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# New Treatment Strategies in Diabetic Neuropathy

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## 1. Introduction

Diabetes mellitus is associated with complications from a variety of tissues in the human body. Among them, diabetic neuropathy is a devastating complication leading to severe disability and even mortality. Neuropathy is common among type 1 and 2 diabetic patients and may yet be detected at the time of diagnosis among type 2 diabetic patients. The symptoms the patients experience vary from sensory disturbances with pain to muscle wasting. The results of autonomic neuropathy should also be considered as a severe problem in the patients, but will not be discussed in the present chapter.

The possibilities to treat diabetic neuropathy are limited and a strict glycaemic control has mainly been advocated. The pathophysiology of diabetic neuropathy is complex and includes e.g. biochemical disturbances and vascular factors. Of the former, the polyol pathway has been the target for pharmacological attention. Based on the detailed knowledge of the polyol pathway, obtained from experimental models and human studies, that sorbitol accumulates in peripheral nerve trunks, pharmacological substances were developed with the purpose to decrease sorbitol levels. Such aldose reductase inhibitors have in different studies shown promising results (Bril et al., 2009; Hotta et al., 2008; Oates, 2008; Schemmel et al., 2010), but are still at a stage of development. Presently, various strategies are emerging on the management of diabetic neuropathy, where it is stressed that an appropriate diagnosis is crucial and that the condition is not untreatable (Perkins & Krolewski, 2005). In the present chapter, we present a different approach than treatment with pharmacological substances or focusing on the glycaemic level; namely, utilization of the capacity of the brain to adapt to alterations. Thus, our intention is to use the plasticity of the brain as a treatment strategy – i.e. targeted plasticity.

## 2. Peripheral neuropathy

A peripheral neuropathy in diabetes may affect both the upper and lower extremities, where the latter location is more common and has gained more attention in research on diabetic neuropathy. Up to 50% of patients with diabetes in the United States may have a neuropathy in the lower extremity (Dyck et al., 1993). The prevalence of neuropathy in diabetes may vary from different studies depending on which diabetic population is examined, e.g. differences in Europe and Asia have been reported (Abbott et al., 2010; Rubino et al., 2007). In addition, various techniques, such as electrophysiology, examination of vibrotactile sense, skin and

nerve biopsies and monofilament tests, have been used to detect neuropathy in diabetes. However, although the intense research over the years on various aspects of diabetic neuropathy the mechanisms, which include biochemical and vascular components, behind the different types of neuropathies in diabetes are not clarified. The pathophysiology of the neuropathy is multifaceted and not completely elucidated, although peripheral nerve dysfunction and established neuropathy in diabetes seem to be related to the degree of hyperglycaemia (Lehtinen et al., 1989; Malik et al., 1993). Recently, some studies on diabetic neuropathy with long term data on HbA1c levels available have not found any association between glycaemic level and larger fibre neuropathy (vibrotactile sense) (Dahlin et al., 2011). A specific issue in this context is if even impaired glucose tolerance can induce neuropathy, but so far large myelinated nerve fibre neuropathy is probably not associated with impaired glucose tolerance (Dahlin et al., 2008). However, reports indicate that small nerve fibre dysfunction is present in patients with impaired glucose intolerance (Dahlin et al., 2008). The latter condition and the question of possible presence of neuropathy is a complex issue and are beyond the focus of the present chapter.

### **2.1 Diabetic foot ulcers**

A particular problem in diabetes is the diabetic foot ulcer, which induces severe problems for the patients (Bengtsson et al., 2008) and causes tremendous costs for society (Prompers et al., 2008). It has long been known that diabetes may itself play an active part in the causation of perforating foot ulcers (Londahl et al., 2010). Foot ulcers are common in diabetic patients and associated with high morbidity and mortality. The prevalence of diabetic foot ulcer is 1.7 – 2.9% and the annual population based incidence among diabetic patients is 1.9 – 3.6%. Interestingly, the annual incidence rates of foot ulcers in patients with diabetic neuropathy vary from 5 to 7% (Abbott et al., 2010) and the recurrence rate is high. It is estimated that 70% of healed foot ulcers recur within five years (Apelqvist et al., 1993). It is generally accepted that the majority of amputations in diabetes are preceded by foot ulcers on the same leg with a lifetime risk of a foot ulcer estimated to reach 15-25%, where the majority of the ulcers are located to the toes.

