it may cut the base of corneal nerves. Those effects are augmented in patients with diabetic keratopathy and decreased corneal sensitivity.[29] Jiang et al[29] found that dry eye syndrome was higher in diabetic patients at seven days and one month after cataract surgery, which predispose them to infection post-surgery, such as endopthalmitis.

Pitchard et al[18] studied corneal confocal microscopy and corneal sensitivity assessment as non-invasive techniques to detect early changes for diabetic neuropathy. Many studies showed that the greater deficits in the neuropathy, the poorer the corneal sensitivity is.[18,22,30] Those findings show that corneal sensitivity does become a part of polyneuropathy in DM. Bikbova et al3 reported there were a relationship between corneal neuropathy and systemic neuropathy from clinical and electrophysiology test of neuropathy.

MANAGEMENT

Diabetic neurotrophic keratopathy is a challenging condition because of its complex management. Pathogenetic-orientated pharmacological treatment for neurotrophic keratopathy is not yet available. There are only supportive treatment such as artificial tears, topical antibiotics, bandage contact lenses, amniotic membrane transplantation, or a conjunctival flap to treat neurotrophic corneal ulcers.[17,25]

Corneal stem cells are likely associated with corneal wound healing. Kramerov et al[31] reported that there was a significant decrease of stem cell number in the corneo-limbal epithelium causing delayed wound healing in diabetic patient. Limbal stem cells are regulated by environmental signals, cytokines, growth factors, and their interaction.[32]

There are numbers of studies exploring cytokines and growth factors that may contribute in activation and proliferation of corneal stem cell. Duan et al[33] studied the effect of pluripotin, an activator of embryonic stem cell self-renewal, in promoting rabbit limbal epithelial cells proliferation by improving the in vitro limbal

stem/progenitor cells. Pluripotin may be a good alternative to improve the expansion of limbal stem/progenitor cells. Ho et al[34] studied the pigment epithelial-derived factor (PDEF) as a promotor self-renewal of limbal stem cell. PDEF and its fragment facilitate corneal wound healing by enhancing limbal stem cell proliferation in vitro. PEDF also has mitogenic effect by induction of p38 MAPK and signal transducer and activator of transcription 3 (STAT3).

Ciliary neurotrophic factor (CNTF) is another neuroprotective cytokine which is important in neurogenesis and regulation of neural stem cells. Zhou et al[24] studied CNTF and found several functions in cornea epithelial cells. CNTF can promote corneal epithelial wound healing; corneal healing in CNTF-treated mice is 48 – 72 hours faster than control. CNTF stimulated the colony-forming efficiency, the mitogenic activity, and upregulated the expression levels of corneal epithelial stem/progenitor cells-associated transcription factors. These give a promising future agent that can be used to prevent complication in patient with diabetic neurotrophic keratopathy.[17,31]

CONCLUSION

Corneal sensitivity which is correlated with diabetic neuropathy and impaired corneal sensitivity may serve as a potential marker of diabetic neuropathy. Doctors, especially ophthalmologists and internists, should anticipate the possibility of observing the following changes in diabetic patients with neuropathy by using corneal sensitivity assessment test. Further study needs to be conducted to investigate progenitor/stem cells as a promising agent to cure diabetic keratopathy.

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