Diabetic Neuropathy:
A Deeper Look into an Unresolved Problem

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LIST OF ABBERVIATIONS

5-HT	Serotonin
ACE	Angiotensin-converting enzyme
AG	Aminoguanidine
AGE	Advanced glycation end-product
AGE-R3	Galectin-3
AGT	Angiotensinogen
ALA	Alpha-Lipoic Acid
ALC	Acetyl-L-carnitine
ALT-711	Alagebrium chloride
ANS	Autonomic nervous system
AR	Aldose reductase
ARBs	Angiotensin II- receptor blocker
ARIs	Aldose reductase inhibitors
BB	Bio breeding rat
BDNF	Brain- derived neurotrophic factor
CAN	Cardiovascular autonomic neuropathy
Cdc42	Cell division cycle 42 protein
CGRP	Calcitonin gene-related peptide
CIDP	Chronic inflammatory demyelinating neuropathy
CNTF	Ciliary neurotrophic factor
COX-2	Cyclooxygenase-2
DAG	Diacylglycerol
DAN	Diabetic Autonomic neuropathy
DCCT	Diabetes Control and Complications Trial
DLRPN	Diabetic lumbosacral radiculoplexus neuropathy

DN	Diabetic neuropathy
DRG	Dorsal root ganglia neurons
DSP	Distal symmetric polyneuropathy
ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthtase
ERM	Ezrin, radixin, and moesin
ET-1	Endothelin-1
FDA	Food and Drug Administration
FFA	Free fatty acid
GABA	γ-aminobutyric acid
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GDNF	Glial-derived neurotrophic factor
GF	growth factors
GFAT	Glutamine fructose-6 phosphate amidotransferase
GI	Gastrointestinal
GK	Goto Kakizaki rat
GLA	Gamma-linolenic Acid
GSH	Reduced Glutathione
HED	High-energy diet.
HFD	High-fat diet
HMG CoA	Hydroxy methyl glutaryl CoA
HMGB1	High mobility group box 1
HSP	Hexosamine pathway
Hsps	Heat shock proteins
ICAM-1	Intercellular adhesion molecule-1
IGFs	Insulin-like growth factors

IGT	Impaired glucose tolerance
IL1B	Interleukin-1B
IL6	Interleukin-6
IL8	Interleukin-8
IVIg	I.V. Imunoglobulins
LETL	Long Evans Tokushima lean rat
MAPNO	Mitogen-activated protein
MNCV	Motor nerve conduction velocity
MNSI	Michigan Neuropathy Screening Instrument or score
NAD+	Nicotinamide adenine dinucleotide
NADP+	Nicotinamide adenine dinucleotide phosphate
NCS	Nerve conduction study
NCVs	Nerve conduction velocity
NE	Norepinephrine
NF-κB	Nuclear factor kappa-B
NGF	Nerve growth factor
NMDA,	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOD	Non-obese diabetic
NOS	Nitric oxide synthase
NPY	Neuropeptide Y
NSAIDs	Non steroidal anti inflammatory drugs
NT-3	Neurotrophin-3
O-GlcNAc	O-linked beta-N-acetylglucosamine

OLETF	Otsuka Long-Evans Tokushima Fatty rat
P. obesus	Psammomys obesus
PAI-1	Plasminogen activator inhibitor
PARP	Poly (ADP-ribose) polymerase pathway
PC12	Pheochromoctoma cell line
PGE_2	Prostaglandin E_2
PGI_2	Prostacycline
PGI2	Prostacycline
PGP9.5	Protein gene product 9.5
PKC	Protein kinase C
PTB	N-phenacylthiazolium bromide
RAGEs	Receptor for advanced glycated end products.
RCT	Randomized control trials
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SDH	Sorbitol dehydrogenase enzyme
SHSY5Y	Neuroblastoma cell line
SNCV	Sensory nerve conduction velocity
SNRIs	Serotonin noradrenaline reuptake inhibitors
Sp	Substance P
Sp1	Specificity protein 1
sRAGE	Soluble RAGE
SSRIs	Selective serotonin reuptake inhibitors
STZ	Streptozotocin
SWM	Semmes-Weinstein monofilaments`
TCAs	Tricyclic antidepressants.