The main cause of diabetic foot ulcers are neuropathy and macro- and microvascular disease, but also other factors may increase the risk for an ulceration (Londahl et al., 2010). Patients with loss of sensation in the foot seem to have a sevenfold increased risk of developing foot ulcers as compared to diabetic patients without neuropathy (Young & Harris, 1994). In addition, a defect proprioception due to neuropathy may also cause impaired balance and postural instability contributing to the risk for foot ulceration. In clinical practice, sensory neuropathy is usually evaluated using monofilaments, 128 Hz tune fork or biothesiometer, where the latter is considered to be the most appropriate method (Edmonds, 2004). However, a multifrequency technique to examine vibrotactile sense has not previously been used to evaluate neuropathy in the foot, particularly as related to the risk for recurrence of foot ulcers. It may be an exiting approach in the future to refine detection of neuropathy. Interestingly, adjunct hyperbaric oxygen therapy, used in a multidisciplinary setting, can improve healing of chronic diabetic foot ulcers (Londahl et al., 2010); a therapy that may also beneficial in nerve regeneration after injury.

### **2.2 Carpal tunnel syndrome in diabetes**

Diabetic patients have an increased prevalence of one of the most common peripheral nerve compression lesions, i.e. carpal tunnel syndrome (CTS), which is compression of the median

nerve at wrist level. It has a prevalence of 2-4% in the general population, while in diabetes it may be as high as 15%. Furthermore, if the subject has diabetic neuropathy in the lower extremity, the prevalence of CTS may approach 30% (Perkins et al., 2002). Interestingly, it has been shown that there seems to be an increased general susceptibility to peripheral nerve compression in diabetic rats (Dahlin et al., 2008), which can be related to disturbed axonal transport and a propensity to inhibit such transport in compression of diabetic nerves (Dahlin et al., 1987; Dahlin et al., 1986).

Previously, it has been stated that surgical release of the median nerve in the carpal tunnel has no benefit for the patients and their symptoms from the CTS. Two previous studies showed diverse results (Mondelli et al., 2004; Ozkul et al., 2002), and proper conclusions can be difficult due to definition and selection of patients, extent of neuropathy and many other factors. Recently, we presented a prospective study where the outcome after surgical release of the carpal ligament was examined in diabetic patients with CTS and compared with age- and gender-matched healthy patients with CTS. The overall conclusion was that diabetic patients with CTS do benefit from surgical release of the carpal ligament. This statement is relevant irrespective of the severity of the compression lesion or if signs of peripheral neuropathy are present (Thomsen et al., 2009). However, our data do not support a general view that any peripheral nerve trunk in diabetic patients should be surgically released.

### 3. Introduction to brain plasticity

The brain has been seen as a rather static organ until about 20 years ago. It was widely believed by neuroscientists that no new neural connections could be formed in the adult brain (Kandel et al., 2000; Purves, 2004). It was assumed that once connections had been established in foetal life, or in early infancy, they hardly changed later in life. This stability of connections in the adult brain has often been used to explain why there is usually very little functional recovery after damage to the nervous system. On the other hand, memory and learning require that some changes are possible also in the adult brain (Kandel et al., 2000). It has often been assumed that these phenomena are based on small changes at the synaptic level and do not necessarily involve alterations in the basic circuit of the brain.

The picture has changed radically in the last decades. One of the most interesting questions in neuroscience concerns the manner in which the nervous system can modify its organisation and ultimately its function throughout an individual's lifetime based on sensory input, experience, learning and injury (Donoghue, 1996; Kaas, 1991); a phenomenon that is often referred to as brain plasticity (Kandel et al., 2000; Purves, 2004).

#### 3.1 Plasticity in the adult somatosensory pathways

There is a complete somatotopic map of the entire body surface in the somatosensory cortex of primates (Kaas et al., 1983; Merzenich et al., 1983). Merzenich et al (Merzenich et al., 1984) showed that after amputation of the middle finger of adult primates, the area in the cortex corresponding to the amputated digit began, within two months, to respond to touch stimuli presented to the adjacent digits; i.e. this area is "taken over" by sensory input from adjacent digits. Merzenich et al (Merzenich et al., 1984) also showed that if a monkey "used" one finger excessively, for an hour and a half a day, then, after 3 months, the area of cortex corresponding to that finger "expanded" at the expense of adjacent fingers. Furthermore, if a monkey was forced to always use two fingers jointly by suturing two of its fingers together, it was found at seven weeks that single neurons in area 3b in the primary

somatosensory cortex had receptive fields that spanned the border separating the two digits. Interestingly, if more than one finger was amputated there was no “take over” beyond about 1 mm of cortex. Merzenich et al (Merzenich et al., 1987) concluded from this that the expansion is probably mediated by arborisation of thalamo-cortical axons that typically do not extend beyond 1 mm. The figure 1 mm has often been cited as the fixed upper limit of reorganization of sensory pathways in adult animals (Calford, 1991). Pons et al (Pons et al., 1991), however, suggested that this view might be incorrect. They found that after long-term (12 years) deafferentation of an upper limb, the cortical area originally corresponding to the hand in the primary somatosensory cortex was taken over by sensory input from the face. The cells in “the cortical hand area” now started to respond to stimuli applied to the lower face region. Since this patch of cortex is more than 1 cm wide, they concluded that sensory reorganisation could occur over at least this distance, i.e. an order of magnitude ten times greater than the original 1 mm limit.

In addition to these long-term changes that are typically seen weeks or months after deprivation or stimulation, Calford and Tweelade (Calford, 1990) reported rapid, short term changes that are based, presumably, on the unmasking of pre-existing connections rather than on anatomical “sprouting”. They anaesthetized the middle finger of flying foxes and found that within 20 minutes the cortical neurons in the primary somatosensory cortex that originally responded to the middle finger could then be activated by touching the adjacent digits, indicating that the receptive fields had expanded to include adjacent digits.

Calford and Tweedale (Calford, 1990) also showed that a small unilateral peripheral denervation in adult flying foxes lead to expansion of the cortical receptive field for neighboring skin areas as predicted from the work of Merzenich et al (Merzenich et al., 1984).

Rapid plasticity changes are typically seen minutes after injury or an intervention, and are often based on decreased inhibition. Decreased inhibition would theoretically increase the receptive field size and enable more neurons to be activated by the stimulus. This is sometimes referred to as unmasking of synapses or neural structures.

Surprisingly, the receptive field of the homotopic region in the other hemisphere mirrored the change. In other words, the second hemisphere learned what the first had done; it copied the revised sensory map. Maintaining symmetric sensory representation of the two sides in the cerebral cortex may be important for the control of symmetric bilateral motor activity.

Experience dependent plasticity refers to the ability of the adult brain to adjust itself to changes in environmental conditions. It relates to the learning of special skills that requires special training and it often requires motivation and concentration on the task.

Another example of brain plasticity is the so called cross-modal plasticity. This phenomenon implies that one sensory modality can substitute for another (Bavelier & Neville, 2002). The most well known example is in blind persons where an improved sensory function is noticed. It has also been shown that when a blind person reads Braille activation in the occipital lobe occurs implying that the somatosensory stimuli from reading activates the cortical area responsible for vision (Gizewski et al., 2003).

Another example is persons in whom the lack of sensibility can be substituted with hearing. Through small microphones on the fingers the persons can, after a short training period, listen to what they feel (Lundborg et al., 1999). A crucial element in such cross-modal plasticity seems to be training, in order for a sensory modality to “take over” another sensory modality.

### 3.2 Mechanisms of plasticity

Several cellular mechanisms by which the adult brain can adjust to changes in the environment or in sensory input have been defined, including the following (Kandel et al., 2000; Purves, 2004).