TGFα	Transforming growth factor α
TGFβ	Transforming growth factor β
TK	Transketolase
TNFα	Tissue necrosis factor α
Trk	Tyrosine receptor kinases
TSOD	Tsumura Suzuki Obese Diabetes mice
TXA2	Thromboxane A_2
UDPG1cNAc	Uridine diphosphate-N-acetyl glucosamine
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide
vitamin B3	Nicotinamide
VPT	Vibration perception threshold
WHO	World Health Organization
ZDR	Zucker fatty rat

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Diabetic Neuropathy

Diabetes is a major public health problem that is becoming more prevalent worldwide. According to the World Health Organization (WHO) reports of 2009, diabetes mellitus affects more than 220 millions, worldwide. In 2010, the number increased to reach 285 millions and it is expected to increase up to 439 millions by the year 2030. Between 2010 and 2030, there will be a 69% increase in adults with diabetes in developing countries and a 20% increase in developed countries **(Shaw et al., 2010).**

Diabetic complication as retinopathy, nephropathy and neuropathy are the leading causes of blindness, end-stage renal disease, and amputations in the US **(American Diabetes Association 2007).** Although type 1 and type 2 diabetes originate from different pathogenic causes, there is association between hyperglycemia and diabetic micro vascular complications in both types **(The Diabetes Control and Complications Trial Research Group, 1993).** Neuropathy is a common complication of diabetes mellitus and is usually related to the duration and severity of hyperglycemia **(Maser et al., 1989; The Diabetes Control and Complications Trial Research Group, 1995**). It can also occur after correction of hyperglycemia ‘‘insulin neuritis’’, where hypoglycemia may cause axonal damage **(Dabby et al., 2009).**

Diabetic neuropathy (DN) is defined as the presence of symptoms and /or signs of nerve dysfunction in diabetic patients. However, we should exclude other causes of nerve dysfunctions such as traumatic, hereditary, nutritional, neoplastic, immune mediated and compressive causes **(Boulton et al., 2004).** Nevertheless, it is the most common form of neuropathies in the developed countries**.** Being the leading cause for non-traumatic amputations **(Pittenger et al., 2004),** DN requires more hospitalization than other complication of diabetes. Amputations risk increase from 1.7 fold to 12 folds in presence of deformity and up to 36 folds in cases of previous ulceration. There are about 96,000 amputations yearly in United States for diabetic patient and about 75% of them can be prevented. Globally there

is amputation secondary to DN every 30 seconds, which results in huge morbidity and mortality and cause huge economic load for diabetes care **(Casellini and Vinik, 2007).** Frequency of DN is equal in both type 1 and type 2 diabetes **(Dyck et al., 1993).** It should be suspected in all type 2 diabetic patients and in patients who had type 1 for more than 5 years **(Aring et al., 2005).**

Epidemiology of Diabetic Neuropathy

Epidemiology of DN is still unclear because of the multiple diagnostic criteria, inability of many physicians to identify the disease and poor methodology to evaluate the patients **(Casellini and Vinik, 2007)**. Therefore, the prevalence of DN in diabetic patients varies widely between 5% and 60% and sometimes even up to 100% of diabetics if abnormalities in nerve conduction in asymptomatic patients are included **(Ugoya et al., 2006)**. Between 1947 and 1973, in a prospective study of 4,400 patients of type-2 diabetes, the prevalence was 7.5% at diagnosis, which increases linearly to 50% after 25 years **(Pirart, 1977)**. In 1993 in United Kingdom, a study showed that the prevalence of over all peripheral neuropathy is about 28.5% with no difference between male and female but type 2 diabetic patients have higher over all incidence about 32.15% compared to 22.7% of type 1 patients. This prevalence reached 44.2 % in patients between 70 and 79 years of age **(Young et al., 1993)**. In 2008, another study on the prevalence of neuropathy in Canadian people found that neuropathy increased by increase glucose level. It affect 5% among those with normal glucose levels, 8% among those with new impaired fasting glucose and newly diagnosed diabetics, and 15% among those with established diabetes **(Bruce andYoung, 2008).** A recent Chinese study conducted in 2010 showed a prevalence of 17.8 % among type 2 diabetic patients **(Liu et al., 2010).**

Types of diabetic neuropathy

DN includes many neuropathic syndromes that occur isolated or in combinations **(Ziegler, 2008)**. According to **Casellini and Vinik (2007)**, DN is classified as follows:

I-Rapidly reversible Hyperglycemic neuropathy

II-Generalized symmetric polyneuropathy

- a- Acute sensory neuropathy
- b- Chronic sensorimotor neuropathy or distal symmetric polyneuropathy (DSP)
  - 1- Small-fiber neuropathy
  - 2- Large-fiber neuropathy
- c- Diabetic autonomic neuropathy (DAN)
  - 1- Cardiovascular autonomic neuropathy (CAN)
  - 2- Gastrointestinal autonomic neuropathy
  - 3- Genitourinary autonomic neuropathy
  - 4 -Sudomotor autonomic neuropathy
  - 5- Abnormal pupillary function
  - 6-Hypoglycemia-associated autonomic failure

III-Focal and multifocal neuropathies

- a- Focal-limb neuropathy
- b- Cranial neuropathy
- c- Proximal-motor neuropathy (amyotrophy)
- d- Truncal radiculoneuropathy
- e- Coexisting chronic inflammatory demyelinating neuropathy (CIDP)