#### *Decreased inhibition*

Many connections between the periphery and the cortex as well as intracortical connections are physiologically “silent” because of inhibitory influences (Wall, 1977). Sensory stimulation of a point on the skin activates neurons in the somatosensory system near the centre of the area of cortical representation and inhibits activity in neurons near the edges. In this way the receptive field appears smaller than its actual size. The inhibition is due to activation of inhibitory interneurons near the edges of the receptive field. Decreased inhibition would theoretically increase the receptive field size and enable more neurons to be activated by the stimulus; this is sometimes referred to as unmasking of synapses or neural structures. Gamma-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the brain (Jones, 1993) and evidence is strong that reduction of GABAergic inhibition is crucial in mediating short term plasticity changes (Chen et al., 2002).

#### *Increase in synaptic strength*

The effectiveness of synaptic connections is continuously adopted in response to functional demands. Synaptic transmission becomes facilitated in a pathway that is frequently used, while those that lay dormant atrophy. In this way, repeated practice of a task leads to increased speed and accuracy of performance. Increased synaptic strength may be a mechanism for learning and also for recovery from brain injury. Repetitive stimulation results in increased excitability and facilitation of transmission in the synapses. These effects persist for some time after the initial stimulus and subsequently show gradual declines (long term potentiation, LTP). Calcium channels in the neuronal membrane appear to be crucial in this process. LTP is probably one of the major mechanism by which learning and memory consolidation takes place in the brain (Kandel et al., 2000).

#### *Axonal and dendritic sprouting*

The sprouting and elongation of new dendrites and axons is a common response to injury and cell loss at all levels in the nervous system. Sprouting can also be seen in response to increased functional demand, such as exposure to conditions requiring more complex motor activity (Kleim et al., 1996). Axons at the edges of a lesion send new axonal branches into the damaged area and re-innervate dendrites that have lost their synaptic input. This leads to new synaptic formation at the point of contact of axonal sprouts with these dendritic trees. This mechanism for recovery has been suggested in, for example, the reaction of the somatosensory cortex to loss of its input from the skin (Merzenich et al., 1984; Pons et al., 1991).

### 3.3 Targeted plasticity

The primary somatosensory and motor cortex is organized somatotopically, where different body parts project to different parts of the primary somatosensory and motor cortex (Figure 1). The somatotopic map does not represent the body in its actual proportions. Instead, larger cortical areas are being assigned to sensitive parts or parts with complex motor demands, such as the hands and face. The cortical representation of different body parts alters constantly, depending on the pattern of afferent nerve impulses, injury and increased or decreased use.

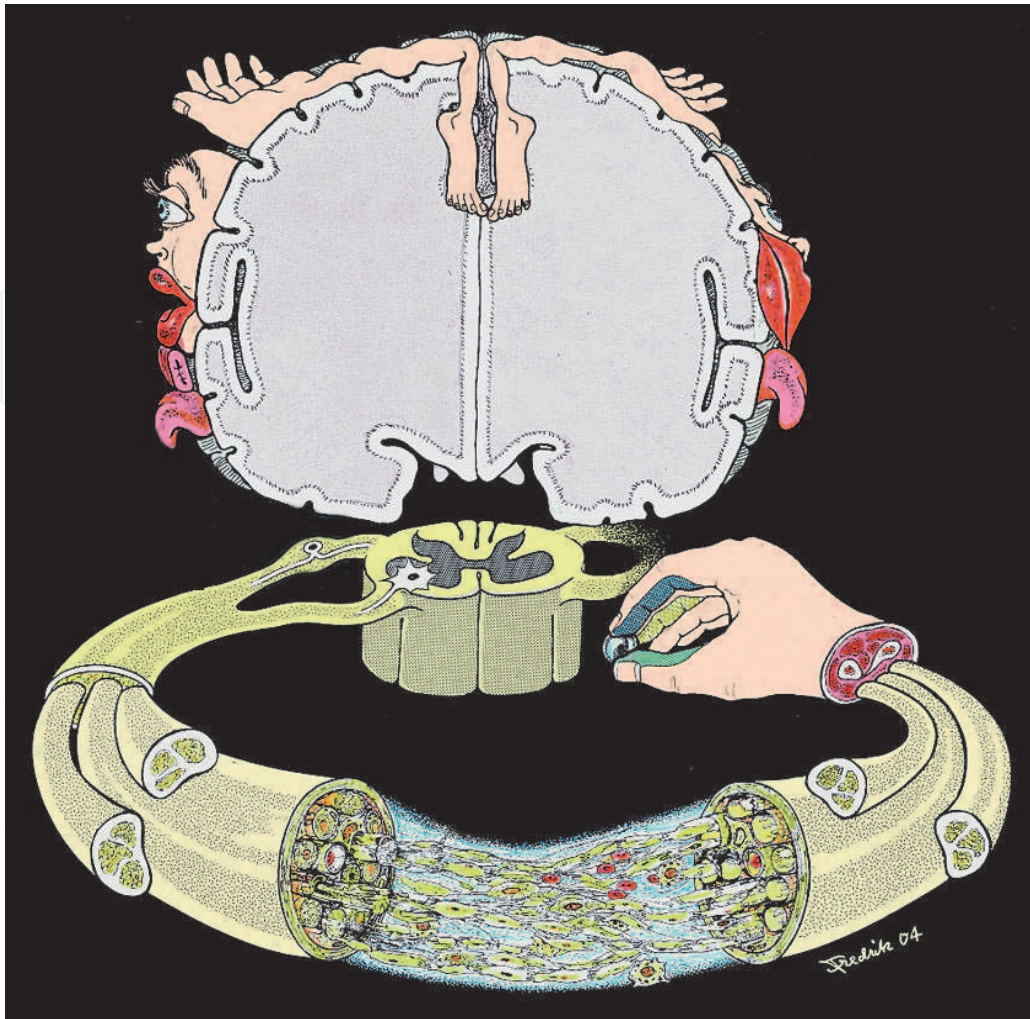


Fig. 1. Sensory information is sent from, in this case, the hand via the peripheral nerve to the dorsal root ganglia, spinal cord and thalamus to the primary somatosensory cortex. Motor information is sent from the primary motor cortex to the spinal cord and the effector muscles.

Both the primary somatosensory and motor cortex are arranged somatotopically. Thus in each hemisphere there is a complete somatotopic map of the body both in the primary somatosensory and motor cortex.

To utilize the central nervous systems' (CNS) ability to change for therapeutic purposes, guided plasticity is an attractive concept with promising results (Duffau, 2006). The potential for cerebral plasticity is, for example, used in treatment of patients to strengthen or promote CNS functions that are lost or weakened. The plastic potential of the brain might be guided using neurosurgical methods, rehabilitation and different pharmacological drugs in order to improve lost or damaged functions (Duffau, 2006). The use of neurosurgical methods is very complicated, sometimes including complex surgical interventions, which limit the usefulness. The use of potent drugs affecting the central nervous system, such as amphetamine (Walker-Batson et al., 2001) and norepinephrine (Plewnia et al., 2004), in order to improve recovery of damaged function, have been described. However, few patients currently benefit from such treatments due to incomplete knowledge of optimal treatment regimes and side effects from the drugs.

Our main objective when starting to develop a treatment regime for diabetic neuropathy was to look for a method more suitable for patient usage, giving a cortical deafferentation “large” enough to induce changes in peripheral function but not unnecessarily large. The method should also be safe with no side effects, pain free, and easy to us for both patient and therapist. Furthermore, it should be specific for sensory functions not affecting the motor function as this would affect the person’s ability to perform motor tasks.

It is well known from animal and human experiments that temporary cutaneous anesthesia of one body part leads to cortical re-organization resulting in a corresponding silent area in the sensory cortex. This allows adjacent nearby body parts to rapidly expand at the expense of the silent cortical area this is likely mediated by unmasking of existing synapses.

The forearm is located next to the hand in the somatotopic map and by anaesthetizing the forearm, the cortical hand area can rapidly expand over the forearm area resulted in improved sensory function of the hand in healthy controls (Bjorkman et al., 2009). Thus, more nerve cells can be available for the hand, resulting in improved hand function. In a randomized, controlled trial, sensory re-learning in combination with cutaneous forearm anesthesia, using an anesthetic cream, EMLA® containing 2.5% lidocain and 2.5% prilokain, improved sensory function of the hand compared with sensory re-learning and placebo in patients with ulnar or median nerve repair (Rosen et al., 2006). The participants received treatment twice a week for two consecutive weeks, and the effects lasted 4 weeks after the last EMLA® treatment. These results suggest that sensory recovery is enhanced by temporary anesthesia of adjacent body parts. The long lasting effect indicates that this treatment is clinically useful and relevant.

Recently, the same principle of temporary cutaneous anesthesia as that used for the hand has been applied on the foot in uninjured subjects. In a randomized controlled trial, improvement in sensory function of the foot was observed after EMLA® treatment of the lower leg compared to placebo (Rosen et al., 2009).

There is no specific treatment for neuropathy in diabetes except a strict control of the glycaemic level. However, recent data in healthy subjects and diabetic patients show that the sensory function in the foot and hand, measured by the monofilament test, can be improved by using the central nervous systems ability to change, i.e. brain plasticity. In a recent double blind randomized placebo controlled study male (n=26) or female (n=5) diabetic patients with type 1 (n=30) or type 2 (n=7) with a median duration of diabetes of 35 years, all with insulin treated diabetes, were either treated with EMLA® cream or placebo cream applied to the skin of the lower leg for 1.5 hours (n=18 and n=19, respectively). All the subjects in the EMLA® group with pre-treatment diminished protective sensibility at the first metatarsal head showed improved touch threshold below limits for protective sensibility after 1.5 and 24 hours, while no such changes were observed after the treatment with placebo cream (Fig 2).

Furthermore, the touch thresholds improved at four other assessment sites (third metatarsal head, fifth metatarsal head, pulp of big toe and central of heal) together with increased vibration threshold at 125 Hz. However, the patients observed no subjective improvement, based on examination with a visual analogue scale, after treatment. This new strategy to improve the thresholds of touch creates new possibilities to treat disturbances in sensation of the diabetic foot. Hypothetically, the local anaesthetic cream results in a deafferentation of the lower leg in the primary somatosensory cortex, which allows the foot to expand. Thus, more nerve cells are available for the foot resulting in the observed improved sensory function.



A challenge is to create a long lasting improvement of the sensory function. Studies using cutaneous anaesthesia in the upper extremity in patients with nerve injuries and neuropathy have shown that a lasting improvement of sensibility is possible using repeated sessions with cutaneous anaesthesia (Rosen et al., 2008; Rosen et al., 2006).

In conclusion, treatment of diabetic neuropathy is complicated. However, new knowledge on the effect of a peripheral nerve injury and neuropathy on the central nervous system opens new perspectives to treat neuropathy by targeted plasticity. Cutaneous anaesthesia of the lower leg in diabetic patients is a good example of how targeted plasticity is used in order to improve foot sensibility in patients with diabetic neuropathy. The method is simple, safe, and cost-effective, although future studies are needed to work out the optimal treatment regime for a long lasting or permanent improvement in sensibility.

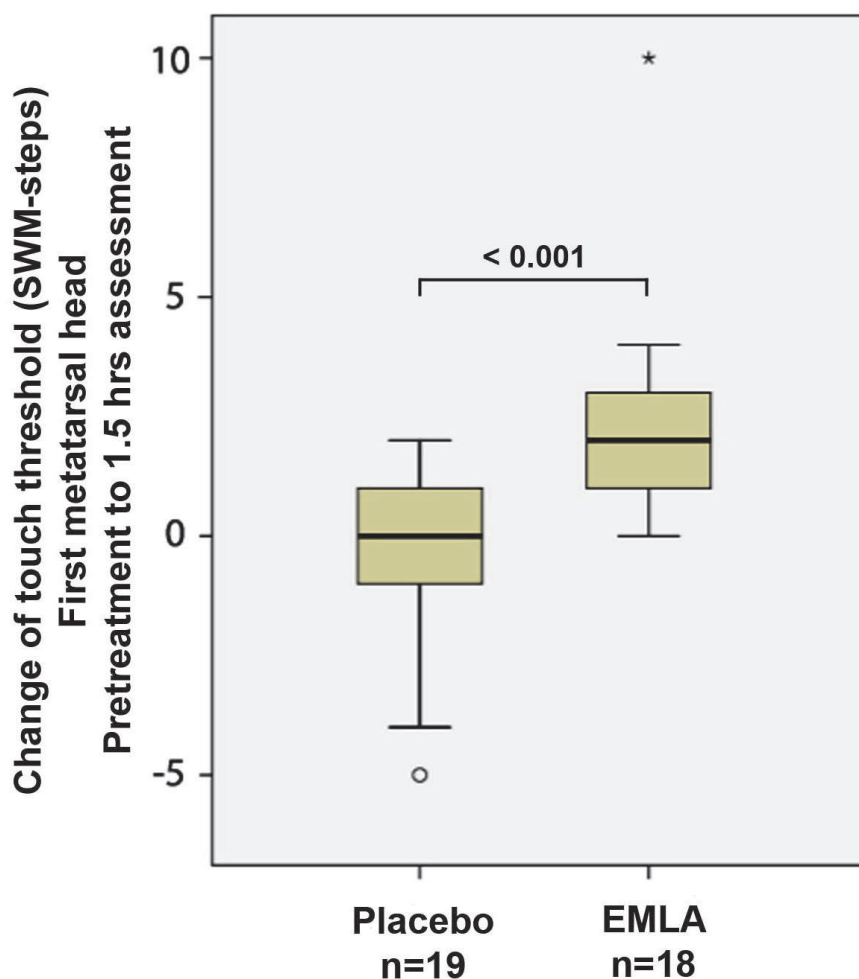


Fig. 2. Change of touch threshold in first metatarsal head in diabetic patients between pretreatment and after 1.5 h of EMLA® treatment compared with placebo ( $P < 0.001$ ).

#### 4. Acknowledgement

The studies on diabetic neuropathy from our group was supported by the Swedish Research Council (Medicine), Crafoord's Fund for Medical Research, Svenska Diabetesförbundet, Diabetesföreningen Malmö, Konsul Thure Carlsson Fund for Medical Research, Region

Skåne, Stiftelsen Sigurd och Elsa Goljes Minne and Funds from the University Hospital Malmö, Sweden.

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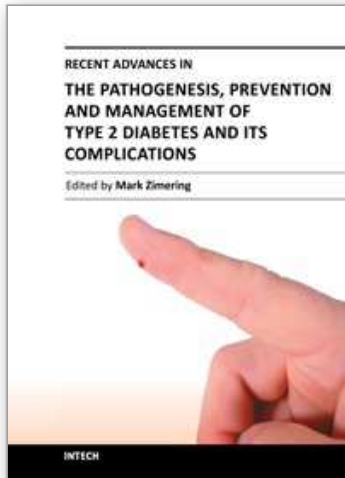
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## **Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications**

Edited by Prof. Mark Zimering

ISBN 978-953-307-597-6

Hard cover, 442 pages

**Publisher** InTech

**Published online** 29, August, 2011

**Published in print edition** August, 2011

Type 2 diabetes (diabetes mellitus) affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Anders Björkman, Niels Thomsen and Lars Dahlin (2011). New Treatment Strategies in Diabetic Neuropathy, Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications, Prof. Mark Zimering (Ed.), ISBN: 978-953-307-597-6, InTech, Available from:  
<http://www.intechopen.com/books/recent-advances-in-the-pathogenesis-prevention-and-management-of-type-2-diabetes-and-its-complications/new-treatment-strategies-in-diabetic-neuropathy>

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